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EDITORIAL

# Bringing gut microbiota into the spotlight of clinical research and medical practice

Efstathia Davoutis, Zoi Gkiafi, Panagis M Lykoudis

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## Abstract

Despite the increasing scientific interest and expanding role of gut microbiota (GM) in human health, it is rarely reported in case reports and deployed in clinical practice. Proteins and metabolites produced by microbiota contribute to immune system development, energy homeostasis and digestion. Exo- and endogenous factors can alter its composition. Disturbance of microbiota, also known as dysbiosis, is associated with various pathological conditions. Specific bacterial taxa and related metabolites are involved in disease pathogenesis and therefore can serve as a diagnostic tool. GM could also be a useful prognostic factor by predicting future disease onset and preventing hospital-associated infections. Additionally, it can influence response to treatments, including those for cancers, by altering drug bioavailability. A thorough understanding of its function has permitted significant development in therapeutics, such as probiotics and fecal transplantation. Hence, GM should be considered as a ground-breaking biological parameter, and it is advisable to be investigated and reported in literature in a more consistent and systematic way.

**Key Words:** Gut microbiota; Biomarker; Fecal microbiota transplantation; Dysbiosis; Prebiotics

**Core Tip:** Gut microbiota (GM) serves as a multifaceted tool in healthcare, acting as a potential biomarker, diagnostic, prognostic, and therapeutic entity. While dysbiosis is linked to various diseases, harnessing microbiome's diagnostic potential introduces challenges due to its variability and complex identification techniques. As a prognostic tool, GM provides insights into an individual's health status and disease risks, influencing treatment outcomes. Moreover, it emerges as a therapeutic pathway, with interventions such as prebiotics and fecal microbiota transplantation showing promise. Despite growing recognition, its integration into clinical practice remains limited, necessitating increased research, educational initiatives, and collaborations, to unlock the full potential of GM in advancing patient care.

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## INTRODUCTION

Although scientists have long been aware of the presence of microorganisms in the human digestive system, since the era of Antonie van Leeuwenhoek in the 17th century, gut microbiota (GM) gained significant momentum and understanding in the late 20th and early 21st centuries. The first reports on GM appeared in literature in 1984, with a frequency of one publication *per* year. The development of advanced DNA sequencing technologies in the late 20th cen-tury contributed to better identifying the diverse array of microbes in the gut. Today, it is a widely discussed and in-creasingly popular indicator. With growing age, factors like host genetics, dietary changes, antibiotics, and stress gra-dually affect the composition of GM-a phenomenon known as dysbiosis[1]. Dysbiosis is associated with the development and outcomes of various pathologies, including inflammatory bowel diseases (IBD)[2], neurodevelopmental disorders[3], breast cancer[4], colorectal cancer (CRC)[5] *etc.* Over the past years, light has been shed on the role of microbiome in therapeutic approaches for the above health conditions. In 2007, the National Institutes of Health in the United States initiated the Human Microbiome Project, aiming to characterize the human microbiome and understand its role in health and disease.

This editorial emphasizes on the crucial role of microbiome, highlighting its recognition not just as a secondary endpoint but as a primary focus in clinical cases and trials, aiming to raise awareness, spark discussions and encourage a collective effort within the medical community to better understand and leverage the microbiome's significance, ultimately enhancing patient care and scientific knowledge.

## GM AS A BIOMARKER

A biomarker is a well-defined characteristic that serves as an indicator of biologic processes, either physiologic or pathologic, or as a measure of response to an exposure or intervention[6]. Biomarkers are objectively measurable variables, well-known for their specificity and sensitivity over a specific biologic process. Several categories of biomarkers have been established based on their potential uses. For instance, a diagnostic biomarker is utilized to identify or validate the existence of a particular disease or medical condition, or to pinpoint an individual with a specific disease subtype[7]. These biomarkers can serve the purpose of identifying individuals with a disease as well as of redefining the categorization of the disease[8].

Dysbiosis is associated with various pathological conditions, both intestinal and extra-intestinal[9]. Hence, GM has been proposed as a biomarker for various conditions[10-14]. For example, some metabolites produced by gut bacteria, such as short-chain fatty acids (SCFAs), can be used as diagnostic markers for cardiovascular diseases[15]. SCFAs, such as butyrate, have also been studied as a potential biomarker for patients with pancreatic cancer. Evidence suggests that SCFAs can modulate several processes associated with pancreatic cancer development, including inflammation, cell proliferation, and immune responses[16]. Moreover, fecal microbes and butyrate have been suggested as biomarkers in order to distinguish patients with pancreatic ductal adenocarcinoma from patients with autoimmune pancreatitis and healthy subjects[17]. However, its use as a biomarker is still in the early stages of development. Further studies are needed to standardize its use in clinical practice and to establish clear causative relationships between GM composition and specific diseases. What makes GM a challenging biomarker is its variability and complexity as its composition can vary significantly among individuals[18]. Another important factor is the sophisticated techniques needed to identify and characterize GM. Collecting and analyzing samples can involve invasive procedures requiring special expertise and equipment. This can render the utilization of GM as a biomarker in routine clinical settings quite challenging.

## GM AS A DIAGNOSTIC TOOL

GM has the potential to serve as a valuable diagnostic tool for various health conditions[19]. For instance, individuals suffering from Crohn's disease often exhibit a reduced diversity and overall imbalance in GM. This encompasses a

diminished variety within the *Firmicutes phylum* and reduced levels of *Faecalibacterium prausnitzii*[20]. Furthermore, according to a recent study, GM could be used as a non-invasive way to diagnose membranous nephropathy[21]. In the same study, a diagnostic model was developed, which demonstrated an excellent identification capability with an area under curve (AUC) of 98.36%, in a standard sensitivity-specificity receiver operating characteristic curve analysis. This model was based on seven operational taxonomic units of the microbiome. Additionally, the involvement of GM in the onset of the disease was highlighted. Changes in GM have also been linked to CRC in various populations, and numerous bacterial species have been found to contribute to tumorigenesis[22]. Through a comprehensive analysis of 526 metagenomic samples from Chinese, Austrian, American, German and French cohorts, researchers identified seven enriched species (*Bacteroides fragilis, Fusobacterium nucleatum*, *Porphyromonas asaccharolytica*, *Parvimonas micra*, *Prevotella intermedia*, *Alistipes finegoldii*, and *Thermanaerovibrio acidaminovorans*) and 62 depleted species in CRC cases compared to controls. Their findings also support the effective performance of these seven CRC-enriched bacteria in distinguishing CRC patients from controls across different cohorts[22]. A decrease in gut *Firmicutes*, including *Faecalibacterium prausnitzii* and *Roseburia sp*. has been noticed in patients with IBD[23]. Reduction in *Firmicutes* may lead to increased local inflammation by reducing anti-inflammatory cytokines. Additionally, it could potentially result in impaired colonic barrier function due to a deficiency in SCFAs[23]. In an assessment of GM as a diagnostic tool, a machine learning approach utilizing generalized linear models with penalized maximum likelihoods was employed. The microbial composition showed a better IBD/irritable bowel syndrome predictive accuracy [mean AUC of 0.91 (0.81-0.99)] than the currently used fecal inflammation biomarker calprotectin [mean AUC of 0.80 (0.71-0.88), $P = 0.002$][24].

However, there are some challenges to overcome in order to clarify the diagnostic potential of GM. The inter-individual variability of GM and the overlap of disrupted microbiota communities among multiple diseases, pose significant obstacles in using taxonomic data for diagnosis and disease characterization[19]. Standardization of methods and distinguishing causation from correlation are also important challenges. Nevertheless, advances in metagenomic sequencing [25], machine learning[26], and multi-omics approaches[27] are helping to identify more specific microbial markers in gut associated with various diseases.

## GM AS A PROGNOSTIC TOOL

Analyzing the composition and function of GM can provide insights into an individual's health status and the risk of developing specific diseases such as Crohn's disease[28], gestational diabetes[29], coronary artery disease[30] and celiac disease[31]. Notably, research has demonstrated that GM can forecast both clinical course of patients and their response to particular treatments including those for cancers[32], *Clostridioides difficile* infection[33], rheumatoid arthritis[34], bariatric surgery[35] and IBDs[36]. For example, Shi *et al*[37] suggested that GM and pathway markers identified in their study may function as a predictive tool for identifying patients with rectal cancer who are likely to benefit from neoadjuvant chemoradiotherapy (nCRT)[37]. Furthermore, the presence of members of the *Bacteroidales* order, such as *Parabacteroides merdae*, was found to be more prominent in non-responders while increased activity in fatty acid metabolism and propionate metabolism pathways seemed to improve effectiveness of anti-tumor treatment[37]. They also suggested that GM could be harnessed for identifying patients who have a lower risk of experiencing diarrhea associated with nCRT[37]. This signifies that microbiota-based medicine has the potential to predict and mitigate the adverse effects of specific medications. In this context, it has been found that GM of patients who will experience weight gain after chemotherapy differed from that of those who will not[38]. Therefore, if responsiveness to treatments can be predicted by pre-screening patients' microbiota, management can be tailored to meet individual needs and determine whether some patients are good candidates for a certain treatment[39].

Yamaoka *et al*[40] found that assessing the levels of *Fusobacterium nucleatum* could serve as a predictive factor of clinical outcomes in patients with CRC[40]. High abundance of *Fusobacterium nucleatum* in colorectal tumors was also associated with poorer overall survival (OS)[41]. Concerning hepatocellular carcinoma, the *Prevotella/Bacteroides* ratio has the potential to serve as a prognostic indicator for the response to nivolumab treatment. A higher ratio is associated with more favorable treatment efficacy[42]. Also, survival analysis demonstrated that patients with increased levels of species *Lachnospiraceae bacterium*-GAM79, *Erysipelotrichaceae bacterium*-GAM147, *Ruminococcus callidus*, *Alistipes megaguti*, and *Bacteroides zoogleoformans* had extended progression-free survival and OS[43]. Even in organ transplantation, GM of both donor and recipient can impact the prognosis and success of the procedure[44]. The composition of GM could additionally function as a predictive marker for the severity of a disease by modulating immune responses[45]. Specifically, when examining the microbial species linked to the severity of corona virus disease 2019 (COVID-19) infection, a negative correlation between disease severity and *Faecalibacterium prausnitzii* and *Bifidobacterium bifidum* was observed. Composition of GM in patients with COVID-19 is also concordant with the plasma levels of various inflammatory cytokines, chemokines and markers of tissue damage[45].

Finally, GM may impact an individual's vulnerability to infectious diseases. In this context, researchers have emphasized the significance of identifying the microbiome of patients admitted to the intensive care unit as a key strategy for averting hospital-acquired infections[46].

## GM AS A THERAPEUTIC TOOL

In addition to serving as a diagnostic and predictive marker, GM is being explored as a potential therapeutic tool in various medical contexts. It has been shown that GM can influence an individual's response to a medical treatment by

altering its bioavailability, bioactivity and toxicity[47]. As discussed above, GM could be used to predict responses to various therapies including chemotherapies and immunotherapies. Moreover, interventions have been designed to manipulate or modify the composition and function of GM in order to improve outcomes. Interventions that aim to restore microbial balance in the gut include prebiotics, probiotics, synbiotics, and fecal microbiota transplantation (FMT). Prebiotics are non-digestible fibers and compounds found in certain foods that promote the activity and growth of beneficial bacteria in the gut[48] while probiotics are alive microorganisms, mainly bacteria and yeast, that confer health benefits to the host by positively modulating gut microflora and reducing pathogenic bacteria releasing toxic compounds in human gut[49]. Synbiotics refer to a mixture of prebiotics and probiotics[50]. Such interventions can be used for treating *Costridium difficile* infection, IBD, and other gastrointestinal disorders[51]. They can also be employed in the field of cancer immunotherapy to enhance the effectiveness of cancer treatments[52]. For instance, interventions aimed at manipulating the GM and promoting SCFA production, such as probiotics, prebiotics, and dietary fiber supplementation, have demonstrated promise in altering the tumor microenvironment and improving the effectiveness of immunotherapy[53]. In a mouse model, the positive impact of microbiota was transferable through FMT. Specifically, introducing stool from responsive donors to germ-free mice resulted in an immune-mediated anti-tumor response[54]. Moreover, FMT can be applied in allergies and autoimmune disorders to either prevent or alleviate allergic reactions and autoimmune conditions. For instance, some early studies have suggested that there are differences in the GM profile of individuals with food allergies (FAs) compared to individuals without FAs, and that FMT could be a promising strategy to prevent allergic symptoms[55]. FMT could also enhance clinical remission, clinical response, and endoscopic remission in individuals with ulcerative colitis, as well as promote clinical remission in those with Crohn's disease[56]. Furthermore, probiotic supplementation has been found to improve subjective sleep quality as measured by the change in Pittsburgh sleep quality index score[57]. In the years ahead, researchers will be capable of leveraging pharmaco-microbiomics, the field of study that seeks to uncover the impact of the microbiome on drug metabolism, efficacy and toxicity, for personalizing medical treatments, optimizing drug therapies, and reducing adverse effects.

## CURRENT STATUS IN LITERATURE AND CLINICAL PRACTICE

GM is increasingly recognized as a significant endpoint in studies. However, upon analyzing their distribution, a notable pattern of predominance of reviews emerges. Only a modest 4% corresponds to clinical studies and clinical trials, and merely 0.35% pertains to case reports. This indicates a conspicuous scarcity of data pertaining to GM in the context of patient-related scenarios. Regrettably, the current application of GM in research appears mostly theoretical, serving as bibliographic knowledge, with limited incorporation into everyday medical practice. This discrepancy arises mainly from two factors. Firstly, there is a notable absence of familiarity with GM indices in clinical practice. Additionally, a substantial proportion of healthcare professionals lack the required background to measure and evaluate these indices.

A frequently posed question revolves around the methodologies employed for studying GM and the feasibility of conducting such analyses within a laboratory setting. Various techniques are utilized to collect samples for evaluating GM, with common sources encompassing fecal samples, samples obtained through endoscopy and samples derived from biopsies. Following sample collection, standard analytical methods involve genomic DNA extraction, amplification of the 16S rRNA gene, sequencing and subsequent bioinformatic analysis of sequencing data[58]. Notably, the 16S rRNA gene and sequencing methodology have garnered extensive utilization. This culture-free approach provides a way to identify and compare bacterial diversity within intricate microbiomes or environments that present challenges for traditional study methods. The employment of this method enhances the capacity to gain valuable insights into composite microbial colonies[59]. 16S rRNA gene sequencing is a culture-independent method, enabling the identification of bacteria that may be challenging to culture or have not been previously characterized[1]. Therefore, this approach facilitates a comprehensive and culture-free exploration of the intricate microbial composition present in diverse environments, such as the complex ecosystems within the human gut.

Despite its fundamental significance as a biomarker, the utilization of GM in this capacity is not as prevalent as that of other frequently referenced markers, such as gender, age, Body mass index, race, smoking habits, and profession, which are universally acknowledged as pivotal factors influencing various pathologies. The consistent reference to these markers underscores their recognized impact on health conditions. Conversely, awareness regarding the association of GM with conditions such as breast cancer or IBD might be less pervasive. This discrepancy is attributable to the extensive and historical use of certain markers like smoking, while the microbiome is a relatively novel consideration. Therefore, the inclusion of microbiome analysis, even as a secondary outcome, is highly desirable. Such inclusion not only broadens baseline knowledge but also contributes to establishing the microbiome's standing in the conscience of the broader medical community, ensuring that a larger readership is well-informed about its relevance and potential implications.

While the integration of GM into medical research is gaining momentum, challenges persist in establishing it as a widely recognized biomarker[60]. The dynamic nature of the microbiome and its relatively recent emergence in scientific discourse contribute to its slower adoption compared to traditional markers. Efforts to bridge this gap involve emphasizing the microbiome's relevance to secondary outcomes[61], thereby enriching the understanding of its intricate connections with health. Researchers are increasingly delving into the complexities of GM to uncover its potential implications for various health conditions[62]. As the scientific community continues to explore and unravel the mysteries of the microbiome, collaborative initiatives are essential to promote its integration into mainstream medical considerations and pave the way for more targeted and holistic approaches to healthcare.

GM should be incorporated as a biomarker in case reports, assuming the role of a routinely integrated indicator in daily clinical practice. Ideally, healthcare practitioners should develop an automated incorporation of GM-related know-

ledge into the overall clinical assessment of the patient, as it occurs with established factors. Moreover, the implementation of GM as a biomarker in case reports would allow for the documentation of challenges and deficiencies that may arise with regards to its utilization, thereby offering valuable feedback for targeted research and subsequent refinements. This approach ensures that the outcomes and implications of integrating GM into case reports are widely disseminated, fostering increased awareness, and encouraging more medical centers to adopt its inclusion on a comprehensive scale.

In this paradigm shift towards incorporating GM as a routine biomarker in case reports, the integration process should extend beyond clinical practice to encompass educational initiatives within medical training programs. Educating healthcare professionals about the intricacies of GM and its potential impact on health outcomes is paramount for successful integration. Developing specialized training modules and incorporating GM-related knowledge into medical curricula would empower future practitioners to understand and utilize this biomarker effectively. By fostering a comprehensive understanding of GM, medical professionals can confidently incorporate it into their clinical assessments, contributing to a more holistic approach. This educational integration ensures that the next generation of healthcare providers is well-equipped to navigate the complexities of the microbiome landscape, further solidifying its place in routine clinical practice.

## SUGGESTIONS FOR IMPROVED INCORPORATION

A pivotal consideration is the integration of GM into routine clinical practice, but this mandates a circumspect and evidence-driven approach, which at the moment cannot be corroborated by existing literature, despite current promising and valuable insights. Therefore, incorporation of GM into research is necessary in order to improve reliability and applicability in healthcare decision-making. Illustrative case studies detailing scenarios wherein comprehension of GM proves pertinent to diagnosis, treatment or management, could serve as a robust argument for the incorporation of microbiome knowledge in clinical practice.

Given the necessity to integrate GM into routine clinical practice, it becomes evident that a collaborative effort among researchers, healthcare professionals, and policy makers is essential. Creating interdisciplinary teams that involve microbiologists, clinicians, and experts in healthcare policy could accelerate the translation of GM research findings into actionable guidelines for clinical settings. This collaborative approach ensures that the incorporation of GM into routine practice aligns with evidence-based standards and regulatory frameworks. By fostering synergy across different domains, this concerted effort strives to establish a robust foundation for the seamless integration of GM into everyday healthcare decision-making.

Potential avenues for increased utilization reside in incorporating GM assessments more frequently within patient research protocols and clinical trials. This approach offers a platform to comprehensively evaluate the method's advantages and disadvantages, thereby presenting opportunities to address challenges and refine methodologies in subsequent targeted research endeavors[63]. In summary, the exploration of GM within the framework of clinical trials yields valuable insights into disease mechanisms, treatment responses, and overall health outcomes. As our understanding of the microbiota is continuously expanding, its integration into clinical research gains escalating importance for the advancement of medical knowledge and the enhancement of patient care.

By systematically integrating GM assessments into clinical trials, researchers gain valuable insights into the dynamic interplay between the microbiota and various health conditions. This approach not only allows for the identification of potential biomarkers and therapeutic targets but also provides opportunities to address challenges and refine methodologies. The continuous expansion of our understanding of the microbiota underscores the escalating importance of its integration into clinical research. Leveraging GM data in clinical trials holds promise for the development of more targeted and effective interventions, contributing to a paradigm shift in healthcare towards personalized and precision medicine.

Another important objective would be improving healthcare practitioners' familiarization with GM. This would empower doctors to provide more comprehensive and individualized care. Provision of educational resources that would bridge the gap between the emerging field of microbiome research and clinical practice could facilitate this objective. Organizing conferences, workshops, and symposia that bring together experts in microbiome research and healthcare professionals could be a great adjunct. Moreover, establishing partnerships could facilitate the translation of research findings into clinical applications and help doctors stay informed about relevant developments.

In tandem with enhancing healthcare practitioners' familiarity with GM, fostering a culture of continuous learning is essential. Developing specialized training programs within medical curricula and professional development courses can provide a structured approach to GM education. Integrating microbiome-related content into medical training modules ensures that future healthcare professionals are well-equipped with the necessary knowledge and skills. Furthermore, leveraging online platforms and digital resources can enhance accessibility, allowing practitioners to stay updated on the latest developments in GM research at their own pace. By cultivating a learning environment that encourages ongoing education and professional growth, the medical community can effectively navigate the complexities of integrating GM insights into routine clinical practice, ultimately facilitating more personalized and informed patient care.

## CONCLUSION

Once overlooked, GM has emerged as a pivotal player in health and disease. Dysbiosis, influenced by factors like genetics, diet, antibiotics and stress, is associated with various pathologies, emphasizing the dynamic nature of the gut

microbial ecosystem. GM shows promise as a diagnostic tool, with potential applications in identifying and categorizing diseases. Its role extends beyond diagnosis, and studies now demonstrate its prognostic significance, as well as its therapeutic role in benign and malignant conditions. While GM is increasingly explored, challenges include inter-individual variability, method standardization, and distinguishing causation from correlation. Future research directions should involve leveraging advances in metagenomic sequencing, machine learning, and multi-omics approaches to identify specific microbial markers associated with various diseases. Given the surprisingly wide variety of conditions and purposes where GM's usefulness emerges, GM should ideally be routinely examined and reported in clinical case reports as well as in comparative studies.

## FOOTNOTES

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EDITORIAL

# Fertility preservation in patients with gynecologic cancer

Nicolae Gică

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## Abstract

In this editorial we comment on the article by Gu *et al*. We focus and debate the necessity of fertility sparing surgery in young women's with gynecologic cancers, specifically on those patients with the desire to conceive. This type of individualized treatment options is often very difficult, due to the risk of disease evolution and multiple disparities in fertility preservation services among women in different countries and societies. For this reason national policy interventions are mandatory in order to ensure equitable access this procedures, in women with cancer.

**Key Words:** Fertility sparing surgery; Pregnancy; Gynecologic cancer; Endometrial cancer; Ovarian cancer



**Core Tip:** Fertility preservation is a delicate balance, requiring multidisciplinary approach. Timely discussions about fertility preservation options should be integrated into the overall treatment plan, allowing patients to make informed decisions about their reproductive future. While not without challenges, fertility preservation provides cancer survivors with the opportunity to conceive and regain a sense of normalcy post-treatment.

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## INTRODUCTION

Fertility preservation is mandatory in women at reproductive age with cancer, with no children, and desire to procreate. There are multiple disparities in fertility preservation services among women in different countries and societies. For this reason, national policy interventions are mandatory to ensure equitable access to these procedures, in women with cancer.

A special category is represented by young women with gynecological cancer or premalignant diseases, who wish to preserve their childbearing potential. Conservative management, to preserve fertility is recommended in these patients, in selected cases[1]. If conservative management is not feasible, different types of fertility preservation (oocyte vitrification, ovarian cortex cryopreservation, or embryo cryopreservation) should be offered to young women with cancer[2].

Fertility preservation is a delicate balance, requiring a multidisciplinary approach. Timely discussions about fertility preservation options should be integrated into the overall treatment plan, allowing patients to make informed decisions about their reproductive future. While not without challenges, fertility preservation provides cancer survivors with the opportunity to conceive and regain a sense of normalcy post-treatment. This evolving field reflects a commitment to holistic care, recognizing the importance of preserving not only life but also the potential for creating new life beyond cancer.

Fertility preservation has become a necessity, to improve the quality of life in young women, after cancer treatment. Increasing survival rates, due to the new therapies and early diagnosis of different types of cancer in young women requires new national and international strategies to improve procreation.

This strategy, in my opinion, should clearly define the importance of onco-fertility care in women at reproductive age, with no children and a desire to procreate.

In this editorial, we want to add this comment, after reading the article published by Gu *et al*[3]. Endometrial neoplasia is now easy to diagnose using hysteroscopy. Moreover, this type of fertility-sparing treatment is reserved for young women with the desire to conceive, after delivery the radical treatment is recommended.

Recent statistics reports highlight the incidence of endometrial neoplasia being 4.5% and mortality of 3.4% of all malignancies. Normally this pathology appears in the postmenopausal period, except in a small group including very young women, with a desire to conceive. The standard treatment is hysterectomy with bilateral salpingo-oophorectomy with or without lymph node dissection but in low-risk patients with endometrioid endometrial cancer (EC) stage IA, grade 1, with or without focal lymphovascular invasion, stage I the fertility-sparing surgery can be an option[4].

Moreover, immune checkpoint inhibitors were recently discovered as a potential game-changer, nowadays predictive biomarkers are mandatory to stratify this category of patients with EC[5].

## CONCLUSION

In conclusion, the fertility-sparing surgery in uterine or ovarian cancer is individualized, to preserve the reproductive function and the patient should be reevaluated after birth for definitive treatment.

## FOOTNOTES

**Author contributions:** There is only one author in the manuscript, and the author has written the manuscript.

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EDITORIAL

# Investigating causal links between gastroesophageal reflux disease and essential hypertension

Gowthami Sai Kogilathota Jagirdhar, Yatinder Bains, Salim Surani

**Specialty type:** Medicine, research and experimental

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## Abstract

Gastroesophageal reflux disease (GERD) is a prevalent global health concern with a rising incidence. Various risk factors, including obesity, hiatal hernia, and smoking, contribute to its development. Recent research suggests associations between GERD and metabolic syndrome, cardiac diseases, and hypertension (HTN). Mechanisms linking GERD to HTN involve autonomic dysfunction, inflammatory states, and endothelial dysfunction. Furthermore, GERD medications such as proton-pump inhibitors may impact blood pressure regulation. Conversely, antihypertensive medications like beta-blockers and calcium channel blockers can exacerbate GERD symptoms. While bidirectional causality exists between GERD and HTN, longitudinal studies are warranted to elucidate the precise relationship. Treatment of GERD, including anti-reflux surgery, may positively influence HTN control. However, the interplay of lifestyle factors, comorbidities, and medications necessitates further investigation to comprehensively understand this relationship. In this editorial, we comment on the article published by Wei *et al* in the recent issue of the *World Journal of Clinical Cases*. We evaluate their claims on the causal association between GERD and HTN.

**Key Words:** Gastroesophageal reflux disease; Hypertension; Metabolic syndrome; Gastroesophageal reflux disease; Hiatal hernia

**Core Tip:** The relationship between gastroesophageal reflux disease (GERD) and hypertension (HTN) is multifaceted, involving mechanisms such as autonomic dysfunction, nitric oxide levels, and medication effects. GERD treatment, including anti-reflux surgery, may improve HTN control, highlighting the clinical relevance of understanding this association. However, the complex interplay of comorbidities and medications warrants further investigation to elucidate causal pathways and optimize patient management strategies.

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is becoming a prevalent disease globally. There were 783.95 million cases of GERD globally per the Global Burden of Diseases, Injuries, and Risk Factors Study of 2019. The prevalence is rapidly rising, with a 77.58% increase in prevalence from 1990 to 2019. Risk factors for GERD include obesity, hiatal hernia, smoking, pregnancy, and many others. In their bidirectional Mendelian randomization study, Wei *et al*[1] found that GERD was associated with hypertension (HTN), and it increased the risk of HTN. We expand on the potential mechanisms, pathophysiology, and relation between GERD and HTN.

## POTENTIAL FACTORS ASSOCIATED WITH GERD

In recent studies, GERD has been found concurrently with metabolic syndrome and cardiac disease[2]. Metabolic syndrome patients have higher GERD symptoms. Metabolic syndrome is associated with autonomic dysfunction, and this can worsen gastroesophageal motility, causing GERD. Further metabolic syndrome is proposed to be an inflammatory state that can cause increased levels of interleukin-1β and interleukin-6, interleukin-8, tumor necrosis factor-alpha, Nuclear factor kappa-β, which can cause chronic stimulation of the lower esophageal sphincter (LES), worsen LES contractility, causing GERD[3,4]. Patients often have concomitant diabetes, which is associated with autonomic nerve damage that affects the Vagus nerve, leading to LES dysfunction and GERD[4,5]. Weight and obesity can predispose to GERD through an increase in intraabdominal fat pressure that causes relaxation of the LES and increased episodes of reflux. Dietary habits associated with obesity, such as increased fat intake, also promote reflux[5,6]. GERD is related to cardiovascular and ischemic heart disease by increasing proinflammatory cytokines, causing endothelial dysfunction and sympathetic tone, and causing autonomic imbalance. This results in decreased nitric oxide (NO) metabolites decreased esophageal tissue resistance, and dysfunction leading to GERD[3,7]. Studies in the literature describe the relationship between GERD and stroke[8]. Some of these studies lack specificity on the definition of GERD and heartburn and the absence of endoscopic diagnosis to confirm it misclassified patients[9]. Often patients have additional comorbidities and are on medications that influence GERD in these studies. If these factors are unadjusted in the analysis, it can lead to false results.

## RELATIONSHIP BETWEEN GERD AND HTN

HTN in prior studies was associated with an odds ratio of 1.5 for the risk of GERD[10]. The mechanism of proposed low blood pressure (BP) in GERD patients is based on decreased sympathetic function in patients with GERD, causing blunting of BP responses to stressors. Recent studies examined the role of NO and low BP, stating that NO causes LES relaxation. Patients with GERD have higher NO levels in their blood, causing low esophageal sphincter resting tone, thus increasing GERD and decreasing BP.

In a prospective study by Li *et al*[2], patients were classified as GERD based on esophageal impedance and pH monitoring. Seventy-five percent have at least one episode of high BP associated with acid reflux symptoms. After treatment with antacid therapy for 14 d, these populations had a statistically significant decrease in BP parameters. However, chronic proton-pump inhibitor (PPI) use may cause elevation in BP by disrupting pathways that cause NO production and bioavailability. They reduce NO synthase activity in the endothelium and endothelium-dependent vasodilation. They decrease the availability of protons in the gastric juice, thereby decreasing NO formation from nitrates. Thus, it decreases the reduction in BP from ingested nitrates by disrupting the nitrate-nitrite-NO pathway[11]. Symptoms of GERD often result in chest pain and discomfort. This can induce neural reflux, causing increased sympathetic activity, which can induce HTN.

In the study by Wei *et al*[1], the authors describe pleiotropy in the initial analysis suggesting the association with the exposure is weak between GERD and essential HTN (odds ratio 1.46) that required changing the data of HTN. The final odds ratio after changing the data is 1.002 between GERD and essential HTN. The authors also state they detected hetero-

geneity and horizonal pleiotropy between GERD and diastolic BP suggesting absence of a strong causal relationship between GERD and diastolic BP. GERD is also thought to provoke arrhythmia and bradycardic episodes predisposing to hypertensive heart disease in literature[7,12]. Wei *et al*[1] also describes the association between GERD and hypertensive heart disease. Similar to prior studies Wei *et al*[1] also describes an association between GERD and renal disease[8].

Patients with HTN are frequently on beta blockers and calcium channel blockers. Yoshida *et al*[13] found that atenolol increased esophageal body contraction, and nifedipine decreased it in the short term. Calcium channel blockers can reduce the tone of the LES and decrease esophageal clearance, thereby increasing GERD. Thus, patients can have higher GERD symptoms while on these medications. Treatment for GERD has improved HTN control in patients in some studies. In a retrospective study by Hu *et al*[14], 40% of patients with GERD who underwent Nissen or Toupet fundoplication either decreased or stopped using anti-hypertensives post-procedure. Further, there was also a decrease in the mean BP that was statistically significant. Often, studies done to evaluate the relationship between GERD and HTN do not consider the antihypertensive drugs or PPI patients are on. Often, the results of these studies are not adjusted for various confounding factors, thus producing variable results. Patients with HTN often have additional comorbidities, including obesity and increased abdominal girth, which can worsen GERD symptoms. Wei *et al*[1] describe a decreased risk of Barrett's esophagus with HTN. Few studies in the literature describe increased risk of Barrett's esophagus in patients with metabolic syndrome in the absence of GERD[15-17]. However, the definition of GERD, reflux esophagitis, and underlying confounding factors, including sex, appear to give conflicting results in these studies compared to controls. Often, the risk of Barrett's metabolic syndrome may be marginally increased and often not clinically significant, necessitating further research on the association[18,19]. GERD is a disease that can be influenced by several factors. Certain lifestyle factors, dietary habits, medications, or comorbidities that were not adequately accounted for in the analysis could influence the observed associations. The Mendelian randomization study conducted by Wei *et al*[1] is unable to measure multiple confounding factors that influence the association between GERD and HTN and therefore the results drawn may be distorted.

The study conducted by Wei *et al*[1] may not be generalizable to the global population since it was conducted in Europe, and genetic factors and disease prevalence may vary in different populations. While the study primarily investigates the causal effect of GERD/BE on HTN, reverse causation cannot be entirely ruled out. HTN may also influence the development or exacerbation of GERD/BE, leading to bidirectional causality. Further, longitudinal studies or alternative causal inference methods may help elucidate the directionality of the observed associations. The efficacy of gastroesophageal reflux treatment (*e.g.*, proton pump inhibitors, anti-reflux surgery) in preventing or managing HTN requires further investigation through randomized controlled trials or observational studies.

## CONCLUSION

The is a causal and bidirectional relationship between GERD and HTN. This correlation is influenced by patients underlying comorbidities, medications, dosage, and duration of usage.

## FOOTNOTES

**Author contributions:** Surani S and Bains Y designed the overall concept and outline of the manuscript; Jagirdhar GSK and Bains Y contributed to the discussion and design of the manuscript; Jagirdhar GSK, Bains Y and Surani S contributed to the writing, editing the manuscript and review of literature.

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ORIGINAL ARTICLE

Case Control Study

# Neutrophil-to-lymphocyte ratio associated with renal function in type 2 diabetic patients

Jin-Li Gao, Jue Shen, Li-Ping Yang, Li Liu, Kai Zhao, Xiao-Rong Pan, Lei Li, Ji-Ji Xu

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## Abstract

### *BACKGROUND*

Type 2 diabetes mellitus (T2DM) is a leading risk factor for the development and progression of chronic kidney disease (CKD). However, an accurate and convenient marker for early detection and appropriate management of CKD in individuals with T2DM is limited. Recent studies have demonstrated a strong correlation between the neutrophil-to-lymphocyte ratio (NLR) and CKD. Nonetheless, the predictive value of NLR for renal damage in type 2 diabetic patients remains understudied.

### *AIM*

To investigate the relationship between NLR and renal function in T2DM patients.

### *METHODS*

This study included 1040 adults aged 65 or older with T2DM from Shanghai's Community Health Service Center. The total number of neutrophils and lymphocytes was detected, and NLR levels were calculated. CKD was defined as an estimated glomerular filtration rate ≤ 60 mL/min/1.73 m². Participants were divided into four groups based on NLR levels. The clinical data and biochemical characteristics were compared among groups. A multivariate logistic regression model was used to analyze the association between NLR levels and CKD.

***RESULTS***
Significant differences were found in terms of sex, serum creatinine, blood urea nitrogen, total cholesterol, and low-density lipoprotein cholesterol among patients with T2DM in different NLR groups ($P < 0.0007$). T2DM patients in the highest NLR quartile had a higher prevalence of CKD ($P$ for trend = 0.0011). Multivariate logistic regression analysis indicated that a high NLR was an independent risk factor for CKD in T2DM patients even after adjustment for important clinical and pathological parameters ($P = 0.0001$, odds ratio = 1.41, 95% confidence intervals: 1.18-1.68).

***CONCLUSION***
An elevated NLR in patients with T2DM is associated with higher prevalence of CKD, suggesting that it could be a marker for the detection and evaluation of diabetic kidney disease.

**Key Words:** Type 2 diabetes mellitus; Neutrophil-to-lymphocyte ratio; Chronic kidney disease; Logistic regression; Diabetes mellitus



**Core Tip:** In elderly type 2 diabetes mellitus (T2DM) patients, elevated neutrophil-to-lymphocyte ratio (NLR) is strongly linked to an increased risk of chronic kidney disease (CKD), uncovering NLR as a potential independent biomarker for early detection of renal damage. This finding holds significant promise for addressing the current challenge of delayed CKD diagnosis in T2DM, signifying the potential utility of NLR as a convenient and sensitive detection method for identifying CKD in diabetic patients.

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## INTRODUCTION

Diabetes is a prevalent metabolic disease with significant implications for global health, and type 2 diabetes mellitus (T2DM) represents the predominant form of diabetes in China, accounting for over 90% of cases[1]. T2DM is one of the leading risk factors for the development and progression of chronic kidney disease (CKD)[2]. In Asia, it is estimated that > 60% of patients with diabetes will develop kidney complications, compared with 30%-40% in Europeans despite having a similar duration of diabetes[3,4]. Furthermore, CKD in diabetic individuals is associated with increased morbidity and premature mortality, which impose a substantial economic burden on healthcare systems[5,6]. Given the continuous increase in the number of people with diabetes, early detection and appropriate management of CKD in individuals with T2DM are crucial to prevent or delay the progression of kidney disease. However, since CKD is a complex multifactorial disease and the pathogenesis of the disease remains unclear, along with limited access to medical resources and the high cost of testing in some regions, patients are hindered from obtaining routine renal function screening and timely diagnosis. Therefore, the identification of an accurate and convenient marker for promptly detecting and assessing kidney function is essential to improve patient outcomes.

Recent studies have shown that the neutrophil-to-lymphocyte ratio (NLR), an inflammatory marker, strongly correlates with acute ischemic stroke, tumors, sepsis, and CKD[7-10]. However, prior research has mostly examined hospitalized patients with more severe conditions, overlooking diabetic patients in the general population. This article mainly explored the relationship between NLR and renal function in patients with T2DM, aiming to establish a theoretical framework for evaluating the predictive value of NLR in the early detection of renal damage in T2DM patients.

## MATERIALS AND METHODS

### *Population*

This study involved 1040 adults aged 65 years old or above diagnosed with T2DM from the health examination platform of the Community Health Service Center in Songnan Town, Baoshan District, Shanghai, China from June to August 2021. The investigation focused on three medical service stations located in the community health service center and affiliated institutes of Songnan Town. The diagnosis of T2DM was in accordance with Chinese guidelines for the prevention and treatment of T2DM (2020 edition)[11], namely, a fasting plasma glucose (FPG) level ≥ 7.0 mmol/L or a previous diagnosis of T2DM and currently receiving oral medication. Participants were excluded if they had incomplete or uncertain basic information, type 1 DM, a history of hormone therapy within a year, any type of malignancy, a current acute infection, or

an established hematologic disease. Oral consent was obtained from all participants, and the study was approved by the central ethics committee.

### Implant procedure

Demographics (sex and age) and disease history, such as hypertension, were self-reported by all participants through comprehensive questionnaires completed by trained general practitioners and volunteers. Height and weight were measured using an electronic height scale, and body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Waist and hip circumferences were measured using a soft skin caliper, and blood pressure was measured using an Omron sphygmomanometer (HBP-1120u).

For laboratory testing, the participants' whole blood was drawn into an EDTA vacuum anticoagulant tube and mixed by inversion several times. Additionally, 6 mL of fasting venous blood was obtained in the early morning, and the supernatant was collected after centrifugation. FPG, serum creatinine (Scr), blood urea nitrogen (BUN), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were detected using an automatic biochemical analyzer (Hitachi 7080). The total number of neutrophils and lymphocytes were detected using a Mairui 5100 automatic hematology analyzer, and NLR levels were calculated. All blood samples were collected by the Department of Laboratory Medicine in the Community Health Service Center, Songnan Town, Baoshan District, Shanghai, China. The laboratory received quality control from the standardized protocol for blood biochemical testing from the Shanghai Centers for Disease Control and Prevention.

### Outcome definition

The estimated glomerular filtration rate (eGFR), expressed in ml/min/1.73 $m^2$, was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation on the basis of Scr[12]. The formula was as follows: (1) if female: Scr ≤ 0.7 mg/dL, eGFR = 144 × $(Scr/0.7)^{-0.329}$ × $(0.993)^{age}$; Scr > 0.7 mg/dL, eGFR = 144 × $(Scr/0.7)^{-1.209}$ × $(0.993)^{age}$; and (2) if male: Scr ≤ 0.9 mg/dL, eGFR = 141 × $(Scr/0.9)^{-0.411}$ × $(0.993)^{age}$; Scr > 0.9 mg/dL, eGFR = 141 × $(Scr/0.9)^{-1.209}$ × $(0.993)^{age}$. CKD was defined as an eGFR of 60 mL/min/1.73 $m^2$ or less[13].

### Other definitions

(1) Hypertension was defined according to the Chinese guidelines for the prevention and treatment of hypertension (2018 Revision)[14], with systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, or with a previous diagnosis of hypertension and currently being treated with oral antihypertensive drugs; (2) Smoking referred to those who smoked ≥ 1 cigarette per day on average, continuously or cumulatively for the past 6 months; (3) Drinking was defined as consuming alcohol at least once a week at a dose of ≥ 50 g of ethanol per occasion, continuously or cumulatively over the past 6 months; and (4) Regular exercise referred to participation in physical activity at least 5 d per week, cumulatively for ≥ 30 min per day, for 6 consecutive months or more.

### Statistical analysis

Continuous variables were expressed as the mean ± SD or median with interquartile range and were analyzed by an independent Student's *t* test or one-way analysis of variance test for normally and nonnormally distributed variables (the Kolmogorov–Smirnov test). Categorical data were analyzed using the chi-square test and are presented as frequencies (percentages). The NLR level was analyzed as a continuous variable and divided by quartiles. Multivariate logistic regression analyses were conducted to assess the independent association between NLR and diabetic kidney disease (DKD). After adjusting for age, sex, BMI, FPG, TG, LDL-C, and lifestyle factors, odds ratios (ORs) with 95% confidence intervals (CIs) were reported. The predictive value of NLR for renal dysfunction in different eGFR groups was tested by the area under the receiver operating characteristic curve (AUROC), and the optimal cutoff point of the NLR was obtained by calculating the Youden index. The Youden index is a method of evaluating the authenticity of a screening test, which represents the total ability of the screening method to detect true patients and nonpatients. A higher index is associated with a better effect and greater authenticity of the screening test. The NLR that corresponded to the maximum Youden index was then determined to be the optimal cutoff NLR in this study.

All statistical analyses were performed using SAS software (version 9.4). A two-tailed $P$ value < 0.05 was considered statistically significant.

## RESULTS

### Implant data

Table 1 shows the general characteristics of the study population. A total of 1040 participants diagnosed with T2DM were included in the analysis and divided into four groups according to their NLR: quartile 1 (NLR < 1.38, 261 patients), quartile 2 (1.38 ≤ NLR < 1.76, 258 patients), quartile 3 (1.76 ≤ NLR < 2.30, 262 patients), and quartile 4 (NLR ≥ 2.30, 259 patients). No significant difference was observed among the groups concerning age, BMI, SBP, DBP, FPG, TG, platelet counts, smoking, drinking, regular exercise, and hypertension (Table 1). However, significant differences were found in terms of sex, BUN, Scr, eGFR, TC, LDL-C, HDL-C, neutrophil, lymphocyte and white blood cell (WBC) counts among the four groups ($P$ < 0.05).

Using the definition of CKD, there were 132 cases in total. As shown in Figure 1, patients in the higher NLR quartile group had a greater prevalence of CKD ($P$ for trend = 0.0011).

**Table 1 Characteristics of all type 2 diabetes mellitus patients categorized by the neutrophil-to-lymphocyte ratio quartiles**

| Variables | Total | Quartile 1 (NLR < 1.38) | Quartile 2 (1.38 ≤ NLR < 1.76) | Quartile 3 (1.76 ≤ NLR < 2.30) | Quartile 4 (NLR ≥ 2.30) |
|---|---|---|---|---|---|
| *N* | 1040 | 261 | 258 | 262 | 259 |
| Male[1], *n* (%) | 490 (47.1) | 99 (37.9) | 119 (46.1) | 130 (49.6) | 142 (54.8) |
| Age (yr) | 71.9 ± 5.5 | 71.5 ± 5.5 | 72.0 ± 5.7 | 71.9 ± 5.4 | 72.3 ± 5.5 |
| BMI (kg/m$^2$) | 25.0 ± 4.0 | 25.1 ± 3.6 | 25.3 ± 4.6 | 25.1 ± 3.7 | 24.7 ± 4.2 |
| SBP (mmHg) | 145.3 ± 20.3 | 144.8 ± 19.7 | 144.4 ± 19.4 | 146.5 ± 20.2 | 145.3 ± 22.0 |
| DBP (mmHg) | 78.7 ± 11.7 | 77.8 ± 11.5 | 79.0 ± 10.8 | 78.9 ± 11.0 | 79.2 ± 13.5 |
| FPG (mmol/L) | 7.8 ± 2.4 | 7.6 ± 1.8 | 8.0 ± 2.8 | 7.8 ± 2.4 | 8.0 ± 2.3 |
| BUN[1] (mmol/L) | 6.8 ± 2.1 | 6.4 ± 1.6 | 6.9 ± 2.2 | 6.6 ± 2.0 | 7.1 ± 2.3 |
| Scr[1] (mmol/L) | 74.1 ± 21.8 | 68.2 ± 16.1 | 73.1 ± 19.4 | 75.3 ± 22.1 | 79.8 ± 26.8 |
| eGFR[1] (mL/min/1.73 m$^2$) | 80.2 ± 15.7 | 83.6 ± 12.9 | 80.7 ± 15.0 | 79.3 ± 16.0 | 77.7 ± 17.0 |
| TC[1] (mmol/L) | 4.7 ± 1.2 | 5.0 ± 1.2 | 4.8 ± 1.3 | 4.7 ± 1.1 | 4.6 ± 1.1 |
| TG (mmol/L) | 1.7 ± 1.5 | 1.6 ± 1.2 | 1.8 ± 2.0 | 1.7 ± 1.5 | 1.5 ± 1.1 |
| LDL-C[1] (mmol/L) | 3.0 ± 0.9 | 3.2 ± 1.0 | 3.0 ± 1.0 | 2.9 ± 0.9 | 2.9 ± 0.9 |
| HDL-C[1] (mmol/L) | 1.5 ± 0.4 | 1.5 ± 0.3 | 1.4 ± 0.3 | 1.5 ± 0.4 | 1.5 ± 0.4 |
| Neutrophil[1] | 3.7 ± 1.0 | 2.9 ± 0.7 | 3.5 ± 0.8 | 3.9 ± 0.9 | 4.5 ± 1.0 |
| Lymphocyte[1] | 2.1 ± 0.6 | 2.6 ± 0.7 | 2.2 ± 0.5 | 1.9 ± 0.4 | 1.5 ± 0.4 |
| WBC[1] | 6.3 ± 1.4 | 6.1 ± 1.3 | 6.3 ± 1.4 | 6.3 ± 1.4 | 6.5 ± 1.4 |
| Platelet | 189.1 ± 48.5 | 187.6 ± 46.3 | 191.7 ± 46.2 | 191.2 ± 52.0 | 185.8 ± 49.4 |
| Smoking, *n* (%) | 174 (16.7) | 36 (13.8) | 48 (18.6) | 47 (17.9) | 43 (16.6) |
| Drinking, *n* (%) | 179 (17.2) | 36 (13.8) | 54 (20.9) | 48 (18.3) | 41 (15.8) |
| Regular exercise, *n* (%) | 197 (18.9) | 53 (20.3) | 52 (20.2) | 51 (19.5) | 41 (15.8) |
| Hypertension, *n* (%) | 714 (68.7) | 171 (65.5) | 182 (70.5) | 187 (71.4) | 174 (67.2) |

[1]Means a significant difference ($P < 0.05$) between four neutrophil-to-lymphocyte ratio quartile groups for corresponding variable.
NLR: Neutrophil-to-lymphocyte ratio; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; BUN: Blood urea nitrogen; Scr: Serum creatinine; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

### *Association between NLR and CKD in T2DM patients*

As shown in Table 2, we found that high NLR was associated with a higher prevalence of CKD in T2DM patients in multivariate regression models even after adjustment for important clinical parameters, including age, sex, smoking, drinking, regular exercise, BMI, SBP, FPG, TG and LDL-C ($P$ value < 0.0001). With an SD increase in the NLR, the prevalence of CKD increased by 44%. Furthermore, when NLR was categorized into quartiles, the association between NLR and CKD remained, and there was a 3.3-fold increased prevalence of CKD in T2DM patients in the highest quartile of NLR (OR 3.30, 95%CI: 1.78-6.12, $P = 0.0001$) compared to those in the lowest quartile. AUROC was analyzed to determine the predictive value of the NLR for the risk stratification of renal dysfunction. As shown in Figure 2, compared with the higher eGFR group (< 90 mL/min/1.73 m$^2$ and < 60 mL/min/1.73 m$^2$), the NLR had the highest AUROC (0.902) when eGFR was < 30 mL/min/1.73 m$^2$ ($P = 0.005$, 95%CI: 0.840-0. 959). The AUROC for eGFR < 90 mL/min/1.73 m$^2$ and eGFR < 60 mL/min/1.73 m$^2$ was 0.553 ($P = 0.019$, 95%CI: 0.515-0.591) and 0.606 ($P = 0.026$, 95%CI: 0.556-0.657), respectively (Figure 2). The cutoff values (sensitivity and specificity) for different eGFR groups (< 90 mL/min/1.73 m$^2$, < 60 mL/min/1.73 m$^2$, and < 30 mL/min/1.73 m$^2$) were 1.525 (69.1%, 40.9%), 1.605 (78.8%, 41.0%) and 2.525 (approximately 100%, 81.1%), respectively.

## DISCUSSION

In this cross-sectional study comprising 1040 patients diagnosed with T2DM, we observed that higher NLR was significantly associated with an increased prevalence of CKD, even after adjusting for various confounding factors. These

**Table 2 Association between neutrophil-to-lymphocyte ratio and chronic kidney disease in type 2 diabetic patients**

| Exposure | Age-and-sex adjusted model | | Multivariate model | |
|---|---|---|---|---|
| | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| NLR (per SD) | 1.39 (1.17-1.65) | **0.0002** | 1.44 (1.21-1.72) | **< 0.0001** |
| Quartile 1 (< 1.38) | Reference | | Reference | |
| Quartile 2 (1.38–1.76) | 1.69 (0.89-3.22) | 0.1100 | 1.57 (0.81-3.04) | 0.1785 |
| Quartile 3 (1.76–2.30) | 2.42 (1.30-4.50) | **0.0052** | 2.52 (1.35-4.73) | **0.0039** |
| Quartile 4 (≥ 2.30) | 3.07 (1.68-5.62) | **0.0003** | 3.30 (1.78-6.12) | **0.0001** |
| *P* for trend | | **0.0001** | | **< 0.0001** |

SD = 0.76; *P* values were calculated from univariate or multivariate regression tests, and the bold typeface indicates significance ($P < 0.05$). The multivariate model was further adjusted for age, sex, smoking, drinking, regular exercise, body mass index, systolic blood pressure, fasting plasma glucose, triglyceride, and low-density lipoprotein cholesterol. OR: Odds ratio; CI: Confidence interval; SD: Standard deviation; NLR: Neutrophil-to-lymphocyte ratio.

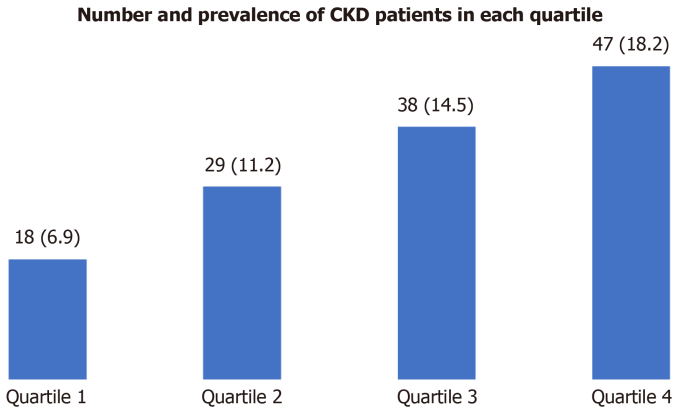


**Figure 1 Comparison of chronic kidney disease prevalence in different neutrophil-to-lymphocyte ratio quartiles.** The numbers above the bars and in brackets represent the cases and corresponding proportions of chronic kidney diseases in each neutrophil-to-lymphocyte ratio quartile group. CKD: Chronic kidney diseases.

findings shed light on the possibility of utilizing NLR as a promising clinical marker, facilitating early detection and subsequent management of CKD among patients with T2DM.

CKD is a common and severe complication in individuals with diabetes, although its precise pathogenesis remains poorly understood. It is recognized that a sequence of pathological events, including parenchymal cell loss, chronic inflammation, renal fibrosis, and reduced regenerative capacity of the kidney, can contribute to the development and progression of CKD[15]. Metabolic disorders in diabetic patients activate inflammatory signals within the body, and elevated levels of inflammatory factors contribute to kidney injury[16]. Chronic inflammation has been implicated in the development of complications associated with T2DM, and various inflammatory molecules, such as adipokines, chemokines, adhesion molecules, and cytokines, have been identified as contributors to CKD development[17]. However, several of these markers, such as C-reactive protein, interleukin-6, and tumor necrosis factor-α, are expensive and not routinely measured in clinical practice.

NLR has recently emerged as a discerning inflammatory indicator that provides insights into the equilibrium between neutrophils and lymphocytes, two critical constituents of the immune system. While neutrophils function as nonspecific instigators of inflammation, lymphocytes play regulatory and protective roles in the context of inflammatory responses [18]. NLR has garnered recognition as a reliable metric for gauging the extent of systemic inflammation[19,20]. Previous studies have shown a positive association between NLR and well-established inflammation markers, such as interleukin-6 and C-reactive protein[21,22]. Notably, in comparison to other inflammatory markers, the NLR exhibits advantages in terms of stability, cost-effectiveness, and accessibility[23].

Growing evidence substantiates the connection between elevated NLR and progression and prognosis of CKD[24-28]. Although DKD is the most common cause of CKD, the relationship between NLR and CKD in T2DM patients is still relatively understudied[29]. Notably, a previous study showed a positive correlation between neutrophil levels and urinary albumin excretion in individuals with T2DM, while lymphocyte levels displayed a negative correlation[30]. Similarly, a hospital-based investigation involving 655 adult patients with T2DM elucidated the independent association of NLR with the risk of developing DKD[31]. Additionally, a cross-sectional survey conducted in seven communities in China involving 4813 diabetic adults revealed a positive relationship between a higher NLR and a higher prevalence of DKD[32]. Furthermore, elevated NLR not only manifested as a risk factor for DKD but also served as a prognostic in-

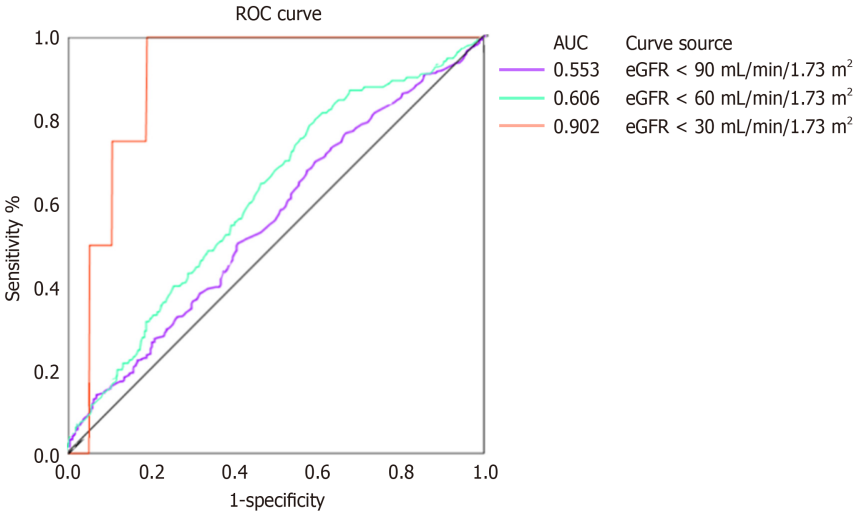


**Figure 2 Predictive value of neutrophil-to-lymphocyte ratio for estimated glomerular filtration rate decline.** ROC: Receiver operating characteristic curve; AUC: Area under the curve; eGFR: Estimated glomerular filtration rate.

dicator for early detection of DKD[33]. In a small case-control study, significant differences were observed in NLR among different groups of T2DM patients based on their albuminuria status[34]. A meta-analysis that included 48 studies demonstrated higher NLR values in patients with DKD than in those without DKD[35]. Last but not least, a longitudinal 3-year follow-up study underscored the potential of NLR as a robust predictor of deteriorating renal function in individuals with diabetes[36].

### *Limits of the study*

Our study adds to the literature by providing compelling evidence of a significant association between NLR and CKD prevalence in patients with T2DM. However, it should be noted that this study had some limitations. First, as a cross-sectional study, a causal relationship between NLR and CKD could not be established. Second, the small sample might have introduced selection bias. Third, due to data constraints, our study population was not assessed for urine albumin and CRP, consequently relying on eGFR to evaluate kidney function and WBC counts to assess inflammatory markers as a control for NLR. Last, as this study was conducted at a single center and only included patients aged 65 years and older, the generalizability of our findings to other settings may be limited. Therefore, future investigations should consider larger sample sizes and adopt prospective study designs to further explore this association.

## CONCLUSION

Our findings revealed a significant association between elevated NLR levels and reduced eGFR, as well as a higher prevalence of CKD in Chinese adults with T2DM. These results suggest that NLR has potential as a valuable biomarker for early detection of kidney damage in diabetes patients. However, it is crucial to emphasize the need for further research to validate these findings and elucidate the potential causal relationship between NLR and CKD.

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## FOOTNOTES

**Co-first authors:** Jin-Li Gao and Jue Shen.

**Co-corresponding authors:** Lei Li and Ji-Ji Xu.

**Author contributions:** Gao JL conceived, designed, and refined the study protocol; Zhao K, Pan XR, Yang LP, and Liu L were involved in the data collection; Xu JJ and Li L analyzed the data; Gao JL and Shen J drafted the manuscript; Xu JJ and Li L revised the manuscript; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Gao JL and Shen J contributed equally to this work as co-first authors; Xu JJ and Li L contributed equally to this work as co-corresponding authors. There are three reasons for designating Xu JJ and Li L as co-corresponding authors. First, this study was a collaborative effort and both Xu JJ and Li L made equally important contributions throughout the course of the study. The designation of co-corresponding authors

accurately reflects the distribution of responsibilities and burdens in terms of time and effort required to complete this study and the paper, and also recognizes and respects their equal contributions. Second, Xu JJ and Li L made great efforts to obtain research funding, which was a key factor in making the research possible. Finally, the fact that the whole research team consisted of authors from different fields with different expertise and skills also contributed to the most comprehensive and in-depth exploration of the research topic, which ultimately enriched the readers' understanding by providing different expert perspectives. In conclusion, we believe that the designation of Xu JJ and Li L as co-corresponding authors is highly appropriate, as it accurately reflects the collaborative spirit, equal contribution and diversity of our team.

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ORIGINAL ARTICLE

Case Control Study

# Impact of stage-specific limb function exercises guided by a self-management education model on arteriovenous fistula maturation status

Yi Li, Li-Jun Huang, Jian-Wen Hou, Dan-Dan Hu

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**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

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## Abstract

### *BACKGROUND*

The exercise of limb function is the most economical and safe method to promote the maturation of arteriovenous fistula (AVF). However, due to the lack of a unified exercise standard in China, many patients have insufficient awareness of the importance of AVF, leading to poor effectiveness of limb function exercise. The self-management education model can effectively promote patients to take proactive health-related actions. This study focuses on the characteristics of patients during the peri-AVF period and conducts a phased limb function exercise under the guidance of the self-management education model to observe changes in factors such as the maturity of AVF.

### *AIM*

To assess the impact of stage-specific limb function exercises, directed by a self-management education model, on the maturation status of AVFs.

### *METHODS*

This study is a randomized controlled trial involving 74 patients with forearm AVFs from the Nephrology Department of a tertiary hospital in Sichuan Province, China. Patients were randomly divided into an observation group and a control

group using a random number table method. The observation group underwent tailored stage-specific limb function exercises, informed by a self-management education model which took into account the unique features of AVF at various stages, in conjunction with routine care. Conversely, the control group was given standard limb function exercises along with routine care. The assessment involves the maturity of AVFs post-intervention, postoperative complications, and the self-management level of the fistula in both groups patients. Analyses were conducted using SPSS version 23.0. Count data were represented by frequency and percentage and subjected to chi-square test comparisons. Measurement data adhering to a normal distribution were presented as mean ± SD. The independent samples *t*-test was utilized for inter-group comparisons, while the paired t-test was used for intra-group comparisons. For measurement data not fitting a normal distribution, the median and interquartile range were presented and analyzed using the Wilcoxon rank sum test.

***RESULTS***

At the 8-wk postoperative mark, the observation group demonstrated significantly higher scores in AVF symptom recognition, symptom prevention, and self-management compared to the control group ($P < 0.05$). However, the variance in symptom management scores between the observation and control groups lacked statistical significance ($P > 0.05$). At 4 wk after the operation, the observation group displayed a superior vessel diameter and depth from the skin of the drainage vessels in comparison to the control group ($P < 0.05$). While the observation group did manifest elevated blood flow rates in the drainage vessels relative to the control group, this distinction was not statistically significant ($P > 0.05$). By the 8-wk postoperative interval, the observation group outperformed the control group with notable enhancements in blood flow rates, vessel diameter, and depth from the skin of drainage vessels ($P < 0.01$). Seven days following the procedure, the observation group manifested significantly diminished limb swelling and an overall reduced complication rate in contrast to the control group ($P < 0.05$). The evaluation of infection, thrombosis, embolism, arterial aneurysm stenosis, and incision bleeding showed no notable differences between the two groups ($P > 0.05$). By the 4-wk postoperative juncture, complications between the observation and control groups were statistically indistinguishable ($P > 0.05$).

***CONCLUSION***

Stage-specific limb function exercises, under the guidance of a self-management education model, amplify the capacity of AVF patients to discern and prevent symptoms. Additionally, they expedite AVF maturation and mitigate postoperative limb edema, underscoring their efficacy as a valuable method for the care and upkeep of AVF in hemodialysis patients.

**Key Words:** Self-management; Education model; Stage-specific; Limb function exercises; Arteriovenous fistula; Maturation status



**Core Tip:** Due to the absence of a unified standard for limb function exercises for arteriovenous fistulas (AVFs) in China, patients lack self-management awareness of AVFs. Therefore, this study focuses on the characteristics of patients during the peri-AVF period and conducts a phased limb function exercise under the guidance of the self-management education model. It was found that autonomous and regular phased limb function exercise during the peri-AVF period can improve the patients' ability to recognize and prevent symptoms of AVF, promote the maturation of AVF, and reduce the occurrence of postoperative swelling.

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## INTRODUCTION

The arteriovenous fistula (AVF) is an essential and safe vascular access method for hemodialysis in patients with renal failure. Its maturation status directly influences the success of dialysis therapy[1]. Existing guidelines suggest that end-stage renal disease patients should undertake limb function exercises both before and after AVF creation to stimulate arm vessels and muscle growth[2,3]. However, a globally accepted standard or protocol for these exercises for AVF patients remains undefined. Notably, studies report that between 20% to 50% of patients display insufficient AVF dilation and inadequate blood flow following surgery[4]. A significant number of these patients also show a limited understanding of AVF's critical role, often neglecting its maintenance and demonstrating a lack of self-management capabilities[5]. These shortcomings can result in delayed AVF maturation, diminished maturity status, or even loss of function, thereby com-

promising treatment effectiveness[5]. Self-management education models, designed to encourage patients to acquire and implement self-management skills, have been effective in prompting patients to adopt health-focused behaviors and actively manage diseases[6,7]. This research seeks to incorporate a self-management education model into the limb function exercises for AVF patients and evaluate the effects of this phased approach on AVF outcomes.

## MATERIALS AND METHODS

### *Materials and methods*

Study population: In the nephrology department of a tertiary hospital in Sichuan Province, China, 74 patients with forearm AVF were enrolled for this study from April 2022 to April 2023. This investigation received approval from the hospital's ethics committee prior to initiation. Participants were randomized into two groups: A control group and an observation group, each comprising 37 patients. During the study, two individuals from each group were lost to follow-up. The detailed information is provided in Figure 1.

The observation group had 22 males and 13 females, averaging an age of 59.46 ± 8.10 years. Detailed medical histories revealed that 34 of these patients had previously undergone dialysis catheter placement before their AVF procedure. Furthermore, 35 individuals reported a history of hypertension, three had diabetes, and 25 disclosed a history of smoking. Conversely, the control group was composed of 26 males and 9 females, with a mean age of 59.77 ± 9.19 years. Among them, 32 had experienced dialysis catheter placement prior to AVF creation. Additionally, 34 members had been diagnosed with hypertension in the past, two had diabetes, and 25 were former or current smokers. A comparative analysis determined that there were no statistically significant disparities in the baseline characteristics between the two groups ($P > 0.05$). The detailed information is provided in Table 1.

### *Inclusion criteria*

**Inclusion criteria:** The study considered patients who qualified for hemodialysis and were undergoing the creation of an AVF for the first time. Eligible participants were aged 18 years or older. Further, they should not have had any prior history of vascular diseases, upper limb trauma, or surgeries. The location of the AVF needed to be at the distal forearm, specifically with a configuration of cephalic vein-radial artery anastomosis. Additionally, these patients provided informed consent and demonstrated a willingness to both participate in the study and cooperate throughout its duration.

**Exclusion criteria:** Patients were excluded if they had known blood disorders or abnormalities related to coagulation. Similarly, those diagnosed with severe cardiovascular or cerebrovascular diseases were not considered suitable for the study.

**Termination criteria:** The study was terminated for any participant who chose to voluntarily withdraw. Moreover, if a patient's condition worsened to a significant extent or if they passed away during the study, their participation was deemed terminated.

### *Study methods*

**Establishment of AVF care team:** The AVF care team comprised an internal medicine nursing expert with over 30 years of professional experience, three specialized nurses in blood purification each boasting more than a decade of experience, and one nursing graduate student. Dedicated patient files were established for AVF creation. A comprehensive perioperative follow-up plan was formulated in alignment with the treatment requirements, encompassing both in-hospital and outpatient follow-ups.

**Control group:** Patients within the control group underwent standard care associated with AVF. This regimen encompassed perioperative care, health education, and limb function exercises. The customary limb function exercise regimen consisted of finger joint movements within the initial 24 h post-surgery. This was followed by finger flexion and extension exercises after 72 h and fist clenching exercises without utilizing any objects. Each clench lasted 5-8 s, with exercises lasting 10 min per session and being conducted 4-5 times daily. Following AVF removal, patients engaged in fist clenching exercises utilizing a pressure ring, maintaining the same clench duration but extending the session to 10-15 min and practicing 5-6 times daily.

**Observation group:** In addition to the standard care, the observation group patients participated in self-management-based phased limb function exercises. These exercises spanned three distinct phases.

**Formation of self-management awareness phase:** Commencing 2 wk prior to surgery, patients were introduced to the concept of limb function exercises using methods such as outcome displays, instructional videos, and mnemonic techniques. These exercises served to foster a proactive mindset towards the preservation of their "life channel". Initial limb function exercises consisted of fist clenching synchronized with elbow and wrist joint movements and coordinated upper arm movement. The intended tension should accommodate two fingers without hampering blood circulation, with no resulting feelings of swelling or numbness in the digits. The recommended exercise duration was set at 1 min per session, with 8-10 such sessions in a set, and three sets daily.

**Physician-led exercise phase:** Spanning from the first to the seventh postoperative day, routine exercises were carried out. On the 8$^{th}$ day post-surgery, the aforementioned preoperative limb function exercises were reintroduced, tailored

**Table 1 Participants characteristics at baseline, *n* (%)**

| Characteristic | Observation group (*n* = 35) | Control group (*n* = 35) | Statistic | *P* value |
|---|---|---|---|---|
| Age (yr) | 59.46 ± 8.10 | 59.77 ± 9.19 | -0.151 | 0.88 |
| BMI (kg/m2) | 23.13 ± 1.88 | 23.00 ± 1.82 | 0.321 | 0.75 |
| Gender | | | 1.062 | 0.30 |
| Male | 22 (62.86) | 26 (74.29) | | |
| Female | 13 (37.14) | 9 (25.71) | | |
| Marital status | | | 0.162 | 0.92 |
| Unmarried | 1 (2.86) | 1 (2.86) | | |
| Married | 30 (85.71) | 31 (88.57) | | |
| Divorce or widowed | 4 (11.43) | 3 (8.57) | | |
| Degree of education | | | 0.342 | 0.84 |
| Elementary school or below | 24 (68.57) | 22 (62.86) | | |
| Secondary school | 9 (25.71) | 10 (28.57) | | |
| College or above | 2 (5.71) | 3 (8.57) | | |
| Per capita monthly income (yuan) | | | 0.332 | 0.96 |
| < 2000 | 8 (22.86) | 10 (28.57) | | |
| ≥ 2000, < 5000 | 20 (57.14) | 18 (51.47) | | |
| ≥ 5000, < 8000 | 5 (14.29) | 5 (14.29) | | |
| ≥ 8000 | 2 (5.71) | 2 (5.71) | | |
| History of smoking | | | 0.002 | 1.00 |
| Yes | 25 (71.43) | 25 (71.43) | | |
| No | 10 (28.57) | 10 (28.57) | | |
| History of central venous catheterization before AVF | | | 0.262 | 0.61 |
| Yes | 34 (97.14) | 32 (91.42) | | |
| No | 1 (2.86) | 3 (8.57) | | |
| History of hypertension | | | / | 1.00[3] |
| Yes | 35 (100.00) | 34 (97.14) | | |
| No | 0 (0.00) | 1 (2.86) | | |
| History of diabetes | | | 0.002 | 1.00 |
| Yes | 3 (8.57) | 2 (5.71) | | |
| No | 32 (91.43) | 33 (94.29) | | |

[1]*t* test.
[2]$\chi^2$ test.
[3]Fisher's test.
AVF: Arteriovenous fistulas; BMI: Body mass index.

based on physician recommendations.

**Patient-led exercise phase:** Starting from the 15th postoperative day and extending to 8 wk, patients, after evaluation by the specialized nursing team, had the autonomy to select the nature, intensity, and frequency of their limb function exercises. Bi-weekly support was offered to fine-tune their exercise regimens, incrementally expanding the variety and frequency of exercises. This included the integration of single fist clenching with pressure ring exercises and coordinated arm movements.

### *Observation indicators and research tools*

**Self-management level of AVF:** The hemodialysis patient autogenous AVF self-management scale[8] was employed to

**Table 2 Status of self-management capacity for arteriovenous fistulae, M (P25, P75)**

| Group | Observation group | Control group | *Z* | *P* value |
|---|---|---|---|---|
| Symptom recognition | 35.00 (34-38) | 33.00 (32-35) | -3.35 | 0.01 |
| Symptom management | 17.00 (16-19) | 17.00 (15-18) | -1.12 | 0.26 |
| Symptom prevention | 14.00 (13-14) | 13.00 (12-14) | -2.12 | 0.03 |
| Total self-management score | 66.00 (63-71) | 63.00 (59-67) | -2.21 | 0.03 |

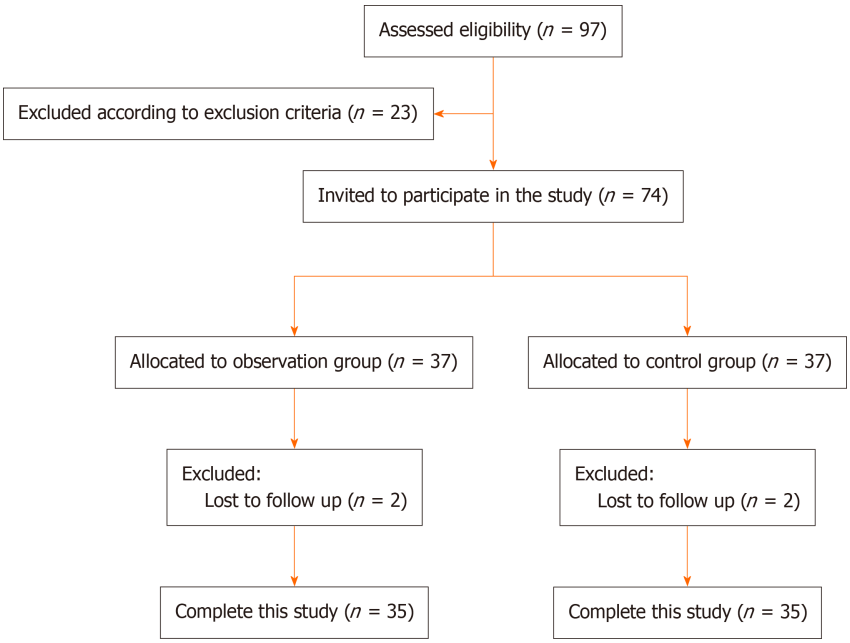


**Figure 1 Impact of stage-specific limb function exercises guided by a self-management education model on arteriovenous fistula maturation status.**

evaluate the AVF self-management level in both patient groups at 8 wk post-surgery. The scale's scoring encompasses three dimensions: Symptom recognition, symptom management, and symptom prevention. Scores can range from 16 to 80, with a higher score indicating an enhanced self-management level of AVF.

**Complications:** Incidence rates of complications, including incision bleeding, limb swelling, infection, thrombosis, embolism, and arteriovenous aneurysm, were compared between the two patient groups at both 7 d and 4 wk post-surgery.

**AVF maturation status:** Postoperative assessments at 4 and 8 wk measured the blood flow rate, vessel diameter, and depth from the skin of AVF drainage vessels in both patient groups[9].

**Data analysis:** Analyses were conducted using SPSS version 23.0. Count data were represented by frequency and percentage and subjected to $\chi^2$ test comparisons. Measurement data adhering to a normal distribution were presented as mean ± SD. The independent samples *t*-test was utilized for inter-group comparisons, while the paired t-test was used for intra-group comparisons. For measurement data not fitting a normal distribution, the median and interquartile range were presented and analyzed using the *Wilcoxon* rank sum test.

## RESULTS

At the 8-wk postoperative mark, the observation group demonstrated significantly higher scores in AVF symptom recognition, symptom prevention, and self-management compared to the control group ($P < 0.05$). However, the variance in symptom management scores between the observation and control groups lacked statistical significance ($P > 0.05$). The detailed breakdown is provided in Table 2.

At 4 wk after the operation, the observation group displayed a superior vessel diameter and depth from the skin of the drainage vessels in comparison to the control group ($P < 0.05$). While the observation group did manifest elevated blood flow rates in the drainage vessels relative to the control group, this distinction was not statistically significant ($P > 0.05$). By the 8-wk postoperative interval, the observation group outperformed the control group with notable enhancements in

**Table 3 Maturity status of arteriovenous fistula (score, mean ± SD)**

| Time | Group | Observation group | Control group | *t* | *P* value |
|---|---|---|---|---|---|
| 4 wk after surgery | Blood flow | 511.51 ± 16.27[a] | 506.06 ± 10.23[c] | 1.68 | 0.10 |
| | Intravascular diameter | 5.13 ± 0.10[a] | 5.00 ± 0.04[c] | 7.10 | 0.00 |
| | Depth from epidermis | 2.62 ± 0.10[a] | 3.05 ± 0.11[c] | -17.45 | 0.00 |
| 8 wk postoperatively | Blood flow | 733.28 ± 10.51 | 707.00 ± 10.25 | 10.59 | 0.00 |
| | Intravascular diameter | 5.88 ± 0.27 | 5.18 ± 0.10 | 14.42 | 0.00 |
| | Depth from epidermis | 2.18 ± 0.10 | 2.62 ± 0.10 | -18.00 | 0.00 |

[a]$P < 0.05$ at the 4-wk postoperative point when juxtaposed with the 8-wk postoperative point within the observation group.
[c]$P < 0.05$ at the 4-wk postoperative stage when compared with the 8-wk postoperative interval in the control group.

**Table 4 Complications**

| Time | Group | Infection | Thrombus | Embolization | Aneurysm | Stenosis | Incision bleeding | Limb swelling | Total | Statistical value | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 d postoperatively | Observation group | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 3 | / | 0.03[1] |
| | Control group | 1 | 0 | 0 | 0 | 0 | 1 | 9 | 11 | | |
| 4 wk postoperatively | Observation group | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | / | 0.36[1] |
| | Control group | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 4 | | |

[1]Fisher's test.

blood flow rates, vessel diameter, and depth from the skin of drainage vessels ($P < 0.01$). These findings are delineated in Table 3.

Seven days following the procedure, the observation group manifested significantly diminished limb swelling and an overall reduced complication rate in contrast to the control group ($P < 0.05$). The evaluation of infection, thrombosis, embolism, arterial aneurysm stenosis, and incision bleeding showed no notable differences between the two groups ($P > 0.05$). By the 4-wk postoperative juncture, complications between the observation and control groups were statistically indistinguishable ($P > 0.05$). A comprehensive overview is available in Table 4.

## DISCUSSION

Prevention and recognition of postoperative symptoms enhanced by phased limb function exercises and self-management education in AVF patients.

AVF, a surgically created vascular access, is susceptible to multiple complications and inherently has a limited lifespan. As such, diligent daily self-management of AVF becomes pivotal for patients[10]. The present study emphasizes the patients' subjective awareness, placing them at the forefront of AVF management. Enhancing patients' comprehension of AVF-related matters and proactively adopting measures for its maturation and daily upkeep enables effective management. This approach facilitates prompt detection of anomalies, safeguarding the operated limb.

Perioperative phased limb function exercise for AVF: Laying groundwork for optimal cannulation.

Limb function exercises were systematized in distinct stages, corresponding to the specific requirements of AVF patients. Pre-AVF creation and during the exercise's early phase, patients often harbored uncertainties about the limb function exercise. This phase was steered by a specialized nursing cadre, centering on nurturing patients' self-management cognizance. As patients gained profound insights into AVF, a transition to autonomous exercise occurred. Subsequent exercise regimens were adapted to individual needs and inclinations, amplifying adherence and self-confidence [11]. Systematic and thorough limb movements, combined with arm exercises, augment local blood circulation and metabolism. This results in increased tension in the drainage vessels and cellular proliferation in the venous vessel wall, bolstering elasticity[12]. Concurrently, fat reduction through exercise underscores AVF's superficial positioning and expedites venous arterialization[13]. Such conditions prime the AVF for its inaugural cannulation while curtailing deep vein puncture risks.

Phased limb function exercise and self-management education: Catalysts for postoperative limb swelling dissipation and complication reduction following avf surgery.

Post-AVF creation, surgical trauma, venous return impediments, and heightened vascular pressure often induce limb swelling[14]. This study's adoption of autonomous and staged exercise amplified metabolic rate and blood flow, enhancing oxygen and nutrient availability around the AVF. This hastened excessive tissue fluid's dissipation, thereby curtailing anastomosis site edema and associated complications such as bleeding and infection[15,16]. By the 4-wk postoperative marker, incidences of AVF infection, thrombosis, and aneurysm appeared minimal in the short-term analysis. Such postoperative complications, encompassing infection, thrombosis, and embolism, are multifactorial, often linked to the patient's inherent disease state and vascular morphology[17]. Multifaceted interventions, encompassing lifestyle, dietary habits, medication, therapeutic approaches, and consistent self-maintenance, are essential to mitigate their prevalence.

## CONCLUSION

In summary, hemodialysis patients are advised to heed the medical team's professional directives pre and post-AVF creation, adopting a holistic approach towards AVF maintenance spanning lifestyle, therapy, care, and self-management. Moreover, adherence to moderate limb function exercise is paramount. It's imperative to maintain appropriate, consistent, and regular AVF exercises, steering clear of overexertion that could compromise anastomosis healing or delay maturation. Regular self-assessment, coupled with hospital follow-ups to evaluate AVF stability and functionality, facilitates the early detection and management of complications, ensuring AVF patency.

## FOOTNOTES

**Author contributions:** Li Y and Huang LJ conducted the research design and project implementation; Hou JW performed the data analysis; Hu DD wrote the manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

# Investigation of risk factors in the development of recurrent urethral stricture after internal urethrotomy

Abdullah Gul, Ozgur Ekici, Salim Zengin, Deniz Barali, Tarik Keskin

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## Abstract

***BACKGROUND***

Urethral stricture is a condition that often develops with trauma and results in narrowing of the urethral lumen. Although endoscopic methods are mostly used in its treatment, it has high recurrence rates. Therefore, open urethroplasty is recommended after unsuccessful endoscopic treatments.

***AIM***

To investigate the risk factors associated with urethral stricture recurrence.

***METHODS***

The data of male patients who underwent internal urethrotomy for urethral stricture between January 2017 and January 2023 were retrospectively analyzed. Demographic data, comorbidities, preoperative haemogram, and biochemical values obtained from peripheral blood and operative data were recorded. Patients were divided into two groups in terms of recurrence development; recurrence and non-recurrence. Initially recorded data were compared between the two groups.

***RESULTS***

A total of 303 patients were included in the study. The mean age of the patients was 66.6 ± 13.6 years. The mean duration of recurrence development was 9.63 ± 9.84 (min-max: 1-39) months in the recurrence group. Recurrence did not occur in non-recurrence group throughout the follow-up period with an average time of 44.15 ± 24.07 (min-max: 12-84) months. In the comparison of both groups, the presence of diabetes mellitus (DM), hypertension (HT), and multiple comorbidities were significantly higher in the recurrence (+) group ($P$ = 0.038, $P$ = 0.012, $P$ = 0.013). Blood group, postoperative use of non-steroidal anti-inflammatory drugs,

preoperative cystostomy, cause of stricture, iatrogenic cause of stricture, location and length of stricture, indwelling urinary cathater size and day of catheter removal did not differ between the two groups. No statistically significant difference was observed between the two groups in terms of age, uroflowmetric maximum flow rate value, hemogram parameters, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood sugar, creatinine, glomerular filtration rate, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, monocyte-lymphocyte ratio and AST/ALT ratios.

*CONCLUSION*

In patients with urethral stricture recurrence, only the frequency of DM and HT was high, while inflammation marker levels and stricture-related parameters were similar between the groups.

**Key Words:** Inflammation; Internal urethrotomy; Recurrence; Urethral stricture; Urethra



**Core Tip:** In our study, we aimed to investigate whether there are inflammation markers in peripheral blood that can predict urethral stricture recurrence after internal urethrotomy and whether other etiological factors have a place in predicting stricture recurrence. According to our results, no inflammation marker was found to predict urethral stricture recurrence. The possibility of recurrence in patients with comorbidities such as diabetes mellitus and hypertension should be taken into consideration and the patient should be informed that more curative methods may be needed.

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## INTRODUCTION

Urethral stricture is defined as the narrowing of the relevant segment of the urethra due to fibrosis of the urethral mucosa and surrounding spongiose tissue due to various causes[1]. The incidence is generally accepted as 229-627 per 100000. The anterior urethra is the most commonly affected part, with the bulbar urethra being the most common. Although the known causes are sexually transmitted infections, external urethral trauma, iatrogenic urethral trauma, and previous prostate surgery, inflammation also plays an important role in the etiology[2].

The underlying cause of the pathophysiology of urethral stricture is still unclear[3,4]. The most commonly proposed hypothesis is inflammation of the mucosa and submucosal connective tissue resulting in scar formation. The spogiofibrotic process is induced by inflammatory mediators. The search for a marker to predict this inflammation is ongoing but has not yet been found[5].

Internal urethrotomy under direct vision is the most common endoscopic surgical method for bulbar and short-segment urethral strictures. Urethral patency rates vary between 8% and 77% after internal urethrotomy[1]. These inadequate patency rates, *i.e.* high recurrence rates, significantly impair patient quality of life. Current guidelines recommend open urethroplasty if an endoscopic treatment has failed or in patients at high risk for recurrence of the stricture[6]. According to studies, patients who have undergone two or more internal urethrotomies have more complex strictures and the need for grafts for urethroplasty is higher than those who have undergone one internal urethrotomy[7].

In this study, we have aimed to investigate whether there are inflammation markers in peripheral blood that can predict urethral stricture recurrence after internal urethrotomy and whether other etiological factors have a place in predicting stricture recurrence.

## MATERIALS AND METHODS

After obtaining ethical approval numbered 2011-KAEK-25/11-17 from the ethics committee of Health Sciences University Bursa Yuksek Ihtisas Training and Research Hospital, we retrospectively accessed the data of patients who underwent internal urethrotomy for urethral stricture between January 2017 and January 2023 from the hospital computer system. Patients' comorbidities [diabetes mellitus (DM), hypertension (HT), coronary artery disease, pulmonary pathologies], possible causes of stricture, stricture segment from the operative notes, estimated stricture length measured endoscopically, catheter diameter used, and catheter withdrawal day were recorded. In patients with postoperative recurrence, the time of recurrence and the number of recurrences were recorded. Having more than one comorbidity was defined as at least having 2 or more diseases, including DM and HT. Postoperative use of intravenous and/or oral non-steroidal anti-inflammatory drugs was recorded. Preoperative haemogram, neutrophil, lymphocyte, platelet, aspartate aminotrans-

ferase (AST), alanine aminotransferase (ALT), fasting blood sugar (FBSG), creatinine, and glomerular filtration rate (GFR) values from peripheral blood were also recorded. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, lymphocyte-monocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and AST/ALT (De ritis ratio) rates were calculated.

No recurrence was defined as patients who did not develop stricture after the first internal urethrotomy throughout the follow-up period. The time to recurrence was defined as the time from the first operation to the first clinical sign of recurrence (symptoms and uroflowmetric evaluation) or the date of the next reoperation.

Patients with a history of malignancy, diseases that may affect inflammation markers and biochemical parameters (liver diseases, renal diseases, hematological diseases, *etc.*), and patients who had undergone open urethral surgery were excluded from the study.

Patients were divided into two groups as with and without recurrence after the first internal urethrotomy. The data were compared between the two groups.

### *Statistical analysis*

Data were presented as mean, standard deviation, median, IQR, number, and percentage. The Kolmogorow-Smirnov test was applied to determine whether the data were suitable for normal distribution. Between the 2 groups, numerical data were compared by the Mann-Whitney *U* test, while non-parametric data were compared by the Chi-square test. Variables predicting recurrence were investigated by regression analysis. $P < 0.05$ was considered statistically significant and the SPSS 21.0 program was used.

## RESULTS

After the exclusion criteria were applied, a total of 303 patients were included in the study. The mean age of the patients was 66.6 ± 13.6 years. The cause of stenosis was iatrogenic in 113 (37.2%) patients, trauma in 17 (5.7%), inflammatory in 4 (1.3%), and idiopathic in 169 (55.8%). During the follow-up period, a total of 51 (16.8%) patients developed recurrence, while 252 (83.2%) patients did not develop recurrence. The mean duration of recurrence development was 9.63 ± 9.84 (min-max: 1-39) months in patients with recurrence. Recurrence did not occur in non-recurrence group throughout the follow-up period with an average time of 44.15 ± 24.07 (min-max: 12-84) months.

The median number of recurrence was 1 (min-max 1-6) in 51 patients with recurrence. There were 36 patients with 1 recurrence, 8 patients with 2 recurrences, 2 patients with 3 recurrences, 2 patients with 4 recurrences, 2 patients with 5 recurrences, and 1 patient with 6 recurrences. In 15 patients with 2 or more recurrences, endoscopic treatment was continued because the patients did not want open surgery. When the strictures recurred during the follow-up period, 8 of these 15 patients accepted the urethroplasty option and urethroplasty was performed, 5 patients wanted to be treated with clean intermittent catheterization, and 2 patients underwent urethral stenting.

In the comparison of both groups, DM, HT, and having more than one comorbid disease was found to be statistically significantly higher in the recurrence group ($P = 0.038$, $P = 0.012$, $P = 0.013$). In multivariate analysis, Exp (B): 0.514 (95%CI: 0.265-0.998, $P = 0.008$) for HT and Exp (B): 0.625 (95%CI: 0.289-1.349, $P = 0.026$) for DM were found as risk factors for urethral stricture recurrence. There was no difference between the two groups in terms of blood group, post-operative non-steroidal anti-inflammatory use, pre-operative cystostomy, cause of stricture, iatrogenic cause of stricture, location of stricture, length of stricture, catheter diameter and catheter withdrawal day (Table 1).

No statistically significant difference was observed between the two groups in terms of age, Q max value on uroflowmetry, haemogram parameters, AST, ALT, FBSG, creatinine, GFR, NLR, PLR, Lymphocyte monocyte ratio (LMR), MLR, and De ritis rates (Table 2).

## DISCUSSION

In the management of urethral stricture, the location, length, and degree of stricture are taken into consideration. Endoscopic methods are often preferred by urologists[8,9]. Easy application, faster recovery, and being more economical can be counted among the reasons for preference. However, urethral stricture tends to recur due to the nature of the disease. In case of recurrence, more curative methods such as open urethroplasty are preferred for the benefit of the patient in appropriate patients. In our study, we investigated the usability of various data to predict urethral stricture recurrence after endoscopic intervention and found that inflammation markers have no place in the prediction of recurrence.

According to our study results, the presence of DM and HT was significantly higher in the group with recurrence of urethral stricture. This relationship may probably be attributed to the fact that these diseases develop on the background of inflammation[10,11]. From a surgical perspective, diseases such as DM and obesity are known to contribute to numerous perioperative complications, including relative vascular insufficiency, chronic low-grade inflammation, impaired collagen synthesis, and micro- and macromolecular deficiency[12]. A similar relationship is observed in patients with lichen sclerosis, which is a serious risk factor in patients with urethral stricture. These patients are more likely to have DM and HT[13,14]. In support of our study results, Breyer *et al*[15] found DM as a predictive factor in the development of recurrence after open urethroplasty according to multivariate analysis.

**Table 1 Comparison of demographic data between the groups, *n* (%)**

| Variables | No recurrent, *n* = 252 | Recurrent, *n* = 51 | *P* value |
|---|---|---|---|
| DM | | | 0.038 |
| Absence | 215 (85.3) | 37 (72.5) | |
| Presence | 37 (14.7) | 14 (27.5) | |
| HT | | | 0.012 |
| Absence | 159 (63) | 22 (43.1) | |
| Presence | 93 (37) | 29 (56.9) | |
| KAD | | | 0.707 |
| Absence | 200 (79.3) | 39 (76.5) | |
| Presence | 52 (20.7) | 12 (23) | |
| Lung pathologies | | | 0.211 |
| Absence | 228 (90.4) | 43 (84.3) | |
| Presence | 24 (9.6) | 8 (15.7) | |
| Comorbidity | | | 0.013 |
| Absence | 121 (48) | 15 (29.5) | |
| One comorbidity | 59 (23.4) | 11 (21.5) | |
| More than one comorbidity | 72 (28.6) | 25 (49) | |
| Primary cause | | | 0.071 |
| Iatrogenic | 87 (34.6) | 26 (60) | |
| Trauma | 13 (5.1) | 4 (7.9) | |
| Post-inflamatuar | 4 (1.6) | 0 (0) | |
| Idiopatic | 148 (58.7) | 21 (41.1) | |
| Cause of iatrojenic | | | 0.488 |
| RP | 12 (13.8) | 5 (19.3) | |
| RT | 12 (13.8) | 4 (15.3) | |
| Others | 53 (60.9) | 12 (46.1) | |
| RP+RT | 10 (11.5) | 5 (19.3) | |
| Stricture localization | | | 0.707 |
| Penile | 25 (10) | 6 (11.8) | |
| Bulbar | 136 (54) | 29 (56.9) | |
| Bulbomembranous | 18 (7.2) | 2 (3.9) | |
| Membranous | 8 (3.1) | 0 (0) | |
| Prostatic urethra | 7 (2.7) | 0 (0) | |
| Bladder neck | 23 (9.1) | 8 (15.6) | |
| Panurethral | 8 (3.2) | 1 (2) | |
| More than one | 27 (10.7) | 5 (9.8) | |
| Postoperative NSAII administration | | | 0.758 |
| Absence | 140 (55.5) | 30 (58.8) | |
| Presence | 112 (44.5) | 21 (41.2) | |
| Preoperative cystostomy | | | 0.764 |
| Absence | 235 (93.2) | 47 (92.1) | |
| Presence | 17 (6.8) | 4 (7.9) | |

| | | | |
|---|---|---|---|
| Blood group | | | 0.405 |
| A+ | 110 (43.7) | 23 (45) | |
| A- | 18 (7.1) | 1 (2) | |
| B+ | 22 (8.8) | 3 (5.9) | |
| B- | 6 (2.3) | 1 (2) | |
| AB+ | 21 (8.4) | 3 (5.9) | |
| AB- | 3 (1.2) | 3 (5.9) | |
| 0+ | 66 (26.2) | 16 (31.3) | |
| 0- | 6 (2.3) | 1 (2) | |
| Scricture lenght | | | 0.196 |
| < 1 cm | 76 (30.1) | 9 (17.7) | |
| 1-2 cm | 154 (61.1) | 39 (76.4) | |
| 2-4 cm | 10 (4) | 2 (3.9) | |
| > 4 cm | 12 (4.8) | 1 (2) | |
| Postoperative inserted indwelling urinary catheter size | | | 0.809 |
| 16 Fr | 25 (10) | 4 (7.8) | |
| 18 Fr | 105(41.6) | 24 (47.1) | |
| 20 Fr | 122 (48.4) | 23 (45.1) | |
| Catheter removal day | | | 0.765 |
| < 3 d | 10 (4) | 2 (4) | |
| 3-5 d | 61 (24.2) | 10 (19.6) | |
| > 5 d | 181 (71.8) | 39 (76.4) | |

DM: Diabetes mellitus; HT: Hypertension; CAD: Coronary artery disease; RP: Radical prostatectomy; RT: Radiotherapy; NSAII: Non-steroidal anti-inflammatory drug.

In infectious conditions developing in the body, neutrophilia or neutropenia with monocytosis and lymphopenia are expected[16]. Changes in neutrophil, lymphocyte, and monocyte ratios reflect the systemic inflammatory response. These ratios are associated with cancer-related prognosis in many cancer types[17-21]. In our study, we investigated the relationship between these rates and urethral stricture, but we did not find a relationship between inflammation markers and urethral stricture recurrence. There are studies in the literature with opposite results. Venugopalan *et al*[22] investigated the role of inflammation markers in the development of stricture after transurethral prostate resection surgery. According to the results, preoperative NLR and PLR were found to be statistically significantly higher in the group with stenosis compared to the group without stenosis. In a study of 512 patients, Urkmez *et al*[23] found that neutrophil count and neutrophil-to-lymphocyte ratio were higher in the group with recurrence than in the group without recurrence. Topaktaş *et al*[24] investigated whether inflammation markers can be used to predict recurrence after urethroplasty. Similar to our results, neutrophil, lymphocyte, and NLR values were similar between recurrence and non-recurrence groups in 117 patients. We think that the different results in some literature and our study may be due to patient-related factors (stricture length, degree of stricture, *etc*.) and different methodological designs.

The increased likelihood of recurrence in patients with multiple comorbidities is another result of our study. The literature supports this conclusion. Chapman *et al*[12] investigated the factors affecting the development of recurrence after urethroplasty. According to multivariate results, infectious etiology, stenosis length, increased patient comorbidity, and obesity were found to be independent predictors of recurrence. The mentioned study included patients after urethroplasty. However, it is thought that the stenosis that develops after urethroplasty develops on a similar basis as after endoscopic methods, that is, based on inflammation[25]. Therefore, although the study population is different, it supports our results in this respect.

Urethral trauma is an important factor in the development of urethral stricture[26]. A few days after transurethral surgery, isolated erythematous areas on the urethral mucosa can be visualized. In addition, leakage of urine into the subepithelial space causes increased inflammation and subsequent scar formation[27]. This process can be progressive, with urethral stenosis resulting from edema and subsequent stenosis formation leading to increased intramural voiding pressure, leading to further leakage across the mucosal barrier. Myofibroblasts are probably responsible for the formation of the stricture and giant cells may play a role in the continuation of collagen synthesis[28]. In the literature, studies are showing that the use of anti-inflammatory or steroid drugs may prevent the development and recurrence of urethral stricture. Sciarra *et al*[29] investigated the effect of cyclooxygenase-2 inhibitor use on the development of urethral stricture

**Table 2 Comparison of data between groups**

| Variables (median-IQR) | No recurrent, *n* = 252 | Recurrent, *n* = 51 | *P* value |
|---|---|---|---|
| Age (yr) | 70 (62-75) | 68 (61-71) | 0.109 |
| Qmax (mL/sn) | 6 (4-7) | 6 (3.5-8) | 0.800 |
| Hgb (g/dL) | 13.8 (12.4-14.7) | 13.8 (12.8-14.7) | 0.987 |
| Hct | 41.7 (37.7-44.4) | 41 (38.8-43.8) | 0.769 |
| Leukocyte ($10^3$/μL) | 7.4 (6.2-9.3) | 7.1 (6.3-8.6) | 0.501 |
| Neutrophil ($10^3$/μL) | 4.7 (3.7-6) | 4.5 (3.6-5.6) | 0.444 |
| Lymphocyte ($10^3$/μL) | 1.9 (1.5-2.4) | 1.7 (1.4-2.3) | 0.558 |
| Platelet ($10^3$/μL) | 251 (207-303) | 241 (214-297) | 0.789 |
| Monocyte ($10^3$/μL) | 0.5 (0.4-0.6) | 0.5 (0.3-0.7) | 0.509 |
| AST (U/L) | 17 (14-20) | 17 (13-21) | 0.421 |
| ALT (U/L) | 15 (11-21) | 16 (12-22) | 0.467 |
| Glucose (mg/dL) | 101 (89-118) | 98 (84-116) | 0.369 |
| Creatinine (mg/dL) | 0.9 (0.8-1.1) | 1 (0.9-1.1) | 0.209 |
| GFR (mL/mn) | 82 (64-93) | 80 (71-89) | 0.613 |
| NLR | 2.4 (1.8-3.4) | 2.3 (1.7-3.6) | 0.743 |
| PLR | 126 (99-173) | 131(96-183) | 0.711 |
| LMR | 3.8 (2.9-4.7) | 3.4 (2.4-4.8) | 0.393 |
| MLR | 0.2 (0.2-0.3) | 0.2 (0.2-0.4) | 0.393 |
| De ritis ratio | 1 (0.8-1.4) | 1 (0.8-1.2) | 0.259 |

Qmax: Maximum flow rate; Hgb: Hemoglobin; Hct: Hematocrit; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GFR: Glomerular filtration rate; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; LMR: Lymphocyte monocyte ratio; MLR: Monocyte lymphocyte ratio.

in patients undergoing transurethral prostate resection. According to the results, the Q max value of the cyclooxygenase-2 inhibitor group in the first postoperative month was significantly higher. Kurt *et al*[30] investigated the effect of triamnisolone and mitomycin-C on urethral stricture recurrence in 24 rabbits. As a result, decreased recurrence rates were found in both treatment groups compared to the control group. In our study, contrary to the mentioned studies, we concluded that the use of post-operative non-steroidal anti-inflammatory drugs did not affect the development of recurrence. In the European Urology Guidelines, it is emphasized that the experience of the use of anti-inflammatory drugs is limited[1]. More detailed studies are needed to address the precise pathophysiology of scar development, remodeling, and epithelialization stages to define new therapeutic targets.

One of the limitations of our study is that our study was performed in a retrospective design with a relatively small number of patients. The fact that internal urethrotomy operations were performed not by a single surgeon but by different surgeons may have caused minimal differences in the information given about the stenosis and the surgical method applied. In addition, the absence of retrograde urethrography, which would have allowed a more objective assessment of stricture, in most patients may be considered another limitation.

## CONCLUSION

According to our results, no inflammation marker was found to predict urethral stricture recurrence. The possibility of recurrence in patients with comorbidities such as DM and HT should be taken into consideration and the patient should be informed that more curative methods may be needed.

## FOOTNOTES

**Author contributions:** Gul A, Ekici O, Zengin S, Barali D, Keskin T contributed equally to this work; Ekici O and Gul A designed the research study; Zengin S and Barali D performed the research; Keskin T and Gul A contributed new reagents and analytic tools; Ekici O, Gul A, Zengin S and Barali D analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

# Clinicopathological characteristics and typing of multilocular cystic renal neoplasm of low malignant potential

Wen-Long Gao, Gang Li, Dong-Sheng Zhu, Yuan-Jie Niu

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## Abstract

### *BACKGROUND*

Up until now, no research has been reported on the association between the clinical growth rate of multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) and computed tomography (CT) imaging characteristics. Our study sought to examine the correlation between them, with the objective of distinguishing unique features of MCRNLMP from renal cysts and exploring effective management strategies.

### *AIM*

To investigate optimal management strategies of MCRNLMP.

### *METHODS*

We retrospectively collected and analyzed data from 1520 patients, comprising 1444 with renal cysts and 76 with MCRNLMP, who underwent renal cyst decompression, radical nephrectomy, or nephron-sparing surgery for renal cystic disease between January 2013 and December 2021 at our institution. Detection of MCRNLMP utilized the Bosniak classification for imaging and the 2016 World Health Organization criteria for clinical pathology.

### *RESULTS*

Our meticulous exploration has revealed compelling findings on the occurrence of MCRNLMP. Precisely, it comprises 1.48% of all cases involving simple renal cysts, 5.26% of those with complex renal cysts, and a noteworthy 12.11% of renal tumors coexisting with renal cysts, indicating a statistically significant difference ($P$ = 0.001). Moreover, MCRNLMP constituted a significant 22.37% of the patient population whose cysts demonstrated a rapid growth rate of ≥ 2.0 cm/year, whereas it only represented 0.66% among those with a growth rate below 2.0 cm/year. Of

the 76 MCRNLMP cases studied, none of the nine patients who underwent subsequent nephron-sparing surgery or radical nephrectomy following renal cyst decompression experienced recurrence or metastasis. In the remaining 67 patients, who were actively monitored over a 3-year postoperative period, only one showed suspicious recurrence on CT scans.

*CONCLUSION*

MCRNLMP can be tentatively identified and categorized into three types based on CT scanning and growth rate indicators. In treating MCRNLMP, partial nephrectomy is preferred, while radical nephrectomy should be minimized. After surgery, active monitoring is advisable to prevent unnecessary nephrectomy.

**Key Words:** Renal cysts; Multilocular cystic renal neoplasm of low malignant potential; Computed tomography; Diagnosis; Treatment



**Core Tip:** A rather uncommon type of renal cell carcinoma, multilocular cystic renal neoplasm of low malignant potential (MCRNLMP), exhibits distinct clinicopathological traits and often has a good prognosis. Although it bears resemblances to clear cell renal cell carcinoma in terms of clinical manifestations, pathology, diagnosis, and therapeutic approaches, there are notable differences as well. Despite ongoing discussions regarding the best practices for diagnosing and treating MCRNLMP, it is essential for clinicians to take into account its imaging features alongside other pertinent clinical considerations. This holistic approach should encompass selecting tailored treatment options and determining optimal follow-up schedules.

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## INTRODUCTION

Multilocular cystic renal neoplasm of low malignant potential (MCRNLMP), previously termed multilocular cystic renal cell carcinoma (MCRCC), is a benign kidney lesion[1]. It typically accounts for merely 2% to 4% of cases of clear cell renal cell carcinoma (CCRCC) and often has a very favorable prognosis[2,3]. Despite MCRNLMP's distinctively benign prognosis, which is devoid of recurrence or progression, the International Society of Urological Pathology recognized its genetic and histopathological similarities to CCRCC and adopted it as a classification in 2012[2-4]. Based on the 2016 World Health Organization (WHO) classification, MCRNLMP is categorized as a tumor consisting exclusively of multiple cysts. These cysts are morphologically akin to low-grade CCRCC, as their septa contain small clusters of clear cells that lack expansive growth[5]. Although histopathological and genetic characteristics have received significant attention, preoperative computed tomography (CT) imaging features and clinical growth rates have been largely overlooked[6,7]. Despite its rarity, constituting < 2% of all cystic RCC cases, and its nonaggressive nature, distinguishing MCRNLMP from renal cysts and MCRCC remains clinically challenging. Accurate diagnosis of MCRNLMP is crucial as it can significantly impact patient management and outcomes. Delayed diagnosis or misdiagnosis may lead to inappropriate treatment or surgical intervention, potentially increasing the risk of morbidity and mortality. Comprehensive patient management and prognostic outcomes for MCRNLMP are not yet reported[8].

Therefore, our research has been dedicated to distinguishing MCRNLMP from renal cysts, taking into account clinical symptoms, medical imaging, and histopathological considerations. This study concentrated on preoperative CT imaging and growth rates to identify distinct characteristics between MCRNLMP and renal cysts in tumor imaging. Additionally, we investigate optimal management strategies for MCRNLMP by analyzing postoperative prognostic outcomes. With the aim of exploring this matter further, we embarked on a retrospective study, delving into the clinicopathological data of 76 patients diagnosed with MCRNLMP at the Second Hospital of Tianjin Medical University, spanning the period from January 2013 to December 2021.

## MATERIALS AND METHODS

### *Study population*

Study participants were 1520 patients treated for renal cystic disease at our institution between January 2013 and December 2021. This group comprised 1444 patients with renal cysts and 76 with MCRNLMP, who underwent renal cyst decompression, radical nephrectomy, or nephron-sparing surgery by laparoscopy. The pathology of each tumor was classified according to the 2004 WHO Histologic Classification of Kidney Tumors[9].

### Study design

We reviewed the medical records and clinical data of the 1520 patients, assessing factors such as age, gender, tumor side, multiplicity, size, operation method, pathological type, and Fuhrman grade. According to European and United States guidelines, recurrent tumors and adverse reactions were monitored during postoperative follow-up[10]. The Bosniak classification system evaluates the malignant potential of renal cysts.

### Inclusion and exclusion criteria

The Bosniak classification categorizes renal cysts into several classes, from I to IV, ranging from lowest to highest malignancy risk; Bosniak IIF to IV can be defined as complex renal cysts with the following characteristics: (1) Irregular or thick walls, with the cyst potentially having thickened or uneven walls; (2) enhancement features, indicating potential malignancy when contrast imaging shows enhancement inside or around the cyst; (3) septations or partitions, with the cyst possibly containing septa or multiple compartments; (4) calcifications on the cyst walls or septa; and (5) solid components, suggesting the presence of a tumor if solid tissue is found[6]. Exclusion criteria: patients with a history of RCC, other variant morphologies, or concomitant RCC. Preoperative imaging diagnosed 746 patients with simple renal cysts, 419 with complex renal cysts, and 355 with renal cysts combined with solid tumor components. We analyzed various factors affecting cyst growth rates during the preoperative period. From the initial diagnosis of renal cystic disease, we recommend that patients undergo imaging examinations, including ultrasound or CT scans, every 6 months until there is an indication for surgery. The number of examinations and the duration of follow-up vary for each patient. We set 2 cm/year as a critical threshold: 304 patients exhibited a cyst growth rate ≥ 2 cm/year, and 1216 < 2 cm/year. Postoperative histopathology confirmed 1444 patients with renal cysts and 76 with MCRNLMP. Of the 76 MCRNLMP patients, 67 underwent active monitoring following renal cyst decompression, while nine required additional kidney-sparing surgery or radical nephrectomy. The study design is shown in Figure 1.

### Surgical pathology

The pathology of surgically removed cystic renal masses was examined by our institutional pathologists. Three representative slides from each patient's sections were independently reviewed by three pathologists with at least 3 years of genitourinary pathology experience at our institute, to identify pathological findings. The 2016 WHO criteria were utilized to define MCRNLMP[11]. Gross and microscopic features of the cystic renal masses were classified according to the Fuhrman nuclear grade (1 and 2: low grade, 3 and 4: High grade) and tumor, node, and metastasis staging[12].

### Statistical analysis

This study utilized continuous and categorical statistical variables. For comparing categorical data, we applied the Fisher's probability and $\chi^2$ independence test. For continuous parameters, independent samples *t*-test was performed. The $\chi^2$ test was used when no expected cell counts less than 1 and at most 20% of expected cell counts less than 5. Fisher's exact probability test was used when expected cell count was < 1[13,14]. All statistical analyses were conducted using SPSS 22 (IBM Corporation, Armonk, NY, United States).

## RESULTS

### Baseline clinical data

Most renal cysts are simple cysts and are asymptomatic, and many of them are found incidentally through routine physical examinations and rarely require therapy. However, when the diameter of the cyst is > 5 cm and renal parenchyma (collection system) compression is present, regardless of the presence of flank or abdominal pain, surgical intervention is required[15]. A laparoscopic approach for renal cyst unroofing was the first described in 1992 and has since become the gold standard of treatment[16]. Our study included 1520 patients confirmed by pathological examination, comprising 1444 with renal cysts and 76 with MCRNLMP. Table 1 offers a detailed breakdown of the patients' general characteristics, clinical manifestations, imaging insights, surgical approaches, and pathological outcomes. The pathological examination confirmed the presence of MCRNLMP in 1.48% (11/746) of patients with simple renal cysts, 5.26% (22/419) with complex renal cysts, and 12.11% (43/355) with renal cysts combined with renal tumors. There were significant differences in the positive rates among these groups.

### CT imaging

Within the vast pool of 1520 patients afflicted with renal cystic disease, a significant portion consisting of 746 individuals were distinctly categorized as harboring simple renal cysts, whereas a subset of 419 patients presented with the more intricate complex renal cysts (Figures 2A and B). Additionally, 355 cases involved renal cysts combined with solid tumors (Figure 2C). Histopathology confirmed all cases, with 1444 diagnosed as renal cysts and 76 as MCRNLMP postoperatively (Figure 3). The tumor tissue, consisting of cysts of various sizes with inner walls that were solely lined by a single layer of clear cells, accounted for 5.0% of the patients.

### Postoperative pathological results and preoperative CT imaging

Postoperative pathology identified MCRNLMP in 11 of 746 cases (1.48%) of simple renal cyst, 22 of 419 (5.26%) cases of complex renal cyst, and 43 of 355 cases (12.11%) of renal cysts combined with renal tumors. The $\chi^2$ test yielded $P < 0.001$, indicating significant differences among the three groups. Consequently, heightened vigilance is required for renal cysts

**Table 1 General information of patients**

| Medical data[1] | Renal cyst | Cyst combined with renal tumor | *P* value |
|---|---|---|---|
| Age (continuous) | | | 0.35 |
| Mean (IQR) | 62 (50–72) | 59 (51–68) | |
| Sex (No. of cases) | | | 0.72 |
| Male, *n* (%) | 675 (57.94) | 180 (50.70) | |
| Side (No. of cases) | | | 0.16 |
| Left, *n* (%) | 561 (48.15) | 165 (46.48) | |
| Cyst diameter (cm) | | | 0.27 |
| Mean (IQR) | 12 (9–14) | 7 (6–9) | |
| Operation method (No. of cases), *n* (%) | | | < 0.001 |
| Renal cyst topping decompression | 1165 (100.0) | 346 (97.46) | |
| Radical nephrectomy | 0 | 3 (0.85) | |
| Nephron sparing surgery | 0 | 6 (1.69) | |
| Pathological type (No. of cases), *n* (%) | | | < 0.001 |
| Renal cyst | 1132 (97.18) | 312 (87.89) | |
| MCRNLMP | 33 (2.82) | 43 (12.11) | |
| Fuhrman grade (No. of cases), *n* (%) | | | 0.06 |
| I | 13 (39.39) | 26 (60.47) | |
| II | 20 (60.61) | 17 (39.53) | |

[1]Continuous variables were compared by independent samples *t*-test.
IQR: Interquartile range; MCRNLMP: Multilocular cystic renal neoplasm of low malignant potential.

combined with renal tumors in imaging. In cases of suspicion, nephron-sparing surgery should be considered over renal cyst decompression, along with frozen pathological examination (Table 2). Based on preoperative CT imaging observations, MCRNLMP can be comprehensively classified into three discrete groups: Group I, encompassing simple renal cysts; Group II, comprising complex renal cysts; and Group III, featuring renal cysts in conjunction with renal malignancies (Tables 2 and 3). When a tumor is highly suspected of malignancy, we recommend nephron surgery in combination with frozen pathology.

### *Cyst growth rates during the preoperative monitoring period and postoperative pathological results*

During the preoperative period, we analyzed various factors influencing cyst growth rates, setting 2 cm/year as a critical threshold. Of the 1520 patients diagnosed with renal cystic disease, 304 exhibited a growth rate of at least 2.0 cm/year, among which 68 (22.37%) were postoperatively confirmed as MCRNLMP. Conversely, 1216 had a growth rate < 2.0 cm/year, with eight (0.66%) diagnosed as MCRNLMP. The $\chi^2$ test showed $P < 0.001$, signifying a significant difference between the two groups. Furthermore, among the 304 patients who exhibited a growth rate of at least 2.0 cm/year, postoperative pathology revealed MCRNLMP in 30 out of 197 patients with simple renal cysts (15.23%), and in 38 out of 107 patients with complex renal cysts (35.51%). This significant difference suggests a distinction between the two groups. Thus, monitoring the growth rate of renal cysts is crucial, regardless of suspected malignant transformation. This is important for patients with complex cysts on imaging, where early surgical intervention may be necessary (Tables 3 and 4). Therefore, vigilance should be paid to the possibility of malignancy in the case of growth rate ≥ 2.0 cm/year and complex renal cysts.

### *No significant difference was observed in positive recurrence rate with various treatment methods*

Postoperative follow-up of 76 patients with MCRNLMP ranged from 12 to 72 months, with an average of 42 mo. Nine patients who initially underwent renal cyst decompression subsequently required a second operation, and pathological analysis confirmed the presence of MCRNLMP in all cases. None of these patients showed recurrence or metastasis during postoperative follow-up. Sixty-seven patients underwent active monitoring without additional surgery after renal cyst decompression, with MCRNLMP confirmed pathologically. During the third year of postoperative follow-up, only one case exhibited suspicious recurrence on CT, but the patient refused to undergo reoperation. According to an exact probability test, the calculated *P* value was 1, suggesting that there was no statistically significant difference between the two groups (Table 5). Among the nine MCRNLMP patients who underwent secondary surgical procedures, six underwent partial nephrectomies, while three underwent radical nephrectomies. Postoperative specimens revealed residual

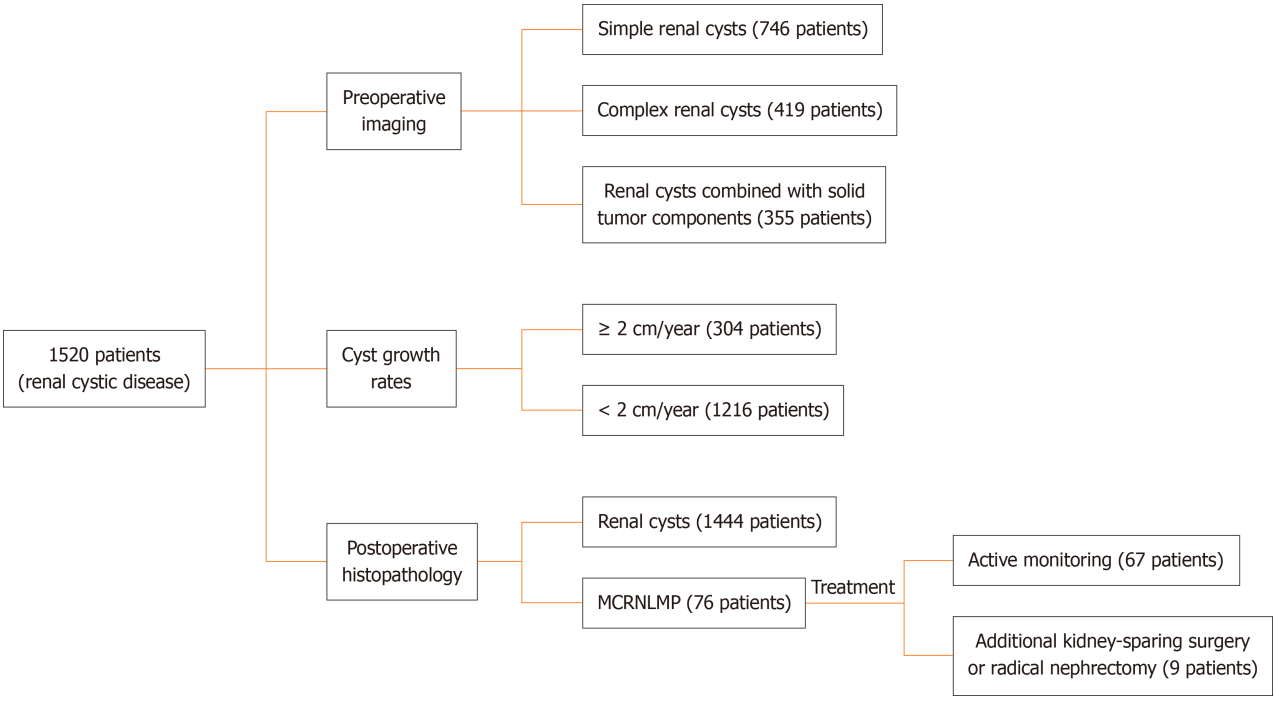


**Figure 1 A flow chart summarizing all the information in the study design.** MCRNLMP: Multilocular cystic renal neoplasm of low malignant potential.

tumors in only two of these patients. During the follow-up period, none of these patients experienced recurrence or metastasis (Table 6). It can be seen that MCRNLMP had low malignancy and good prognosis.

## DISCUSSION

The 2016 WHO standards classify RCC into 10 pathological types[9]. MCRCC is a rare form, comprising only 1%–2% of renal malignancies. MCRNLMP is even less common, representing < 1%[17]. Generally, these tumors are low-grade with few malignant cells, resulting in good prognosis. Notably, there is no clear correlation between tumor size and prognosis [7]. The clinical diagnosis of MCRNLMP poses significant challenges due to its rarity and the absence of distinct clinical or histopathological characteristics. Like renal cysts, most MCRNLMP patients show no noticeable symptoms. However, patients with large tumors may experience abdominal or flank discomfort. Imaging studies typically reveal renal cysts as single, fluid-filled cystic structures with clear boundaries, whereas MCRNLMP is characterized by a multilocular cystic structure, comprising multiple separated cystic chambers. However, MCRNLMP is often incidentally identified and can be difficult to distinguish from other complex cystic renal tumors in imaging, leading to a high risk of misdiagnosis or missed diagnosis[18].

Our findings demonstrated that MCRNLMP comprised less than 5% of kidney diseases, corroborating prior reports that estimated its occurrence to be between 2% and 4% among various kidney ailments, encompassing both cystic and renal tumor conditions[6]. Significant challenges are posed by the cystic growth pattern of MCRNLMP in preoperative diagnosis. Currently, Bosniak grading remains the primary diagnostic standard for renal cystic lesions. Recently, a Chinese scholar introduced the Renal CYST INDEX (RCI), a new weighted quantitative scoring system based on CT performance, currently undergoing prospective validation[19]. The RCI system evaluates four parameters—cyst wall, separation, solid nodules, and contents—potentially offering greater accuracy than Bosniak grading, particularly in suspected malignant cysts[20]. However, this new scoring system has not yet supplanted Bosniak grading and requires further exploration and validation. Previous studies suggest that MCRNLMP can occur across various Bosniak grades[21-24]. In our study, pathological examination confirmed MCRNLMP in 1.48% (11/746) of patients with simple renal cysts, 5.26% (22/419) with complex renal cysts, and 12.11% (43/355) with renal cysts combined with renal tumors, showing significant differences in positive rates among these groups. Consequently, we suggest the following hypothesis for clinical application: MCRNLMP should be categorized into three distinct types, utilizing preoperative CT imaging as the basis for classification. Type I typically manifests as simple renal cysts, Type II as complex renal cysts, and Type III as a combination of renal cysts and renal tumors. Given the varying postoperative pathological positive rates, each type necessitates distinct treatment approaches. Given the significant risk of MCRNLMP, utmost vigilance is imperative when managing renal cysts, especially those of the complex nature, that are comorbid with renal tumors.

The diameter of a kidney mass is critical for assessing its severity. In kidney cancer T staging, tumors < 7 cm are classified as T1, while those > 7 cm but < 10 cm are classified as T2[25,26]. Presently, various surgical methods exist for RCC, with the tumor diameter being a vital criterion in selecting the surgical approach[27]. Current guidelines, including those of the European Association of Urology and the American Urological Association, dictate treatment strategies for renal

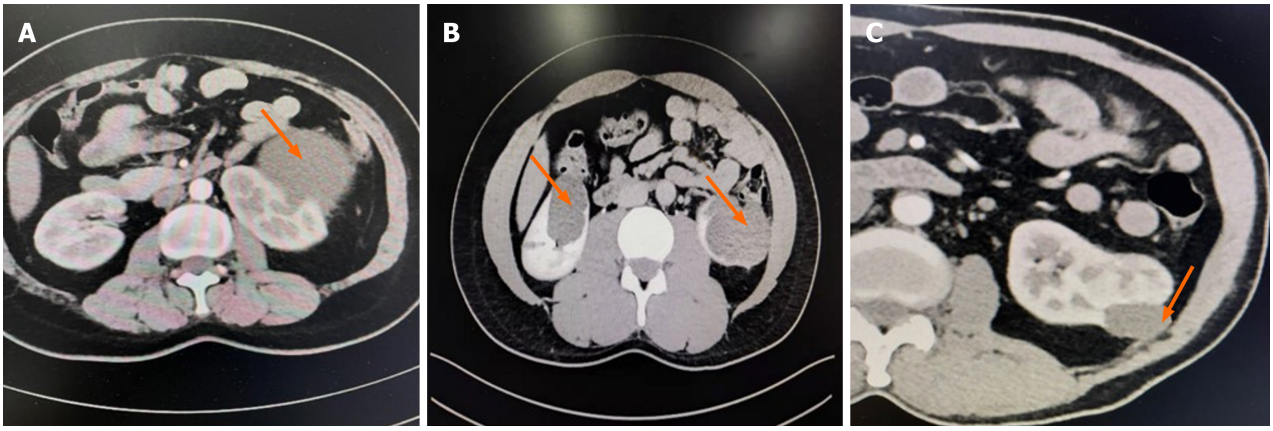


**Figure 2 Three types of computed tomography imaging of 1520 patients afflicted with renal cystic disease.** A: Computed tomography (CT) imaging manifestations of a simple renal cyst in the left kidney, Bosniak grade I, with clear and smooth borders, uniform simple fluid density (0-20 HU), and no separation or calcification; B: CT imaging manifestations of a complex renal cyst in both kidneys, Bosniak grade II, with compartmental enhancement and irregularities; C: CT imaging manifestations of a renal cyst in the left kidney with a tumor in the right kidney, and the cyst is of Bosniak grade II, with clear boundaries, uniform high-density signals, and without enhancement.

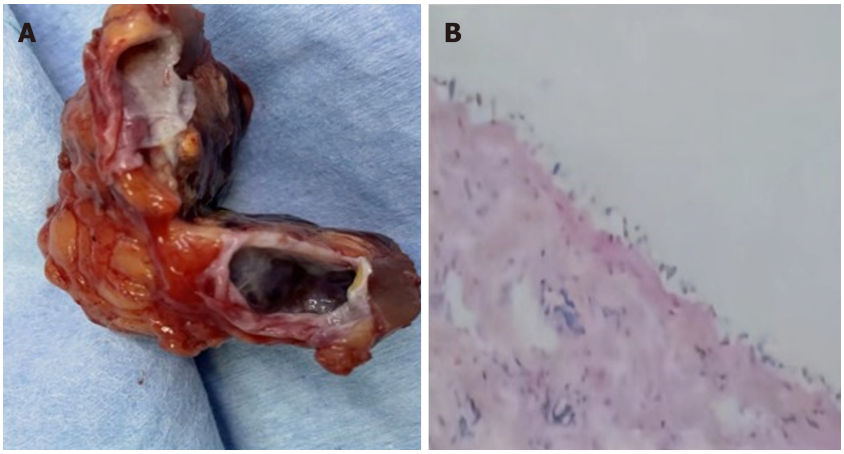


**Figure 3 The operative specimens and histopathology of multilocular cystic renal neoplasm of low malignant potential.** A: The fresh operative specimens of multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) postoperatively; B: Microscopic histopathologic observations of MCRNLMP (Hematoxylin-Eosin staining and counted under microscopy with 400-fold magnification), the tumor tissue is composed of cysts in different sizes, and the inner wall is covered with a single layer of clear cells.

cysts based on their size. Cysts < 4 cm warrant observation, close follow-up, and regular imaging rechecks; cysts between 4 and 8 cm may be treated with puncture and aspiration sclerotherapy under color Doppler ultrasound; and cysts > 8 cm typically require laparoscopic operation[28]. Our investigation delved deep into numerous factors that could potentially impact the rates of cyst growth during the crucial preoperative surveillance stage. Setting 2 cm/year as the critical growth rate, we found that ≥ 2.0 cm/year is a high-risk factor. In our study of 304 patients with a cyst growth rate ≥ 2.0 cm/year, 30 of 197 patients with simple renal cysts (15.23%) and 38 of 107 with complex renal cysts (35.51%) were confirmed as MCRNLMP postoperatively, indicating a significant difference between the two groups. Therefore, monitoring the growth rate of renal cysts is important. For cysts with an annual growth rate > 2 cm, and particularly complex cysts visible on imaging, early surgical intervention is crucial due to the increased likelihood of MCRNLMP.

Several studies with follow-up > 5 years have been conducted. Highlighting this fact, one study found zero recurrences or metastases among the 45 MCRNLMP patients who underwent either radical resection or partial nephrectomy[29]. Another study confirmed 16 cases of polycystic kidney cancer as MCRNLMP. Following decompression of the renal cysts, 15 patients underwent supplementary nephrectomies, and residual cancer cells were detected in eight of them. The remaining case, closely monitored for 96 mo, showed no recurrence. The above studies indicate that patients undergoing supplementary radical nephrectomy after renal cyst topping decompression experienced no recurrence or metastasis, and the likelihood of residual cancer tissue exceeded 50%, suggesting the necessity of supplementary radical nephrectomy. However, our results differed. Among 76 MCRNLMP patients, only one suspected recurrence occurred. Nine patients underwent secondary operations after renal cyst topping decompression: Six had secondary partial nephrectomies, three had radical nephrectomies, and only three cases showed residual tumors in postoperative samples. No recurrence or metastasis was noted during follow-up, suggesting a potential for overtreatment in MCRNLMP. As a result, patients with preoperative imaging revealing simple renal cysts and normal cyst walls can be closely monitored postoperatively, there-

**Table 2 Comparison of postoperative pathological positive rates between simple renal cysts and cysts combined with renal tumors diagnosed preoperatively, *n* (%)**

| Index[1] | Group | Benign | MCRNLMP | *P* value |
|---|---|---|---|---|
| Preoperative diagnosis | Simple renal cyst (type I) | 735 (98.52) | 11 (1.48) | < 0.001 |
| | Complex renal cyst (type II) | 397 (94.74) | 22 (5.26) | |
| | Cysts combined with renal tumors (type III) | 312 (87.89) | 43 (12.11) | |

[1]The above results with $\chi^2$ test showed significant difference in the pathological positive rate of various preoperative diagnosis ($P < 0.001$).
MCRNLMP: Multilocular cystic renal neoplasm of low malignant potential.

**Table 3 Univariate cox regression analysis of positive rates in patients with multilocular cystic renal neoplasm of low malignant potential**

| Univariate analysis | Odds ratio | 95%CI | *P* value |
|---|---|---|---|
| Preoperative diagnosis | | | < 0.001 |
| Simple renal cyst (type I) | 1 (reference) | | |
| Complex renal cyst (type II) | 3.67 | 2.57–5.13 | |
| Cysts combined with renal tumors (type III) | 9.19 | 6.46–12.88 | |
| Growth rates | | | < 0.001 |
| < 2.0 cm/yr | 1 (reference) | | |
| ≥ 2.0 cm/yr | 43.51 | 30.90-61.66 | |

**Table 4 Comparison of postoperative pathological positive rates in various growth rates during preoperative monitoring, *n* (%)**

| Index[1] | Group | Benign | MCRNLMP | *P* value |
|---|---|---|---|---|
| Growth rates | ≥ 2.0 cm/yr | 236 (77.63) | 68 (22.37) | < 0.001 |
| | < 2.0 cm/yr | 1208 (99.34) | 8 (0.66) | |

[1]The above results of $\chi^2$ test showed the significant difference in the pathological positive rate of various growth rates ($P < 0.001$).
MCRNLMP: Multilocular cystic renal neoplasm of low malignant potential.

by avoiding unnecessary secondary surgical procedures. Nonetheless, nephron-sparing surgery remains crucial for those patients who exhibit complex renal cysts, which are preoperatively indicated and subsequently confirmed as MCRNLMP through pathological examination. Clinically, caution is advised when managing renal cystic diseases. Special attention should be given to preoperative examinations and imaging of renal cysts combined with tumors, with vigilance for MCRNLMP. Simple renal cyst topping surgery should be avoided. For rapidly growing renal cystic lesions, particularly those with complex cysts identified on imaging, prompt surgical intervention is necessary. For patients with preoperative diagnoses of simple renal cysts, surgery should not be delayed based on the small size of the cyst. Additionally, we propose that potential predictors such as CT scanning and growth rate can aid in differentiating MCRNLMP from renal cysts. If postoperative pathology reveals MCRNLMP in patients initially diagnosed with simple renal cysts and treated with decompression, proactive monitoring is recommended to avoid unnecessary secondary surgeries.

Our study has several limitations, including the retrospective observational design, the relatively small number of patients, single-center data, and the lack of long-term follow-up. Despite these shortcomings, we have gained some experience and hope to provide some information for surgeons.

## CONCLUSION

MCRNLMP, a rare type of RCC, with unique clinicopathological features and favorable prognosis. It shares similarities with, but also differs from, CCRCC in clinical presentation, pathology, diagnosis, and treatment. While controversies remain in the diagnosis and treatment of MCRNLMP, clinicians should consider its imaging characteristics and other clinical factors comprehensively. This approach includes adopting suitable and personalized treatment methods and determining the appropriate follow-up intervals.

**Table 5 Comparison of differences in the positive recurrence rate of various treatments, *n* (%)**

| Index[1] | Group | Renal cyst topping decompression + active monitoring | Renal cyst topping decompression + nephron-sparing surgery or radical nephrectomy | *P* value |
|---|---|---|---|---|
| Re-examination | No recurrence or metastasis | 66 (98.50) | 9 (100.0) | 1 |
| | Recurrence or metastasis | 1 (1.50) | 0 (0.00) | |

[1]The above statistical results of the Fisher's probability test showed that the positive rate of recurrence after various surgical methods was not significant ($P = 1$).

**Table 6 Comparison of differences in the positive recurrence rate of various surgical methods, *n* (%)**

| Index[1] | Group | Renal cyst topping decompression + nephron-sparing surgery | Renal cyst topping decompression + radical nephrectomy | *P* value |
|---|---|---|---|---|
| Re-examination | No recurrence or metastasis | 6 (100.0) | 3 (100.0) | 1 |
| | Recurrence or metastasis | 0 | 0 | |

[1]The above statistical results of the Fisher's probability test showed that the positive rate of recurrence after various surgical methods was not significant ($P = 1$).

## FOOTNOTES

**Co-first authors:** Wen-Long Gao and Gang Li.

**Co-corresponding authors:** Dong-Sheng Zhu and Yuan-Jie Niu.

**Author contributions:** Niu YJ, Zhu DS, Gao WL, and Li G conceptualized and designed the research; Gao WL, and Li G screened patients and acquired clinical data; Niu YJ, Zhu DS contributed new reagents/analytic tools; Zhu DS, Gao WL, and Li G performed Data analysis; Gao WL and Li G wrote the paper. All the authors have read and approved the final manuscript. Gao WL proposed, designed and conducted the research, performed data analysis and prepared the first draft of the manuscript. Li G was responsible for patient screening, enrollment and collection of clinical data. Both authors have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-first authors of the paper. Both Niu YJ and Zhu DS have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Niu YJ applied for and obtained the funds for this research project. Niu YJ conceptualized, designed, and supervised the whole process of the project. Zhu DS searched the literature, revised and submitted the early version of the manuscript with the focus on the clinicopathological characteristics and typing of multilocular cystic renal neoplasm of low malignant potential. Zhu DS was instrumental and responsible for data re-analysis and re-interpretation, figure plotting, comprehensive literature search, preparation and submission of the current version of the manuscript with a new focus on the correlation between CT imaging, growth rate and effective management strategies of MCRNLMP. This collaboration between Niu YJ and Zhu DS is crucial for the publication of this manuscript and other manuscripts still in preparation. Zhu DS was designated as the corresponding author responsible for contact.

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ORIGINAL ARTICLE

Retrospective Study

# Non-improvement of atrophic gastritis in cases of gastric cancer after successful *Helicobacter pylori* eradication therapy

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## Abstract

### *BACKGROUND*

*Helicobacter pylori* (*H. pylori*) infection is closely related to the development of gastric cancer (GC). However, GC can develop even after *H. pylori* eradication. Therefore, it would be extremely useful if GC could be predicted after eradication. The Kyoto classification score for gastritis (GA) is closely related to cancer risk. However, how the score for GC changes after eradication before onset is not well understood.

### *AIM*

To investigate the characteristics of the progression of Kyoto classification scores for GC after *H. pylori* eradication.

### *METHODS*

Eradication of *H. pylori* was confirmed in all patients using either the urea breath test or the stool antigen test. The Kyoto classification score of GC patients was evaluated by endoscopy at the time of event onset and three years earlier. In addition, the modified atrophy score was evaluated and compared between the GC group and the control GA group.

### *RESULTS*

In total, 30 cases of early GC and 30 cases of chronic GA were evaluated. The pathology of the cancer cases was differentiated adenocarcinoma, except for one case of undifferentiated adenocarcinoma. The total score of the Kyoto classification was significantly higher in the GC group both at the time of cancer onset and three years earlier (4.97 *vs* 3.73, $P = 0.0034$; 4.2 *vs* 3.1, $P = 0.0035$, respectively). The modified atrophy score was significantly higher in the GC group both at the

time of cancer onset and three years earlier and was significantly improved only in the GA group (5.3 *vs* 5.3, $P$ = 0.5; 3.73 *vs* 3.1, $P$ = 0.0475, respectively).

***CONCLUSION***

The course of the modified atrophy score is useful for predicting the onset of GC after eradication. Patients with severe atrophy after *H. pylori* eradication require careful monitoring.

**Key Words:** *Helicobacter pylori*; Kyoto classification; Gastritis; Eradication therapy; Gastric cancer



**Core Tip:** *Helicobacter pylori* (*H. pylori)* infection is closely related to the development of gastric cancer (GC). Therefore, *H. pylori* eradication therapy is very important. However, GC can develop even after *H. pylori* eradication. Thus, it would be very useful if the onset of GC could be predicted. The Kyoto classification of gastritis is useful for endoscopic diagnosis. In this study, we showed that a modified atrophy score may be useful for predicting GC after eradication. In cases of GC after eradication, the modified atrophy score did not decrease during endoscopic follow-up. Gastric mucosal atrophic findings should be noted during post-eradication surveillance.

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## INTRODUCTION

In 1983, *Helicobacter pylori (H. pylori*) was successfully isolated and cultured, and this bacterium was found to be the cause of histological gastritis (GA)[1]. Accumulation of genetic abnormalities due to persistent inflammation leads to gastric carcinogenesis[2]. Many studies, basic, clinical, and epidemiological, have shown the relationship between *H. pylori* and gastric cancer (GC)[3-5]. Though eradication of *H. pylori* prevents GC development[6]. The incidence of GC does not completely disappear after eradication[7]. Therefore, it is very important to identify risk factors for carcinogenesis during post-eradication surveillance. The most reliable method may be to screen for genetic mutations and methylation levels in gastric mucosa[6,8]. Methylation levels of certain microRNAs after eradication are associated with an increased risk of developing metachronous GC[9]. However, this method cannot yet be easily used in general practice. Therefore, regular endoscopy after eradication is important.

The Kyoto classification of GA aims to predict the onset of GC by scoring and evaluating the mucosal condition of GA [10]. It can be easily scored using an endoscope, and there have been several reports of the usefulness of the score at the onset of GC [11]. We have also reported that scores obtained several years before the onset of GC are useful for predicting the subsequent onset of GC[12]. However, its usefulness for predicting GC after eradication is unknown. In this study, whether the time course of Kyoto classification scores for GC after eradication shows any specific characteristic was investigated.

## MATERIALS AND METHODS

### *Patients and settings*

Patients were selected from among cases who underwent endoscopic submucosal dissection (ESD) for GC after eradication at our hospital from 2015 to 2023. Patients who developed cancer more than five years after eradication and who had undergone endoscopy three years before the onset of cancer were considered (Figure 1). As controls, cases of GA diagnosed by upper gastrointestinal endoscopy in our hospital seen at the same time as the cases of GC were selected. The exclusion criteria were as follows: *H. pylori*-negative status, history of gastrointestinal surgery, or presence of systemic disease. Ethics approval was obtained from the review board of Dokkyo Medical University, Saitama Medical Center (No. 23036).

### *H. pylori infection status*

The urea breath test (UBT tablets 100 mg; Otsuka Pharmaceutical, Tokyo, Japan) or a stool antigen test (Meridian HpSA ELISA2, Fujirebio, Tokyo, Japan) was also used to confirm eradication of *H. pylori*. If a patient showed negative results for all tests and had a history of eradication, the patient was diagnosed as an *H. pylori*-eradication patient.

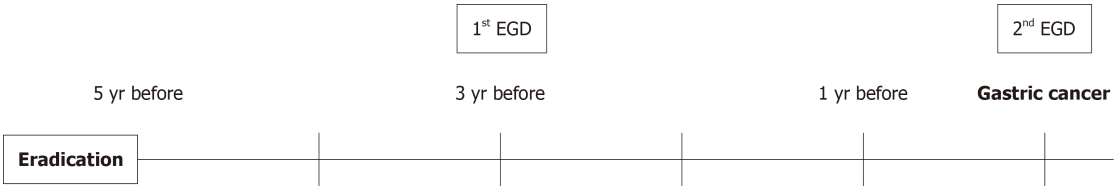


**Figure 1 Schematic diagram of the retrospective study design.** 1st EGD: First esophagogastroduodenoscopy three years prior to diagnosis of gastric cancer (GC); 2nd EGD: Second esophagogastroduodenoscopy, GC diagnosed at that time.

### *Endoscopic examination*

Endoscopic examinations were performed using Olympus electroscopes (GIF-260H, GIF-290H, GIF-290Z; Olympus, Tokyo, Japan). The Kyoto classification score of GA was evaluated: Atrophy (Kimura-Takemoto classification: C0-CI = A0, CII-CIII = A1, and OI-OIII = A2), intestinal metaplasia (none, IM0; intra-antral, IM1; up to the body, IM2), hypertrophy of gastric folds (negative, H0; positive, H1), nodularity (negative, N0; positive, N1), and diffuse redness (none, DR0; mild, DR1; severe, DR2) (Table 1). The total score was calculated by adding the scores for each parameter. In addition, the atrophy score was calculated and considered in more detail as the modified atrophy score, as C0-C3 (0 to 3) and O1-O3 (4 to 6) (Table 2). Two expert endoscopists assessed and compared the Kyoto classification scores at the time of event onset and three years earlier. Two expert endoscopists reviewed the photographs. In each case, more than 40 endoscopic photographs were taken and reviewed.

### *Outcome measurement*

The outcome was the risk score obtained using the Kyoto classification of changes in gastric mucosa at the time of GC onset and three years earlier.

### *Statistical analysis*

Fisher's exact tests were used for sex comparisons. The Wilcoxon rank-sum test was performed to compare age and risk scores obtained using the Kyoto classification of GA between the GC and GA groups. The modified atrophy score was compared by the Wilcoxon rank-sum test. Changes over time in each of the two groups were examined using the Wilcoxon signed-rank test. A two-sided value of $P < 0.05$ was considered significant. All statistical analyses were performed using the software (SAS Institute, Cary, NC, United States).

## RESULTS

### *Patients' characteristics*

Thirty cases of early GC and thirty cases of chronic GA were evaluated. Although no difference in mean age was observed between the two groups, there were significantly more male patients in the GC group. The pathology of the cancer cases was differentiated adenocarcinoma, except for one case of undifferentiated adenocarcinoma, and the depth of invasion was 96% mucosal carcinoma (Table 3).

### *Overlooked cancers*

In the case of GC, the examination findings taken three years before the onset of cancer were evaluated to see if any cancer had been missed, focusing on the area where ESD was performed. No oversights could be confirmed.

### *Kyoto classification score of all cases at the time of onset of GC and three years earlier*

The total score was significantly higher in the GC group both at the time of cancer onset and three years earlier (4.97 *vs* 3.73, $P = 0.0034$; 4.2 *vs* 3.1, $P = 0.0035$, respectively). In terms of changes over time, total scores decreased significantly in both groups (4.97 *vs* 4.2, $P = 0.0003$; 3.73 *vs* 3.1, $P = 0.0007$, respectively) (Figure 2). The atrophy score was higher in the GC group at all time points, and no significant changes over time were observed in either group. The intestinal metaplasia score was higher in the GC group at all time points. There were no changes over time in both groups. There was no difference in hypertrophy of gastric folds and nodularity between the two groups at any time point, and no changes over time were observed in either group. The diffuse redness score was higher in the GC group at all time points and improved significantly over time in both groups (Table 4). The decrease in the total score was thought to be mainly due to the decrease in diffuse redness. Image-enhanced endoscopy was performed in some cases, but not all cases.

### *Modified atrophy score in all cases at the time of onset of GC and three years earlier*

The modified atrophy score was significantly higher in the GC group both at the time of cancer onset and three years earlier (5.3 *vs* 4.93, $P = 0.0319$; 4.93 *vs* 4.63, $P = 0.0038$, respectively), and it was significantly improved only in the GA group (5.3 *vs* 5.3, $P = 0.5$; 3.73 *vs* 3.1, $P = 0.0475$, respectively) (Figure 3).

**Table 1 Grading system for the Kyoto classification score**

| Parameter | Score | |
|---|---|---|
| Atrophy | 0 | C0–CI according to Kimura-Takemoto classification |
| | 1 | CII–CIII |
| | 2 | OI–OIII |
| Intestinal metaplasia | 0 | None |
| | 1 | Within the antrum |
| | 2 | Up to corpus |
| Hypertrophy of gastrid folds | 0 | None |
| | 1 | Positive |
| Nodularity | 0 | None |
| | 1 | Positive |
| Diffuse redness | 0 | None |
| | 1 | Mild (with RAC) |
| | 2 | Severe |

The score was evaluated by five parameters, with the total score as the sum of these five parameter scores. RAC: Regular arrangement of collecting venules.

**Table 2 Modified atrophy score**

| Modified atrophy score | Kimura-Takemoto classification |
|---|---|
| 0 | C0 |
| 1 | CI |
| 2 | CII |
| 3 | CIII |
| 4 | OI |
| 5 | OII |
| 6 | OIII |

**Table 3 Patients' characteristics**

| Characteristics | Gastric cancer | Gastritis | *P* value |
|---|---|---|---|
| Number | 30 | 30 | |
| Age (yr ± SD) | 75.3 | 73.9 | 0.695 |
| Sex (M:F) | 21:9 | 17:13 | 0.422 |
| Differentiation (tub1-2: Sig-por) | 29:1 | | |
| Depth (m: Sm) | 30:0 | | |

SD: Standard deviation; tub1-2: Well to moderate differentiated adenocarcinoma; sig: Signet ring cell carcinoma; por: Poorly differentiated adenocarcinoma; m: Mucosa; Sm: Submucosa.

## DISCUSSION

Although the number of deaths from GC is decreasing, its incidence remains high[13]. *H. pylori* infection is the most important cause of GC, and eradication therapy reduces the risk of GC[14,15]. However, the risk of cancer is not eliminated, and GC may develop after eradication[16]. The factors responsible for cancer development after eradication have not been completely elucidated. In this study, it was found that gastric atrophy did not improve in GC cases after era-

**Table 4 Each parameter of the Kyoto classification at the time of onset of gastric cancer and three years before onset of gastric cancer**

| Parameters | 1st EGD | 2nd EGD | *P* value | 1st EGD | 2nd EGD | *P* value | 1st EGD | 2nd EGD | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | **A** | | | **IM** | | | **H** | | |
| GC | 2 | 2 | 1 | 1.27 ± 0.74 | 1.27 ± 0.74 | 1 | 0.43 ± 0.09 | 0.50 ± 0.504 | 0.543 |
| GA | 1.9±0.305 | 1.9±0.305 | 1 | 0.8 ± 0.76 | 0.87 ± 0.78 | 0.326 | 0.37 ± 0.09 | 0.367 ± 0.490 | 0.184 |
| *P* value | 0.0415 | 0.0415 | | 0.0192 | 0.046 | | 0.605 | 0.281 | |
| | **N** | | | **DR** | | | | | |
| GC | 0.03 ± 0.183 | 0.03 ± 0.183 | 1 | 1.27 ± 0.83 | 0.5 ± 0.82 | 0.0004 | | | |
| GA | 0.03 ± 0.183 | 0 | 0.326 | 0.95 ± 0.17 | 0.07 ± 0.37 | 0.0008 | | | |
| *P* value | 1 | 0.326 | | 0.017 | 0.012 | | | | |

A: Atrophy; IM: Intestinal metaplasia; H: Hypertrophy of gastric folds; N: Nodularity; DR: Diffuse redness; GC: Gastric cancer; GA: Gastritis; 1st EGD: First esophagogastroduodenoscopy three years prior to diagnosis of gastric cancer; 2nd EGD: Second esophagogastroduodenoscopy, gastric cancer diagnosed at that time.

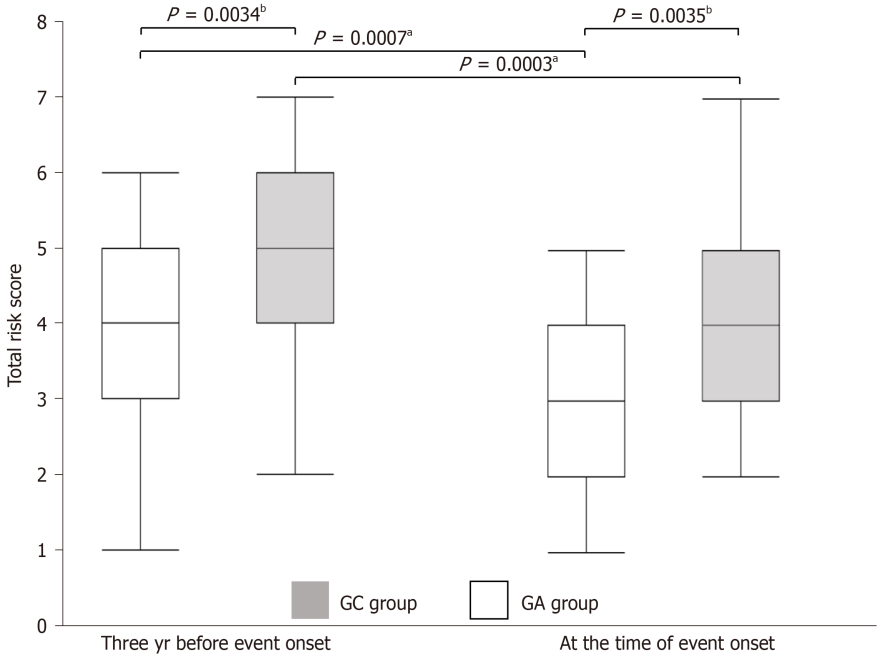


**Figure 2 Kyoto classification score at the time of onset of gastric cancer and three years before onset of gastric cancer.** Data are medians with interquartile ranges. [a]Wilcoxon signed-rank test; [b]Wilcoxon rank-sum test. GC: Gastric cancer; GA: Gastritis.

dication.

There have been many reports of the relationship between endoscopically diagnosed GA and GC. Therefore, endoscopic diagnosis of GA is very important. Various classifications of GA have been proposed to date. Schindler created the basis for the endoscopic classification of GA[17]. Schindler pointed out the importance of atrophic GA as an origin of GC and stated the importance of follow-up. Later, in Japan, the Kimura-Takemoto classification of atrophic GA was devised [18]. The pathophysiological concept of gastric disease has changed significantly since Warren and Marshall successfully isolated and cultured *H. pylori* in 1983[1]. The classification of GA also changed to take *H. pylori* infection into account, and in 1996, the revised updated Sydney system was created and adopted widely.

The Kyoto classification of GA is based on the previous diagnosis and classification of GA, and it distinguishes among those uninfected, currently infected, and previously infected (including after eradication) with *H. pylori*[19]. The Kyoto classification of GA aims to reflect GC risk. Five elements are included in the endoscopic finding score for GC risk: Atrophy, intestinal metaplasia, diffuse redness, hypertrophy of gastric folds, and nodularity[10].

Sugimoto *et al*[20] reported a comparison of risk scores obtained using the Kyoto classification of GA at the time of GC detection[20]. Scores of GC were significantly higher than GA scores in both non-eradicated and eradicated cases. They identified atrophic GA and intestinal metaplasia as related factors. Shichijo *et al*[21] also reported that atrophy was more involved in the risk score for GC[21]. However, those reports evaluated the risk score obtained using the Kyoto classification of GA at the time of diagnosis of GC. It would be clinically very useful if the Kyoto classification score could be

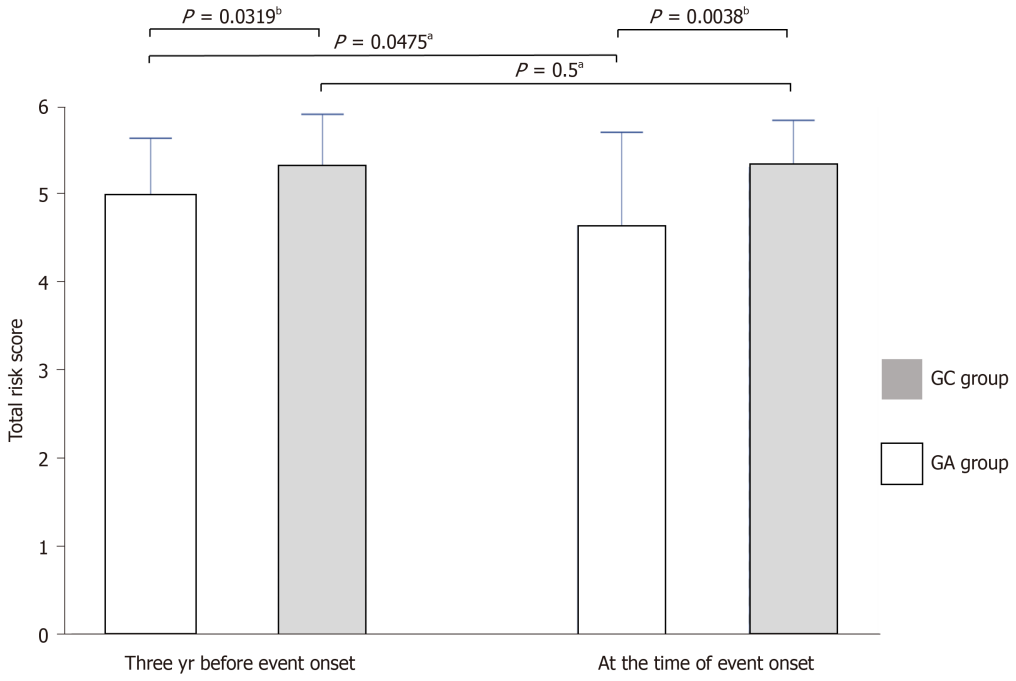


**Figure 3 Modified atrophy score at the time of onset of gastric cancer and three years before onset of gastric cancer.** [a]Wilcoxon signed-rank test; [b]Wilcoxon rank-sum test. GC: Gastric cancer; GA: Gastritis.

used to show changes in the gastric mucosa after eradication until the onset of gastric cancer. Because it is difficult to conduct a prospective study at a single institution, the present study was a retrospective review.

In the present study, the atrophy score, intestinal metaplasia, diffuse redness, and total score were significantly higher both at initial endoscopy and at the onset of GC after eradication (Table 4). There were no differences in fold enlargement and nodularity between GC cases and GA cases at the time of initial endoscopy or at the time of GC onset. The modified atrophy score was significantly higher both at initial endoscopy and at the onset of GC after eradication. The modified atrophy score did not improve during the course of GC cases after eradication. It is a very important finding that atrophy does not improve in GC cases compared to GA even after eradication. The atrophy score of the Kyoto classification is only 0, 1, or 2, making it difficult to distinguish between the two groups and difficult to interpret the results. In the present study, atrophy was divided into seven categories from 0 to 6.

We previously reported that post-eradication atrophy scores are useful for predicting subsequent cancer[12]. In addition, there are many reports that atrophy scores are high at the time of onset of GC[22]. Atrophic GA is associated with hypermethylation[23]. Aberrant CpG island methylation, particularly in the promoter regions of tumor suppressor genes, is associated with tumorigenesis[24]. Eradication of *H. pylori* has been reported to improve atrophic GA in some cases[3]. Furthermore, improved methylation is reported after eradication[25]. On the other hand, the methylation level of miR-124a-3 was associated with an increased risk of developing metachronous GC[9]. However, it will likely take some time before it can be translated into general clinical practice. In the present cases of GC, these improvements may have been very slow or beyond the so-called point of no return[14,26]. The degree of improvement in the atrophy score is useful for predicting GC after eradication.

All GC in the present study were differentiated adenocarcinomas except for one case, and all were intramucosal carcinomas. Patients with severe atrophy and slow improvement may develop GC after eradication. Even if GC develops after eradication, it can be treated with endoscopy if detected early. Patients at high risk require regular, careful follow-up. The present study included only one case of undifferentiated cancer, so it will be important to evaluate more such cases.

### *Limitations*

This was a single-center, retrospective study with a limited number of cases. In this study, image-enhanced endoscopy was used only for the diagnosis of some cases of intestinal metaplasia. Since endoscopic data at the time of eradication were not available for all cases, endoscopic data from three years before the onset of GC after eradication were used.

## CONCLUSION

In conclusion, the results of this retrospective study suggested that the course of the modified atrophy score is useful for predicting the onset of GC after eradication. In particular, patients with severe atrophy even after *H. pylori* eradication should be carefully monitored to detect GC early.

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## FOOTNOTES

**Author contributions:** Suzuki Y, Katayama Y, and Fujimoto Y conceptualized and designed the study, collected data, carried out the initial analysis, and drafted the initial manuscript; Kobori I and Tamano M coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Institutional review board statement:** This study was approved by the ethics committee of the Dokkyo Medical University Saitama Medical Center (Approval No. 23036).

**Informed consent statement:** Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient gave informed consent to treatment. For full disclosure, the details of this retrospective, observational study were published on the home page of the medical center.

**Conflict-of-interest statement:** The authors have no financial relationships to disclose.

**Data sharing statement:** No additional data are available.



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ORIGINAL ARTICLE

Retrospective Study

# Lymphatic plastic bronchitis and primary chylothorax: A study based on computed tomography lymphangiography

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## Abstract

***BACKGROUND***

This study presents an evaluation of the computed tomography lymphangiography (CTL) features of lymphatic plastic bronchitis (PB) and primary chylothorax to improve the diagnostic accuracy for these two diseases.

***AIM***

To improve the diagnosis of lymphatic PB or primary chylothorax, a retrospective analysis of the clinical features and CTL characteristics of 71 patients diagnosed with lymphatic PB or primary chylothorax was performed.

***METHODS***

The clinical and CTL data of 71 patients (20 with lymphatic PB, 41 with primary chylothorax, and 10 with lymphatic PB with primary chylothorax) were collected retrospectively. CTL was performed in all patients. The clinical manifestations, CTL findings, and conventional chest CT findings of the three groups of patients were compared. The chi-square test or Fisher's exact test was used to compare the differences among the three groups. A difference was considered to be statistically significant when $P < 0.05$.

***RESULTS***

(1) The percentages of abnormal contrast medium deposits on CTL in the three groups were as follows: Thoracic duct outlet in 14 (70.0%), 33 (80.5%) and 8 (80.0%) patients; peritracheal region in 18 (90.0%), 15 (36.6%) and 8 (80.0%) patients; pleura in 6 (30.0%), 33 (80.5%) and 9 (90.0%) patients; pericardium in 6 (30.0%), 6 (14.6%) and 4 (40.0%) patients; and hilum in 16 (80.0%), 11 (26.8%) and 7 (70.0%) patients; and (2) the abnormalities on conventional chest CT in the three groups were as follows: Ground-glass opacity in 19 (95.0%), 18 (43.9%) and 8 (80.0%) patients; atelectasis in 4 (20.0%), 26 (63.4%) and 7 (70.0%) patients; interlobular septal thickening in 12 (60.0%), 11 (26.8%) and 3 (30.0%) patients; bronchovascular bundle thickening in 14 (70.0%), 6 (14.6%) and 4 (40.0%) patients; localized mediastinal changes in 14 (70.0%), 14 (34.1%), and 7 (70.0%) patients; diffuse mediastinal changes in 6 (30.0%), 5 (12.2%), and 3 (30.0%) patients; cystic lesions in the axilla in 2 (10.0%), 6 (14.6%), and 2 (20.0%) patients; and cystic lesions in the chest wall in 0 (0%), 2 (4.9%), and 2 (4.9%) patients.

***CONCLUSION***

CTL is well suited to clarify the characteristics of lymphatic PB and primary chylothorax. This method is an excellent tool for diagnosing these two diseases.

**Key Words:** Lymphatic; Plastic bronchitis; Primary chylothorax; Direct lymphangiography; Computed tomography lymphangiography



**Core Tip:** Lymphatic plastic bronchitis and primary chylothorax are rare lymphatic drainage disorders. The pathological and physiological mechanisms, clinical manifestations, and imaging findings of the two are similar, making differential diagnosis difficult. Computed tomography lymphangiography (CTL) is an appropriate method to detect abnormal lymphatic vessels and pulmonary abnormalities. CTL is an effective diagnostic method for distinguishing between the two diseases.

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## INTRODUCTION

Lymphatic plastic bronchitis (PB) is a rare lung disease. Abnormal lymph flow caused by various causes leads to the abnormal accumulation of lymph in the bronchus and the formation of bronchial casts. This disease is often accompanied by local or widespread bronchial obstruction or varying degrees of respiratory dysfunction, leading to severe and life-threatening respiratory distress[1,2]. Chylothorax refers to the accumulation of chylous fluid in the pleural cavity. It is mainly formed when lymph leaks from the thoracic duct or other lymphatic vessels into the pleural cavity due to various causes. According to the aetiology, chylothorax can be divided into primary and secondary chylothorax[3]. The former is related to congenital lymphatic abnormalities, such as generalized lymphatic anomalies, lymphatic malformations in Gorham-Stout disease, and channel-type lymphatic malformations[4-7]. Both lymphatic PB and primary chylothorax are lymphatic reflux disorders caused by primary lymphatic vessel dysplasia. The morbidity is low, and most cases have been reported in small samples[8-10].

Direct lymphangiography (DLG) can be used to intuitively and dynamically observe abnormal changes such as tortuous lymphatic vessels, lymph leakage, or reflux. DLG is the gold standard for visualizing lymphatic vessels, cisterna chyli, and the thoracic duct and detecting lymphatic fistulas; it can help diagnose lymphatic diseases and anatomical abnormalities[11-13]. Computed tomography lymphangiography (CTL) was performed on the chest and abdomen after DLG. CTL can compensate for the limitations of DLG in affecting image overlap and is valuable for revealing changes in the lung, abnormal deposits and reflux of lipiodol, pleural effusion, and extrathoracic lymphatic malformations and their degree[14-16]. Although scholars have applied CTL to the study of lymphatic PB and primary chylothorax[17], we had the largest sample size.

The purpose of our study was to retrospectively analyse the clinical characteristics and CTL features of 71 patients diagnosed with lymphatic PB or primary chylothorax.

## MATERIALS AND METHODS

### *Patients*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Beijing Shijitan Hospital Affiliated to Capital Medical University Hospital, and informed consent

was waived because the study was a retrospective review. Between January 2009 and December 2021, 295 consecutive patients with suspected lymphatic PB and chylothorax admitted to Shijitan Hospital were retrospectively analysed.

The inclusion and exclusion criteria are shown in Figure 1. Patients without CTL data ($n$ = 3) were excluded. The diagnostic criteria for lymphatic PB are the presence of bronchial casts and the abnormal development of lymphatic vessels. Chylothorax patients met at least one of the following criteria: (1) Had a positive chylous test in the effusion; (2) had a triglyceride level > 1.25 mmol/L in the effusion; (3) had a DLG showing contrast medium in the pleural cavity; and (4) had nuclear imaging showing contrast medium entry into the pleural space[18,19]. Patients who met the following criteria were selected for the study: Patients who were clinically diagnosed with lymphatic PB and primary chylothorax. The exclusion criteria were as follows: (1) Had chylothorax or PB caused by secondary factors (tumour, infection, trauma, surgery); (2) had chylous ascites; and (3) did not undergo DLG or CTL. The clinical and CTL data of 71 patients (20 with lymphatic PB, 41 with primary chylothorax, and 10 with lymphatic PB with primary chylothorax) were collected retrospectively.

The main demographic and clinical variables of the patients in the three groups are shown in Table 1.

In our study, 61 of 71 patients underwent thoracic duct outlet surgery. Twenty patients in group A, 33 patients in group B, and 8 patients in group C underwent this operation.

### DLG and CT

Before the lower extremity DLG, consent was obtained from the patients or their guardians. DLG was performed using a GE Innova 2000-IQ DSA machine (AXIOM, Siemens, Erlangen, Germany). The patient was placed in the supine position. The surgeon punctured the skin between the first and second toes of the healthy or less oedematous side of the foot. Methylene blue dye (2.5% Patent Blue V dye; 1 mL, Guerbet Laboratories, Aulnay-Sous-Bois, France) and 1 mL of 2% lidocaine (1:1) were injected into the skin. Subsequently, the superficial lymphatic vessels were examined under a microscope and injected *via* fine needle puncture with 8-20 mL of superfluid contrast agent (Lipiodol; Guerbet Laboratories, Villepinte, France). The reflex of the contrast agent (lipiodol) along the lymphatic vessels can be observed dynamically. Depending on the patient's age and the development of lymphatic vessels, the injection time was approximately 2 h. In normal people, lipiodol cannot enter tissues or lesions through the lymphatic vessel wall and can only be removed through the thoracic duct. The DLG lasted approximately 5-6 h.

All patients underwent CTL within 30 min-2 h after DLG. CT (Somatom Sensation Cardiac 16, Siemens Healthcare; Brilliance iCT, Philips Medical Health Care, Best, the Netherlands) scans were performed bilaterally from the inferior border of the thyroid cartilage in the neck to the lower border of the lungs. Patients were asked to hold their breath after deep inhalation during the scan, and a CT scan was performed at the end of inhalation. After the scan, the patients breathed freely. The scanning parameters were as follows: Tube voltage of 120 kVp, collimation of 1 mm, pitch of 1, and tube current of 110 mAs. After scanning, the raw data were transferred to the workstation for three-dimensional reconstruction with a layer thickness of 2 mm and a layer spacing of 2 mm.

### Thoracic duct outlet surgery

The patient was placed in the supine position and under general anaesthesia. The patient's shoulders are padded with pillows so that the head is tilted slightly to the right. After disinfection of the neck area with iodine, a sterile towel, a medium sheet, and a small opening sheet were laid out. A transverse skin incision is made from the left sternoclavicular joint to the left external jugular vein between the body projection lines, approximately one finger above the clavicle. Under the microscope (12.5 /8-10 magnification), the subcutaneous layer, the broad cervical muscle, and the left sternocleidomastoid muscle were cut with an electric knife. The cut edge was treated with electrocoagulation to stop the bleeding. The left jugular vein angle (located under the clavicle) was revealed by posterior dissection, and the thoracic duct was explored and released from the obstruction. The wound surface was checked for obvious blood and fluid spillage, and sodium hyaluronate was injected locally to prevent adhesions. The gauze and instruments were counted, and silk sutures were interrupted to close the sternocleidomastoid dissection, the cervical brevis layer, and the subcutaneous layer. The skin incision was glued with tissue glue, and the wound was covered with a sterile dressing. At the end of the operation, the tracheal tube and gastric tube were removed upon awakening from anaesthesia.

### Image analysis

All 71 patients underwent DLG successfully, and the quality of the CTL images met the criteria for disease assessment. All CTL images were double-blind reviewed by two radiologists (diagnostic radiologists with over 15 years of experience).

After the contrast agent (lipiodol) has been injected into the superficial lymphatic vessels of the unilateral foot, the lipiodol follows the lymphatic fluid up to the lumbar trunk and converges into the cisterna chyli, then into the thoracic duct, and finally into the blood at the angle of the left jugular vein. During this process, the distribution of lipiodol deposits in any other part of the body, such as the diaphragm, peritracheal region, pericardium, pleura, and hilum, is considered abnormal. Such deposits represent dilated lymphatic vessel hyperplasia, reflux, or fistula.

CTL and conventional chest CT were performed to assess the following features: (1) Abnormal distribution of lipiodol in the peritracheal region, pleura, pericardium, hilum, and thoracic duct outlet; and (2) ground-glass opacity, atelectasis, interlobular septal thickening, bronchovascular bundle thickening, pleural effusion, and mediastinal and extrapleural soft tissue changes.

### Statistical analysis

Statistical analysis was performed by using software (SPSS, version 26.0; IBM, Armonk, NY, United States). Normally

**Table 1 Main demographic and clinical variables of 71 patients with lymphatic plastic bronchitis or primary chylothorax, *n* (%)/ mean ± SD/25th-75th percentiles**

| Characteristic or symptoms | Group A (*n* = 20) | Group B (*n* = 41) | Group C (*n* = 10) | *P* value |
|---|---|---|---|---|
| Ages (yr) | 33.1 ± 17.3 | 34.0 ± 19.0 | 48.3 ± 11.7 | 0.060 |
| Gender | | | | 0.472 |
| Male | 11 | 16 | 5 | |
| Female | 9 | 25 | 5 | |
| Course (m) | 36.0 (6.5-129.0)[a] | 6 (2.5-20.0)[a] | 33 (5-108) | 0.005 |
| Cough | 20 (100)[a] | 9 (22.0)[a,b] | 9 (90.0)[b] | < 0.001 |
| Sputum | 20 (100)[a] | 0 (0)[a,b] | 10 (100)[b] | < 0.001 |
| Chest tightness | 12 (60.0) | 29 (70.7) | 8 (80.0) | 0.501 |
| Fever | 5 (25.0) | 4 (9.8) | 0 (0) | 0.125 |
| Hemoptysis | 4 (20.0)[a] | 0 (0)[a] | 0 (0) | 0.008 |

[a]*P* < 0.05, indicates a statistically significant difference between group A and group B.
[b]*P* < 0.01, indicates a statistically significant difference between group B and group C.
Unless otherwise indicated, data are number of patients.

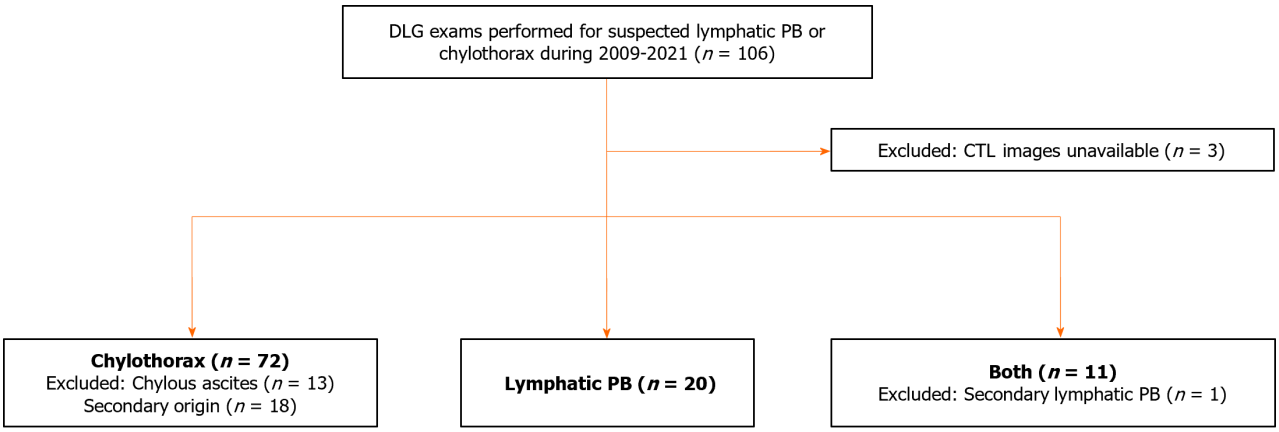


**Figure 1 Flow diagram of study cohort.** DLG: Direct lymphangiography; PB: Plastic bronchitis; CTL: Computed tomography lymphangiography.

distributed quantitative data are expressed as the mean ± SD, and nonnormally distributed continuous variables are expressed as the median (25th-75th percentiles). Normally distributed and nonnormally distributed variables were evaluated by using one-way analysis of variance and the Kruskal-Wallis H test, respectively. The chi-square test or Fisher's exact test was used to compare the differences in abnormal CTL lipiodol deposition and abnormal changes in the lungs among the three groups. The Bonferroni correction was used for pairwise comparisons when the overall difference was statistically significant. Statistical significance was established at *P* values less than 0.05 for overall and pairwise adjusted tests of significance.

## RESULTS

### *Patient demographics*

The data of 71 patients (mean age: 35 ± 18 years; age range: 1-73 years; 32 men) with a diagnosis of lymphatic PB (*n* = 20), primary chylothorax (*n* = 41), or lymphatic PB with primary chylothorax (*n* = 10) were reviewed. For further characteristics of the patients, see Table 1.

### *Imaging findings in the DLG*

All DLG examinations (100%) were technically successful at visualizing anatomic variations or lymph reflux.

In 1 patient in group A, the lipiodol did not continue upward at the first lumbar vertebra. In the remaining 19 patients, reflux was observed in 3 patients in the left bronchomediastinal lymphatic trunk, 5 patients in the bilateral bronchomedi-

astinal lymphatic trunk, 3 patients in the left subclavian lymphatic trunk, 1 patient in the right subclavian lymphatic trunk, 3 patients in the bilateral subclavian lymphatic trunk, 2 patients in the left jugular lymphatic trunk and 4 patients in the bilateral jugular lymphatic trunk.

In group B, 4 patients did not experience continued upward movement of lipiodol at the level of the 10$^{th}$ thoracic vertebra to the first lumbar vertebra. Among the remaining 37 patients, 7 had reflux in the left bronchomediastinal lymphatic trunk, 15 had reflux in the left subclavian lymphatic trunk, 1 had reflux in the bilateral subclavian lymphatic trunk, 14 had reflux in the left jugular lymphatic trunk, and 2 had reflux in the bilateral jugular lymphatic trunk. During lymphangiography, lipiodol leakage into the pleural cavity was observed in 2 patients.

In group C, 1 patient experienced lipiodol obstruction at the level of the second lumbar vertebra, and 1 patient experienced lipiodol obstruction at the level of the sixth thoracic vertebra. In the remaining 8 patients, reflux was observed in 2 patients with a left bronchomediastinal lymphatic trunk, 5 patients with a left subclavian lymphatic trunk, 4 patients with a left jugular lymphatic trunk, and 1 patient with a bilateral jugular lymphatic trunk.

### *Imaging findings in CTL and conventional chest CT*

The abnormal deposition of lipiodol in patients in groups A, B and C was as follows: Terminal thoracic duct in 14, 33 and 8 patients ($P = 0.674$); peritracheal region in 18, 15 and 8 patients ($P < 0.001$); pleura in 6, 33 and 9 patients ($P < 0.001$); pericardium in 6, 6 and 4 patients ($P = 0.134$); and hilum in 16, 11 and 7 patients ($P < 0.001$) (Figures 2-4).

The abnormalities on conventional chest CT in the three groups were as follows: Ground-glass opacity in 19, 18 and 8 patients ($P < 0.001$); atelectasis in 4, 26 and 7 patients ($P = 0.003$); interlobular septal thickening in 12, 11 and 3 patients ($P = 0.037$); bronchovascular bundle thickening in 14, 6 and 4 patients ($P < 0.001$); mediastinal confined speckle or tubular shadow in 14, 14, and 7 patients ($P = 0.012$); diffuse mediastinal changes in 6, 5, and 3 patients ($P = 0.146$); cystic hypodense foci in the axilla in 2, 6, and 2 patients ($P = 0.796$); and cystic hypodense foci in the chest wall in 0, 2, and 2 patients ($P > 0.999$) (Figure 5).

The proportions of imaging features in the three groups of patients are detailed in Table 2.

### *Comparison of imaging findings between patient cohorts*

There were significant differences between groups A and B in the following presentations: Lipiodol deposition in the peritracheal region ($P < 0.001$), lipiodol deposition in the pleura ($P < 0.001$), lipiodol deposition in the hilum ($P < 0.001$), ground-glass opacity ($P < 0.001$), atelectasis ($P < 0.001$), interlobular septal thickening ($P = 0.036$), and bronchovascular bundle thickening ($P < 0.001$). These significant differences were also detected between groups A and C in terms of the following manifestations: Lipiodol deposition on the pleura ($P = 0.006$) and atelectasis ($P = 0.045$).

The pairwise comparison of patients between the three groups is shown in Table 2.

### *Surgical and postoperative CT review findings*

In our study, 61 of 71 patients underwent thoracic duct outlet surgery. Twenty patients in group A, 33 patients in group B, and 8 patients in group C underwent this operation. Among them, 12 patients in group A underwent chest CT reexamination 3-19 d after the operation, and the signs were alleviated in 10 patients, similar in 1 patient, and aggravated in 1 patient. In group B, 8 patients were reexamined with chest CT 4-10 d after the operation, and the chest CT signs were alleviated in 3 patients, similar in 1 patient, and aggravated in 4 patients. Twenty-seven patients in group C were reexamined *via* chest CT 5-9 d after the operation; 13 patients were relieved, 9 patients were similar, and 5 patients were worse than before.

## DISCUSSION

In our study, we retrospectively analysed the clinical features, CTL findings, and conventional chest CT findings of patients with thoracic lymphatic reflux disorder. Lymphatic PB, primary chylothorax, and lymphatic PB with primary chylothorax showed no differences according to sex or age. There were some differences in clinical symptoms among the three groups. In addition, there were tortuous and dilated lymphatic vessels in the corresponding lesion sites in the three groups, and fistulas formed in the adjacent airway cavity or pleural cavity. This finding supports a common cause of the formation of lymphatic PB and chylothorax.

It has been reported in the literature[4,20-22] that both lymphatic PB and primary chylothorax are more prevalent in children and adolescents. Clinical symptoms, such as cough, sputum, chest tightness, and fever, are nonspecific. The incidence of lymphatic PB is slightly greater in males than in females, and the specific clinical manifestation is the formation of bronchial casts in the bronchi. There are no sex differences or specific clinical manifestations in patients with primary chylothorax. In our study, the mean ages of the patients in groups A, B, and C were all over 30 years, with a wide age distribution that was not limited to only children and adolescents. The ratios of male to female patients were 11:9, 16:25, and 5:5, respectively. There were no statistically significant differences in age or sex among the three groups. The above characteristics were different from those reported in the literature. In our study, there were statistically significant differences in cough ($P < 0.001$), sputum ($P < 0.001$), and haemoptysis ($P = 0.027$) between group A and group B. The differences in cough ($P < 0.001$) and sputum ($P < 0.001$) were statistically significant between group B and group C. There were no significant differences in chest tightness or fever among the three groups. The differences between the clinical symptoms of these diseases have not been reported in the literature.

**Table 2 Computed tomography lymphangiography features and conventional chest computed tomography features in the three groups, *n* (%)**

| Imaging features | Group A (*n* = 20) | Group B (*n* = 41) | Group C (*n* = 10) | *P* value |
|---|---|---|---|---|
| Thoracic duct outlet obstruction | 14 (70.0) | 33 (80.5) | 8 (80.0) | 0.674 |
| Location of lymphatic reflux | | | | |
| Peritracheal region | 18 (90.0)[a] | 15 (36.6)[a] | 8 (80.0) | < 0.001 |
| Pleura | 6 (30.0)[a] | 33 (80.5)[a] | 9 (90.0) | < 0.001 |
| Pericardium | 6 (30.0) | 6 (14.6) | 4 (40.0) | 0.134 |
| Hilum | 16 (80.0)[a] | 11 (26.8)[a] | 7 (70.0) | < 0.001 |
| Pulmonary abnormalities | | | | |
| Ground-glass opacity | 19 (95.0)[a] | 18 (43.9)[a] | 8 (80.0) | < 0.001 |
| Atelectasis | 4 (20.0)[a,b] | 26 (63.4)[a] | 7 (70.0)[b] | 0.003 |
| Interlobular septal thickening | 12 (60.0)[a] | 11 (26.8)[a] | 3 (30.0) | 0.037 |
| Bronchovascular bundles thickening | 14 (70.0)[a] | 6 (14.6)[a] | 4 (40.0) | < 0.001 |
| Localized changes in mediastinum | 14 (70.0)[a] | 14 (34.1)[a] | 7 (70.0) | 0.012 |
| Diffuse changes in mediastinum | 6 (30.0) | 5 (12.2) | 3 (30.0) | 0.146 |
| Cystic lesions in the axilla | 2 (10.0) | 6 (14.6) | 2 (20.0) | 0.796 |
| Cystic lesions in the chest wall | 0 (0.0) | 2 (4.9) | 2 (4.9) | < 0.999 |

[a]$P < 0.05$, indicates a statistically significant difference between group A and group B.
[b]$P < 0.01$, indicates a statistically significant difference between group B and group C.
Unless otherwise indicated, data are number of patients.

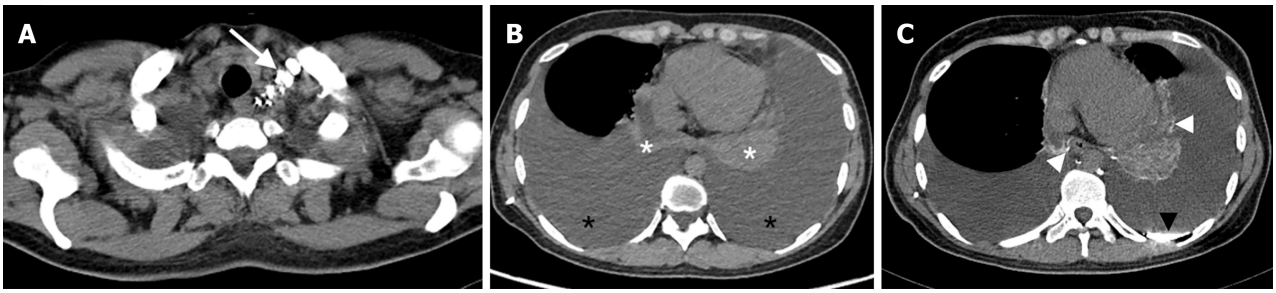


**Figure 2 A 34-year-old woman with primary chylothorax.** A: The axial computed tomography lymphangiography (CTL) shows abnormal contrast medium accumulation in the thoracic duct outlet (long white arrow); B: A nonenhanced axial CT scan shows massive bilateral pleural effusions (black asterisk). Compressive atelectasis can be seen in both lungs (white asterisk); C: The CTL in the same plane as B shows abnormal contrast medium accumulation in the left pleura (black arrowhead), bilateral lung tissue (white arrowhead).

In our study, lipiodol deposition at the thoracic duct outlet was not significantly different among the three groups: 14 patients (70.0%) in group A, 33 patients (80.5%) in group B, and 8 patients (80%) in group C ($P = 0.674$). The differences in lipiodol deposition around the bronchus and pleura were statistically significant among the three groups. There were statistically significant differences in abnormal lipiodol deposition around the bronchi and pleura among the three groups. Pairwise comparison revealed that there was more abnormal lipiodol deposition around the bronchi in group A ( $n = 18$, 90.0%) than in group B ($n = 15$, 36.6%), and there was significantly more abnormal lipiodol deposition in the pleura in group B ($n = 33$, 80.5%) than in group A ($n = 6$, 30.0%). More importantly, 61 patients underwent thoracic duct outlet surgery in this study. We found that the dense fibrous tissue surrounding the thoracic duct outlet compressed the surrounding structures and obstructed the distal thoracic duct. When the obstruction was removed, the flow of lymph increased significantly. Combining the findings of the patients' CTL and thoracic duct outlet surgery, we speculate that one of the aetiologies of lymphatic PB and primary chylothorax may be as follows: Thoracic duct obstruction leads to poor lymph return into the bloodstream, which results in slow lymph return or even reflux downstream. The lymph refluxes into the peritraceal lymphatics or pleural lymphatics *via* the bronchomediastinal lymphatic trunk and subclavian lymphatic trunk. Subsequently, the lymph infiltrates or leaks into the corresponding lumen, forming bronchial plastic substances or pleural effusion. This finding is similar to the findings of abnormal pulmonary lymphatic perfusion proposed by O'Leary *et al*[23]; they suggested that obstruction at the thoracic duct outlet or large branches results in the

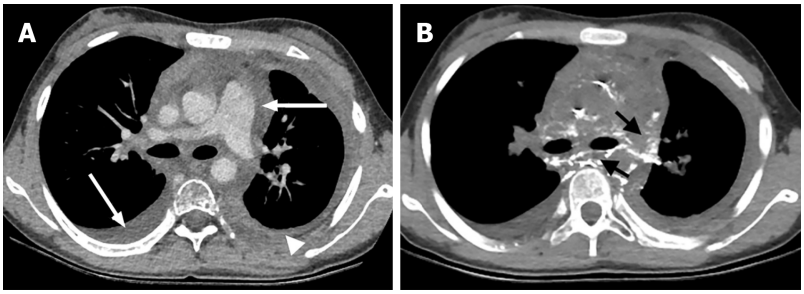


**Figure 3 A 16-year-old woman with primary chylothorax.** A: The contrast-enhanced thoracic axial mediastinal window shows diffuse mediastinal soft-tissue infiltration (long white arrow), right pleural effusion (short white arrow), left pleural thickening (white arrowhead); B: The computed tomography lymphangiography in the same plane as A shows abnormal contrast medium scattered in surrounding mediastinum (short black arrow).

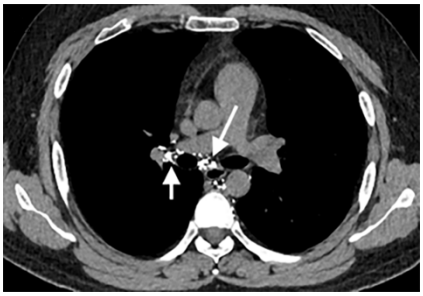

**Figure 4 A 28-year-old man with plastic bronchitis.** The axial omputed tomography lymphangiography shows an abnormal contrast medium surrounding the right main bronchus (long white arrow), right hilar lung (short white arrow).

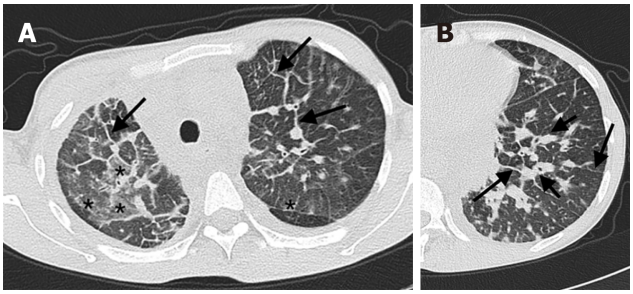


**Figure 5 A 41-year-old woman with plastic bronchitis and primary chylothorax.** A and B: The thoracic axial lung window shows interlobular septal thickening (long black arrow), bronchovascular bundles thickening (short black arrow), diffuse ground-glass opacities in pulmonary parenchyma (black asterisk).

backflow of lymph from the thoracic duct into the mediastinum, lungs, pleura, and submucosa of the bronchi, which is the common cause of the formation of lymphatic PB and chylothorax.

In addition, in our study, the differences in pulmonary signs (ground-glass opacity, atelectasis, interlobular septal thickening, and bronchovascular bundle thickening) were statistically significant between group A and group B. The difference in atelectasis between group A and group C was also statistically significant. More ground-glass opacity, interlobular septal thickening, and bronchovascular bundle thickening were observed in group A than ingroup B. Atelectasis was more common in group B than in group A. These differences have not been reported in the literature. We speculate that 3 reasons may account for its occurrence: (1) Congenital tortuosity, dilatation, and hyperplasia of the pulmonary lymphatic vessels are more common in group A than in group B patients. This developmental abnormality can lead to thickening of interstitial lymphatic tissues, such as thickening of interlobular septa and bronchovascular bundles; (2) leakage of lymph into the bronchi, small branches, or even pulmonary acinus manifests as limited or diffuse ground-glass opacity in the lungs; and (3) patients in group A may cough up part of the tubular substances on their own, and the volume of the sputum may be reduced on admission. Thus, relatively few patients have obstructive pulmonary atelectasis. In contrast, compressive atelectasis caused by moderate to massive pleural effusion compression was more common in group B than in group B.

There are several limitations of our study. First, this was a retrospective study with a small sample size and possible selection bias. Further studies with larger sample sizes are needed in the future. Second, this study only explored primary chylothorax and did not include secondary patients. Future studies will explore this disease further. Finally, the study was a single-center study.

In conclusion, lymphatic PB and primary chylothorax are rare lymphatic drainage disorders. The physiological mechanisms of the two diseases have both similarities and differences. Similarities: Both are caused by obstruction of the thoracic duct, resulting in slow lymphatic reflux and even downstream reflux. However, the location of the lymph reflux differed between the two groups. CTL is an appropriate method for detecting abnormal lymphatic vessel positioning and pulmonary abnormalities. It can provide a crucial imaging basis for diagnosing lymphatic PB and primary chylothorax and provide information for treatment.

## CONCLUSION

lymphatic PB and primary chylothorax are rare lymphatic drainage disorders. The physiological mechanisms of the two diseases have both similarities and differences. Similarities: Both are caused by obstruction of the thoracic duct, resulting in slow lymphatic reflux and even downstream reflux. Difference: The location of lymph reflux between the two is different. CTL is an appropriate method to detect abnormal lymphatic vessels position and pulmonary abnormalities. It can provide a crucial imaging basis for diagnosing lymphatic PB and primary chylothorax and provide information for treatment.

## FOOTNOTES

**Co-first authors:** Xing-Peng Li and Yan Zhang.

**Author contributions:** Li XP and Zhang Y contributed equally to this work. Li XP, Zhang Y, and Wang RG were the guarantors of the integrity of the entire study; Li XP, Zhang Y, Sun XL, and Wang RG performed the study concept and design; Li XP and Hao Q performed the literature study; Hao K and Liu MK pro conducted the study; Li XP and Zhang Y conducted the experimental study; Li XP, Zhang Y, and Hao K conducted the statistical analysis; Sun XL, Hao K, and Wang RG prepare the manuscript; Sun XL, Hao K, and Wang RG wrote the manuscript. All authors have access to the data and played a role in writing this manuscript.

**Institutional review board statement:** This retrospective study was approved by the Ethics Committee of Beijing Shijitan Hospital Affiliated to Capital Medical University.

**Informed consent statement:** The requirement for informed consent to review medical records and images was waived because this was a retrospective study. The presented data are anonymized and risk of identification is low.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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ORIGINAL ARTICLE

Clinical and Translational Research

# Genetically predicted fatty liver disease and risk of psychiatric disorders: A mendelian randomization study

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## Abstract

### *BACKGROUND*

Non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ArLD) constitute the primary forms of chronic liver disease, and their incidence is progressively increasing with changes in lifestyle habits. Earlier studies have documented a correlation between the occurrence and development of prevalent mental disorders and fatty liver.

### *AIM*

To investigate the correlation between fatty liver and mental disorders, thus necessitating the implementation of a mendelian randomization (MR) study to elucidate this association.

### *METHODS*

Data on NAFLD and ArLD were retrieved from the genome-wide association studies catalog, while information on mental disorders, including Alzheimer's disease, schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder, multiple personality disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and schizophrenia was acquired from the psychiatric genomics consortium. A two-sample MR method was applied to investigate mediators in significant associations.

### *RESULTS*

After excluding weak instrumental variables, a causal relationship was identified between fatty liver disease and the occurrence and development of some psychiatric disorders. Specifically, the findings indicated that ArLD was associated with a significantly elevated risk of developing ADHD (OR: 5.81, 95%CI: 5.59-6.03, $P$ <

0.01), bipolar disorder (OR: 5.73, 95%CI: 5.42-6.05, $P = 0.03$), OCD (OR: 6.42, 95%CI: 5.60-7.36, $P < 0.01$), and PTSD (OR: 5.66, 95%CI: 5.33-6.01, $P < 0.01$). Meanwhile, NAFLD significantly increased the risk of developing bipolar disorder (OR: 55.08, 95%CI: 3.59-845.51, $P < 0.01$), OCD (OR: 61.50, 95%CI: 6.69-565.45, $P < 0.01$), and PTSD (OR: 52.09, 95%CI: 4.24-639.32, $P < 0.01$).

*CONCLUSION*

Associations were found between genetic predisposition to fatty liver disease and an increased risk of a broad range of psychiatric disorders, namely bipolar disorder, OCD, and PTSD, highlighting the significance of preventive measures against psychiatric disorders in patients with fatty liver disease.

**Key Words:** Non-alcoholic fatty liver disease; Alcohol-related liver disease; Psychiatric disorders; Mendelian randomization; Single nucleotide polymorphisms



**Core Tip:** Non-alcoholic fatty liver disease and alcohol-related liver disease are the predominant forms of chronic liver diseases, with their incidence gradually increasing due to changing lifestyle habits. Observational studies have indicated a potential association between fatty liver and psychiatric disorders, necessitating Mendelian randomization studies to elucidate this relationship. The findings revealed significant associations between genetic susceptibility to hepatic steatosis and an elevated risk of a wide spectrum of psychiatric disorders, including bipolar disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. These results underscore the imperative for preventive measures targeting mental health conditions in individuals with fatty liver disease.

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## INTRODUCTION

As is extensively documented, non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ArLD) have emerged as the most important causes of hepatic injury, and their incidence is steadily increasing due to changes in lifestyle habits[1]. The former is a chronic liver condition associated with obesity and metabolic syndrome, with a prevalence of approximately 15%-20% and 30%-40% in women and men, respectively[2]. Existing evidence suggests that NAFLD not only affects the liver but is also a multi-system disease, influencing multiple extrahepatic organs and regulatory pathways[3]. ArLD is closely related to alcohol intake, with a prevalence ranging from 10% to 35% in individuals engaged in long-term heavy drinking[4]. The prevalence of NAFLD and ArLD has escalated, establishing them as the most prevalent forms of chronic liver disease and imposing a substantial clinical and economic burden[5].

While psychiatric disorders can be treated *via* various approaches, according to the World Health Organization (WHO), their incidence increases on a yearly basis[6]. Although the relationship between fatty liver and psychiatric disorders remains elusive, a higher prevalence of metabolic syndrome is observed in patients with psychiatric disorders [7]. Common psychiatric disorders, such as bipolar disorder, depressive disorder, or schizophrenia, may be associated with metabolic syndrome or substance abuse[8]. Elwing *et al*[9] observed a higher prevalence of major depression as well as anxiety disorders in NAFLD patients. At the same time, the incidence of ArLD is closely associated with excessive and chronic alcohol consumption, with addictive misuse of alcohol considered a highly prevalent psychiatric disorder[10]. For instance, anxiety is a common comorbidity in patients with alcohol abuse, causing significant discomfort and cognitive impairment[11].

Mendelian randomization (MR) is an approach for investigating causality between exposures and outcomes of interest [12] that utilizes single nucleotide polymorphisms (SNPs) as unconfounded proxies for exposures, thereby circumventing residual confounders and reverse causality commonly present in conventional observational studies[13]. The MR design represents a crucial strategy for causal inference without randomized clinical trials (RCTs), given that genetic variants are randomly assorted during meiosis, mimicking an RCT[14]. There is a non-negligible relationship between fatty liver and mental disorders, necessitating a comprehensive understanding of their shared characteristics to facilitate the development of appropriate assessments and interventions. Therefore, this MR study was conducted to determine the association between fatty liver and mental disorders.

## MATERIALS AND METHODS

In this study, all data were derived from the Genetic Alliance's publicly available compilation of statistical data from genome-wide association studies (GWAS). All original studies underwent a thorough ethical review process and obtained informed consent from participants.

### Study design

Summary statistics on fatty liver disease and psychiatric disorders were collected from published GWAS to explore the causal effect of fatty liver disease on the risk of psychiatric disorders using two-sample MR.

The MR Approach was constructed based on three primary assumptions: (1) Genetic variants as instrumental variables (IVs) should be significantly associated with the risk factor of interest; (2) the genetic variants used should not be associated with potential confounding factors; and (3) selected genetic variants influence the risk of outcome only *via* risk factors and not *via* other pathways (Figure 1).

### Outcome and exposure data source

Summary statistics on fatty liver disease were downloaded from published GWAS. The GWAS Catalog database is publicly available for download and accessible at https://www.ebi.ac.uk/gwas/. Data on psychiatric disorders were retrieved from the psychiatric genomics consortium (https://pgc.unc.edu/). Among them the exposure groups were ArLD [15] and NAFLD[16], the outcome groups were psychiatric disorders (including Alzheimer's disease[17], anorexia nervosa[18], anxiety disorder[19], attention deficit hyperactivity disorder[20], bipolar disorder[21], major depressive disorder [22], multiple disorders[23], obsessive-compulsive disorder[24], post-traumatic stress disorder[25], schizophrenia[26]). Details of the psychiatric disorders are presented in Table 1. The entire cohort consisted exclusively of individuals with European heritage.

### Genetic variants selection criteria

The genetic instruments for each exposure trait or disease were meticulously chosen from the corresponding GWASs, surpassing the threshold of genome-wide significance ($P < 5 \times 10^{8}$). Independent SNPs were defined by $R^2 < 0.001$ and clump window > 10 kb without linkage disequilibrium (LD) were proposed as instrumental variables. LD among SNPs for each risk factor was calculated based on 1000 genomes LD reference panel European population[27] using the PLINK clumping approach (PLINK: a tool set for whole-genome association and population-based linkage analyses)[28].

### Statistical analysis

The variance in fatty liver disease explained by the IVs was calculated, and weak IVs bias was analyzed using *F*-statistics. $R^2$ was calculated based on the effect estimates (β) and allele frequencies (EAF) of each single SNP using the following formula: $R^2 = 2\times EAF (1-EAF) \times \beta^2$[29]. The F value was further calculated according to the formula $F = R^2 \times (N-2)/(1-R^2)$ [30]. *F* value > 10 was considered a strong genetic IV; otherwise, the SNP was discarded.

An assessment of heterogeneity across SNPs was conducted using Cochran's Q statistics. The primary analytical method used to examine causal associations was the random-effect inverse-variance-weighted model[31]. The MR-Egger method was used to determine the pleiotropic effects of the instrumental SNPs[32].

## RESULTS

### Selection of instrumental variables

*F* values for each SNP were individually calculated, and SNPs with values greater than 10 were retained, suggesting a low risk of bias due to weak IVs. Consequently, all SNPs in this study had F-statistics larger than 10 (Table 2).

### Mendelian estimations

**ArLD:** In the ArLD population, one SNP (rs738408) was retained following screening and filtering. The findings indicated that ArLD significantly elevates the likelihood of developing attention deficit hyperactivity disorder (ADHD) (OR: 5.81, 95%CI: 5.59-6.03, $P < 0.01$), bipolar disorder (BD) (OR: 5.73, 95%CI: 5.42-6.05, $P = 0.03$), obsessive-compulsive disorder (OCD) (OR: 6.42, 95%CI: 5.60-7.36, $P < 0.01$), and post-traumatic stress disorder (PTSD) (OR: 5.66, 95%CI: 5.33-6.01, $P < 0.01$). In contrast, there was no evidence suggesting that ArLD increased the risk of anorexia nervosa (OR: 0.97, $P = 0.37$), anxiety disorder (OR: 1.00, $P = 0.14$), major depressive disorder (MDD) (OR: 1.00, $P = 0.88$), multiple personality disorders (OR: 0.96, $P = 0.47$), and schizophrenia (OR: 0.97, $P = 0.14$) (Figure 2). Considering that only one SNP was included, tests for heterogeneity and pleiotropy could not be performed.

**NAFLD:** In the NAFLD population, 3 SNPs (rs28601761, rs3747207, and rs73001065) were included in the analysis of their association with Alzheimer's disease. At the same time, 2 SNPs (rs3747207 and rs429358) were analyzed for their association with other mental disorders. The results revealed that NAFLD was associated with a significantly increased risk of developing bipolar disorder (OR: 55.08, 95%CI: 3.59-845.51, $P < 0.01$), OCD (OR: 61.50, 95%CI: 6.69-565.45, $P < 0.01$), and PTSD (OR: 52.09, 95%CI: 4.24-639.32, $P < 0.01$). On the other hand, there was no evidence implying that ArLD increased the risk of Alzheimer's disease, anorexia nervosa, anxiety disorder, ADHD, MDD, multiple personality disorders, and schizophrenia (Figure 3). Due to significant heterogeneity, the random-effects model was used.

**Table 1 Detailed information on genome-wide association studies**

| Ref. | Outcome | PMID | Sample size | |
|---|---|---|---|---|
| | | | Cases | Controls |
| Bellenguez *et al*[17], 2022 | Alzheimer's disease | 35379992 | 39106 | 401577 |
| Watson *et al*[18], 2019 | Anorexia nervosa | 31308545 | 16992 | 55525 |
| Schoeler *et al*[19], 2023 | Anxiety disorder | 37106081 | 282802 | |
| Demontis *et al*[20], 2023 | Attention deficit hyperactivity disorder | 36702997 | 38691 | 186843 |
| Stahl *et al*[21], 2019 | Bipolar disorder | 31043756 | 20352 | 31358 |
| Howard *et al*[22], 2019 | Major depressive disorder | 30718901 | 246363 | 561190 |
| Cross-Disorder Group of the Psychiatric Genomics Consortium[23], 2019 | Multiple disorders | 31835028 | 232964 | 494162 |
| IOCDF-GC, OCGAS[24], 2018 | Obsessive-compulsive disorder | 28761083 | 2688 | 7037 |
| Nievergelt *et al*[25], 2019 | Post-traumatic stress disorder | 31594949 | 30000 | 170000 |
| Trubetskoy *et al*[26], 2022 | Schizophrenia | 35396580 | 76775 | 243649 |

**Table 2 Details of variance explained by the selected instruments and *F*-statistics for the mendelian randomization analysis based on the sample size of autoimmune diseases**

| Exposure/Outcome | SNPs | $R^2$ | *F*-statistic |
|---|---|---|---|
| **Alcohol-related liver disease** | | | |
| Alzheimer's disease | / | / | / |
| Anorexia nervosa, anxiety disorder, attention deficit hyperactivity disorder, bipolar disorder, major depressive disorder, multiple disorders, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia | rs738408 | 0.11 | 57352.08 |
| **Non-alcoholic fatty liver disease** | | | |
| Alzheimer's disease | rs28601761, rs3747207, rs73001065 | 0.04 | 35089.81 |
| Anorexia nervosa, anxiety disorder, attention deficit hyperactivity disorder, bipolar disorder, major depressive disorder, multiple disorders, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia | rs3747207, rs429358 | 0.02 | 26942.59 |

SNPs: Single nucleotide polymorphisms.

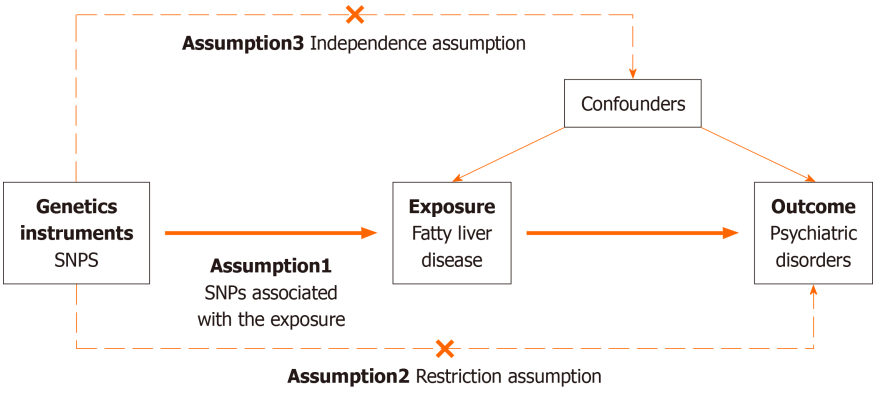


**Figure 1 The overall design of Mendelian randomization analyses in the present study.** SNPs: Single nucleotide polymorphisms.

## DISCUSSION

As fatty liver disease has emerged as a leading cause of chronic liver disease worldwide, and with a deeper understanding of its pathogenesis, attention has increasingly focused on its impact on the extrahepatic system, particularly psychiatric disorders. Indeed, exposing their relationship is conducive to the prevention of related diseases. Herein, publicly

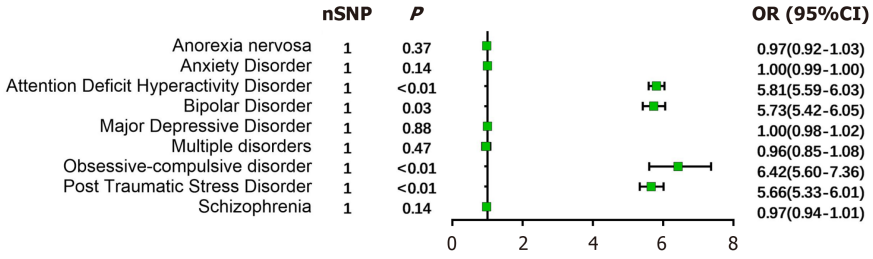


**Figure 2 Mendelian randomization analysis of alcohol-related liver disease with psychiatric disorders risk.**

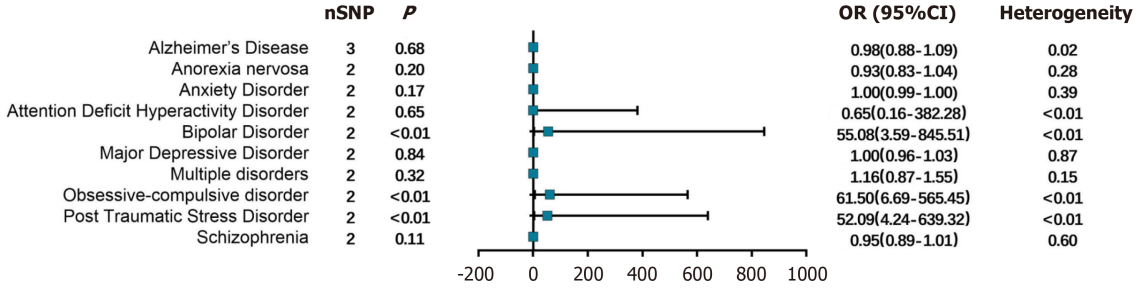


**Figure 3 Mendelian randomization analysis of the relationship between non-alcoholic fatty liver disease and the risk of psychiatric disorders.**

available GWAS data were obtained and analyzed using two-sample MR. Interestingly, the results uncovered that ArLD significantly elevates the likelihood of developing ADHD, BD, OCD, and PTSD, whilst NAFLD significantly increased the risk of BIP, OCD and PTSD.

According to the WHO, 5.1% of the global burden of disease can be attributable to alcohol misuse, ranking it as the seventh leading risk factor globally[33]. Of note, persistent alcohol use disorder is strongly correlated with progressive hepatic damage and increased mortality[34]. Among patients diagnosed with fatty liver disease, non-interrupted consumption of alcohol results in cirrhosis in 8% to 20% of cases. Furthermore, ongoing alcohol use significantly increases mortality rates in those already suffering from cirrhosis[35]. It is worthwhile emphasizing the close correlation between alcohol dependence and other neuropsychiatric disorders such as non-alcoholic substance abuse, bipolar disorder, and ADHD[36]. The lifetime prevalence of PTSD in Western countries is estimated to be 8%, showing a strong correlation with substance use disorders, particularly alcohol addiction[37]. The reward-seeking processes that drive alcohol-seeking in alcohol-dependent patients are also implicated in some patients with OCD[38]. Moreover, alcohol use disorder results in higher recurrence rates and worse prognosis in OCD[39]. Additionally, alcohol use disorder with comorbid PTSD generates a mutually reinforcing cycle that exacerbates the risk of trauma[40]. Besides, the rewarding effects of alcohol may aggravate cognitive impairments and attention deficits associated with ADHD[41].

Alcohol dependence and BD frequently coexist, with chronic alcoholism being associated with 24%-62% of BD cases worldwide[42]. Prolonged alcohol consumption can exert detrimental effects on both the immune system and nervous system while also increasing the frequency and severity of emotional episodes in individuals with BD[43]. Abnormalities in the N-methyl-d-asperate (NMDA) receptor play a critical role in the occurrence and development of BD. Conversely, ethanol acts on the brain to inhibit NMDA receptors, thereby elevating the risk of BD[44]. However, the risks of fatty liver appear to outweigh the risks associated with alcohol abuse, and patients with NAFLD seem to be at a higher risk compared with patients with ArLD[45]. The results of this study demonstrated that NAFLD patients had a higher risk of developing BD than ArLD (NAFLD: OR = 55.08; ArLD: OR = 5.73). Clinically, compared with other psychiatric disorders, BD patients are more likely to suffer from metabolic syndrome, which is also a characteristic of NAFLD[46]. Hence, the vulnerability of individuals with NAFLD to BD has been hypothesized to be associated with the presence of metabolic syndrome[45]. MiR-34a tightly regulates lipid metabolism by suppressing the expression of sirtuin 1 (Sirt1), contributing to hepatic steatosis[47,48]. Noteworthily, its level is elevated in the serum of patients with NAFLD. At the same time, miR-34a is also a component of the molecular network that mediates neurodevelopment and synaptogenesis, and its increased level is considered a risk factor for bipolar disorder[49].

NAFLD is closely linked to metabolic disorder syndrome that is characterized by obesity, insulin resistance, and hyperlipidemia[50]. Animal experiments have validated that metabolic syndrome can lead to astrogliosis and microgliosis, causing damage to adjacent neuronal processes and aggravating PTSD-like symptoms[51]. Furthermore, a long-term observational study noted a significant correlation between metabolic syndrome and OCD, suggesting a potential synergistic interaction between the two conditions[52]. In parallel, chronic inflammation also plays a key role in NAFLD, with the levels of several proinflammatory cytokines being significantly higher in NAFLD patients[53]. According to an earlier study, the levels of proinflammatory markers (such as interleukin-1β, interleukin-6, and tumor necrosis factor-α), which are closely related to the development of the disease, were elevated in PTSD patients[54]. Elevated levels of inflammatory factors can elicit neuroinflammation within the basal ganglia, leading to abnormalities in the cortico-striato-

thalamo-cortical circuitry, which is a significant mechanism underlying OCD[55]. Therefore, metabolic syndrome and high levels of inflammatory factors in NAFLD patients play an instrumental role in the occurrence and development of OCD and PTSD.

The combination of fatty liver and persistent inflammation is associated with neuroinflammation, disruptions in neurotransmission, and hypothalamic-pituitary-adrenal axis dysfunction, which are important pathogenesis of mental diseases[56]. A high correlation was also observed between NAFLD and MDD, with chronic stress-mediated increase in glucocorticoid levels playing a vital role[57]. However, no association was observed between fatty liver disease and other psychiatric disorders in this study.

This is the first study to explore the causal relationship between psychiatric disorders and fatty liver disease using a two-sample MR analysis with pooled GWAS-level statistics, thereby minimizing potential confounding and reverse causality by aggregating a large amount of genetic data. However, this study has some limitations that merit acknowledgment. To begin, independent SNPs ($P < 5 \times 10^{8}$) with genome-wide significance levels were utilized in this study, with F statistics being greater than 10 to avoid weak IVs from compromising the validity of the MR results. This ultimately resulted in a limited number of SNPs after screening, warranting future GWAS with larger sample sizes to identify more SNPs. Secondly, the results of our study may not be generalizable to the global population, given that the study population in this study was limited to individuals of European ancestry. Therefore, the conclusions of this study should be interpreted with caution.

## CONCLUSION

In summary, this MR study provides genetic evidence supporting a causal relationship between fatty liver disease and psychiatric disorders. Our results collectively suggest that ArLD is a risk factor for ADHD, bipolar disorder, OCD, and PTSD. Moreover, our findings highlight a correlation between the presence of NAFLD and a higher risk of bipolar disorder, OCD, and PTSD. Thus, patients with fatty liver disease should be more vigilant to prevent the onset of mental disorders.

## FOOTNOTES

**Co-first authors:** Wei-Ming Xu and Hai-Fu Zhang.

**Author contributions:** Zhang HF and Xu WM conceived and designed the study; Li SJ and Feng YH collected data and performed data analysis; Zhang HF and Xu WM wrote the draft of this manuscript; Xu WM and Xie BY edited the manuscript.

**Institutional review board statement:** This study employed a Mendelian randomization design, and all the data were sourced from an open-access database; hence, these regulations were not applicable.

**Informed consent statement:** This study used only publicly available data, especially summary level data from GWAS, did not involve sensitive personal information, did not cause harm to individuals, and did not compromise their privacy; hence, these regulations were not applicable.

**Conflict-of-interest statement:** All authors have no conflicts of interest to disclose.

**Data sharing statement:** No additional data are available.



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ORIGINAL ARTICLE

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# Different effects of 24 dietary intakes on gastroesophageal reflux disease: A mendelian randomization

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## Abstract

### *BACKGROUND*

In observational studies, dietary intakes are associated with gastroesophageal reflux disease (GERD).

### *AIM*

To conduct a two-sample mendelian randomization (MR) analysis to determine whether those associations are causal.

### *METHODS*

To explore the relationship between dietary intake and the risk of GERD, we extracted appropriate single nucleotide polymorphisms from genome-wide association study data on 24 dietary intakes. Three methods were adopted for data analysis: Inverse variance weighting, weighted median methods, and MR-Egger's method. The odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the causal association between dietary intake and GERD.

### *RESULTS*

Our univariate Mendelian randomization (UVMR) results showed significant evidence that pork intake (OR, 2.83; 95%CI: 1.76-4.55; $P = 1.84 \times 10^{-5}$), beer intake (OR, 2.70, 95%CI: 2.00-3.64; $P = 6.54 \times 10^{-11}$), non-oily fish intake (OR, 2.41; 95%CI: 1.49-3.91; $P = 3.59 \times 10^{-4}$) have a protective effect on GERD. In addition, dried fruit intake (OR, 0.37; 95%CI: 0.27-0.50; $6.27 \times 10^{-11}$), red wine intake (OR, 0.34; 95%CI: 0.25-0.47; $P = 1.90 \times 10^{-11}$), cheese intake (OR, 0.46; 95%CI: 0.39-0.55; $P = 3.73 \times 10^{-19}$), bread intake (OR, 0.72; 95%CI: 0.56-0.92; $P = 0.0009$) and cereal intake (OR, 0.45;

95%CI: 0.36-0.57; $P = 2.07 \times 10^{-11}$) were negatively associated with the risk of GERD. There was a suggestive association for genetically predicted coffee intake (OR per one SD increase, 1.22, 95%CI: 1.03-1.44; $P = 0.019$). Multivariate Mendelian randomization further confirmed that dried fruit intake, red wine intake, cheese intake, and cereal intake directly affected GERD. In contrast, the impact of pork intake, beer intake, non-oily fish intake, and bread intake on GERD was partly driven by the common risk factors for GERD. However, after adjusting for all four elements, there was no longer a suggestive association between coffee intake and GERD.

*CONCLUSION*

This study provides MR evidence to support the causal relationship between a broad range of dietary intake and GERD, providing new insights for the treatment and prevention of GERD.

**Key Words:** Dietary; Gastroesophageal reflux disease; Mendelian randomization; Disease management; Randomized controlled trial



**Core Tip:** Through genetic prediction, this study demonstrated the protective effect of dried fruit, red wine, cheese, bread, and cereal intake against gastroesophageal reflux disease (GERD) and the detrimental effects of pig, beer, and non-oily fish intake. Furthermore, even after accounting for body mass index, major depressive disorder, smoking, and alcohol consumption, the effect of genetically predicted dried fruit, red wine, cheese, and cereal on GERD persisted. Additionally, this study discovered that the consumption of tea, milk, yogurt, oily fish, beef, lamb, bacon, processed meat, cooked and raw vegetables, fresh fruit, salted and unsalted nuts, salted and unsalted peanuts, and cooked and raw vegetables were not linked to GERD.

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) refers to the flow of gastric contents back into the esophagus, causing discomfort and complications[1]. Meanwhile, GERD can progress to Barrett's esophagus and even increase the risk of esophageal adenocarcinoma[2]. It is estimated that about 20% of people in Western countries suffer from GERD[3]. The prevalence of GERD has gradually transitioned from the developed world to developing countries[4]. GERD patients in developing countries face a financial burden and discomfort due to deficient appropriate treatment[5]. As an easily accessible and modifiable factor, many researchers have begun to focus on the impact of diet on GERD. A cohort study has demonstrated that diet plays a vital role in gastroesophageal reflux disease in American women[6]. The NIH and the American College of Gastroenterology have also identified dietary modification as the first-line treatment for patients with GERD [7]. However, the evidence for most studies is incomplete and inconsistent[8-10]. In observational studies, causal inference of associations may be prevented by unobserved confounding, misclassification, reverse causation, and other biases [11]. Determining the causal relationship between these diets and GERD is critical to disease management.

Mendelian randomization (MR) is a powerful tool for epidemiological research; The central idea is to use genetic variation as an instrument to evaluate the causal relationship between exposure and outcomes[12]. The basic principle refers to Mendel's second law of inheritance: One of the alleles is randomly passed on to the next generation during meiosis, so the genetic information is fixed at the time of formation of the fertilized egg[11]. Similar to a traditional randomized controlled trials (RCT), subjects are randomly assigned to treatment or control groups based on MR rule[13]. In addition, the random distribution of genetic variation is not affected by external environmental factors, and the direction of causal relationships is determined, imitating the randomization process of RCT[14].

No MR studies are exploring the causal effect of multiple diets on GERD. We conducted a two sample MR study to examine the correlation between 24 dietary intake and GERD risk.

## MATERIALS AND METHODS

### *Study design*

We evaluated the causal effects of 24 dietary incomes on GERD using two-sample Mendelian randomization. Then, we used multivariable MR (MVMR) to adjust for risk factors that could affect GERD occurrence. Our MR study is based on three hypotheses: Genetic variants are closely associated with the exposure of interest, not causally related to the outcome

but only through the exposure, and not confounded by other variables[15]. An overview of the principles, design, and procedures of our MR study is shown in Figure 1.

### Data source

Genetic variations of 24 dietary intakes were collected from participants of the UK Biobank cohort. Related exposure included coffee, tea, milk, yogurt, cheese, cereal, bread, oily fish, non-oily fish, beef, lamb, pork, bacon, processed meat, cooked vegetables, raw vegetables, fresh fruit, dried fruit, salted nuts, unsalted nuts, salted peanuts, unsalted peanuts, red wine, and beer. Genetic data for gastroesophageal reflux disease was also obtained from the genome-wide association study (GWAS) catalog database with single nucleotide polymorphisms (SNP) volumes of 2320781[16]. Furthermore, we identified variables commonly associated with esophageal disorders: body mass index (BMI)[17], major depressive disorder (MDD)[18], smoking, and alcohol consumption[19]. The specific GWAS data information is shown in Table 1 and Supplementary Table 1.

### Instrument variable selection

First, SNPs with significant association with dietary intake ($P < 5.0 \times 10^{-8}$) were selected. A parameter $R^2$ threshold of 0.001 and a kilobase pair (kb) of 10000 were set to exclude interference from linkage disequilibrium (LD)[20]. Then, The SNPs were obtained and isolated from the outcome data, and the SNPs significantly associated with the outcomes ($P < 1\times10^{-5}$) were excluded[21]. If any SNPs were not found in the outcome datasets, proxies with LD $R^2 > 0.8$ were used[22]. However, if the proxy SNP is also not found, remove this SNP from the tool variable. Finally, to ensure that the effect allele is consistent in the exposure and outcome data, we harmonize the exposure and outcome data of the unification. Alleles that were either allele incompatible (*e.g.*, A/C paired with A/G) or being palindromic with intermediate allele frequency were also excluded, yielding the final SNP data[23]. Additionally, we calculated the F value to exclude the presence of weak instrumental variable bias. This is the formula to calculate F: $F = [(N-k-1)/k] \times [R^2/(1-R^2)]$. Here, N refers to the number of samples, k is the total number of SNPs selected for MR analysis, and R2 is the total proportion of phenotypic variation that is explained by all SNPs in the MR analysis[24]. $R^2 = \Sigma [2 \times (1\text{-MAF}) \times \text{MAF} \times (\beta/\text{SD})^2$ where SD and β are the standard deviations and β coefficients of the effect sizes and MAF is the minor allele frequency for each SNP[25]. When F values > 10, there was no weak instrumental variable bias[26].

### Statistical analysis

Three methods were used for MR analysis: inverse variance weighted analysis (IVW), MR egger, and weighted median. The IVW approach integrates the Wald ratio estimated for each SNP through meta-analysis[27]. IVW method was used as the primary statistical method, which is divided into two models: fixed effect (exposure constructed by ≥ 3 SNPs) and random effect (exposure constructed by < 3 SNPs)[27]. We prioritize using random effect-IVW, which assumes that MR estimates obtained for different SNPs conform to a normal distribution. This assumption is more reasonable and is somewhat tolerant of heterogeneity[28]. Assuming that > 50% of the weights come from effective SNPs, the weighted median (WM) method can provide consistent estimates. It has lower statistical efficacy than the IVW method[29]. The MR-Egger method is the most tolerant of horizontal pleiotropy, allowing all SNPs to fail to satisfy the three MR hypotheses[30]. It is the least statistically effective. In addition, MR Egger intercept can be used to test significant level pleiotropy[30]. Genetically predicted, the *P* value of the IVW method is substantial, and other methods are in the consistent direction as IVW. Then, the results are significant. To investigate whether the genetic predisposition of dietary intake is independently associated with GERD risk after adjusting for BMI, MDD, smoking, and alcohol consumption, we conducted a multivariate MR analysis using genetic predictive risk factors. We utilized the Steiger filtering method to determine correct inference directions and mitigate reverse association. The Steiger filtering directionality test was implemented through the TwoSampleMR R package.

The MRPRESSO method is a useful tool to evaluate horizontal pleiotropy. It consists of three components: Firstly, the MR-PRESSO global test is used to detect the presence of horizontal pleiotropy. Secondly, the MR-PRESSO outlier test is utilized to remove any abnormal SNPs (outliers) and estimate the corrected outcome, which eliminates horizontal pleiotropy. Lastly, the MR-PRESSO distortion test is conducted to compare pre- and post-correction results[31]. Cochran's Q test assessed the heterogeneity of the IVW. Cochran's *Q*-test $P < 0.05$ indicated heterogeneity, which can be tolerated using the random effect-IVW[27]. Additionally, the "Leave-one-out" approach removes each SNP in turn. Then, the remaining SNPs serve as instrumental variables in a two-sample MR analysis to determine the impact of a single SNP on the causal association effect[12].

The study used the 95% confidence interval (CI) of the odds ratio (OR) to evaluate the impact of dietary intakes on GERD. $P < 0.05$ was considered suggestive; Significant associations required $P < 0.002$ (= 0.05/24) by Bonferroni correction[32]. Bonferroni correction was not applied to MVMR analysis due to its mutual adjustment nature[33].

## RESULTS

Supplementary Tables 2-17 show SNPs associated with 24 dietary intake and GERD. The total F-value of the intake of cooked vegetables, salad/raw vegetables, and fresh fruits is less than 10, indicating a weak instrumental bias among these three variables. Therefore, it is believed that there is no causal relationship between them and GERD. The F statistics for the rest of the phenotypes was > 10, indicating a small probability of weak instrument variable bias. Furthermore, we applied Steiger filtering to determine the accurate direction of inference.

**Table 1 Univariate Mendelian randomization analysis for genetically causal associations of 24 dietary intake with gastroesophageal reflux disease risk**

| Dietary intake | $R^2$ | F-statistic | SNPs | IVW | | WM | | MR-egger | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | OR (95%CI) | *P* value | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Pork intake | 0.0004 | 20.499 | 9 | 2.83 (1.76, 4.55) | 1.84E-05 | 3.60 (2.14, 6.07) | 1.52E-06 | 49.55 (1.55, 1579.54) | 0.063 |
| Bacon intake | NA | NA | 0 | NA | NA | NA | NA | NA | NA |
| Processed meat intake | 0.0014 | 40.506 | 12 | 0.96 (0.69, 1.33) | 0.794 | 1.12 (0.78, 1.59) | 0.544 | 0.19 (0.01, 3.67) | 0.296 |
| Cooked vegetable intake | 0.0003 | 10.983 | 9 | 1.87 (1.28, 2.75) | 0.001 | 1.56 (0.95, 2.55) | 0.081 | 0.71 (0.01, 64.25) | 0.885 |
| Salad/raw vegetable intake | 0.0003 | 18.628 | 10 | 0.84 (0.60, 1.18) | 0.309 | 0.90 (0.57, 1.42) | 0.639 | 2.39 (0.42, 13.44) | 0.352 |
| Fresh fruit intake | 0.0008 | 18.132 | 37 | 0.79 (0.56, 1.11) | 0.178 | 0.87 (0.60, 1.27) | 0.472 | 1.65 (0.46, 5.88) | 0.443 |
| Dried fruit intake | 0.0009 | 12.062 | 26 | 0.37 (0.27, 0.50) | 6.27E-11 | 0.44 (0.30, 0.61) | 9.00E-07 | 0.13 (0.02, 0.86) | 0.045 |
| Salted nuts intake | NA | NA | 1 | NA | NA | NA | NA | NA | NA |
| Unsalted nuts intake | NA | NA | 0 | NA | NA | NA | NA | NA | NA |
| Salted peanuts intake | NA | NA | 0 | NA | NA | NA | NA | NA | NA |
| Unsalted peanuts intake | NA | NA | 1 | NA | NA | NA | NA | NA | NA |
| Average weekly red wine intake | 0.0007 | 15.584 | 12 | 0.34 (0.25, 0.47) | 1.90E-11 | 0.33 (0.24, 0.47) | 7.03E-10 | 0.35 (0.04, 3.37) | 0.388 |
| Average weekly beer plus cider intake | 0.0005 | 11.283 | 11 | 2.70 (2.00, 3.64) | 6.54E-11 | 2.59 (1.75, 3.83) | 1.82E-06 | 5.19 (0.73, 36.97) | 0.134 |
| Coffee intake | 0.0017 | 23.483 | 26 | 1.22 (1.03, 1.44) | 0.019 | 1.28 (1.06, 1.56) | 0.010 | 1.43 (1.05, 1.94) | 0.034 |
| Tea intake | 0.0025 | 33.827 | 28 | 1.12 (0.97, 1.29) | 0.119 | 1.23 (1.04, 1.45) | 0.014 | 1.32 (0.97, 1.80) | 0.086 |
| Milk intake | NA | NA | 2 | NA | NA | NA | NA | NA | NA |
| Yogurt intake | NA | NA | 1 | NA | NA | NA | NA | NA | NA |
| Cheese intake | 0.0020 | 21.543 | 38 | 0.46 (0.39, 0.55) | 3.73E-19 | 0.57 (0.47, 0.69) | 8.65E-09 | 0.83 (0.33, 2.13) | 0.704 |
| Cereal intake | 0.0012 | 16.373 | 27 | 0.45 (0.36, 0.57) | 2.07E-11 | 0.49 (0.38, 0.63) | 4.36E-08 | 0.58 (0.20, 1.64) | 0.314 |
| Non-oily fish intake | 0.0002 | 13.416 | 5 | 2.41 (1.49, 3.91) | < 0.001 | 1.96 (1.06, 3.62) | 0.033 | 13.70 (0.11, 1761.13) | 0.368 |
| Oily fish intake | 0.0020 | 19.800 | 37 | 0.88 (0.76, 1.03) | 0.122 | 0.89 (0.74, 1.08) | 0.244 | 0.64 (0.32, 1.30) | 0.227 |
| Lamb intake | NA | NA | 0 | NA | NA | NA | NA | NA | NA |
| Beef intake | 0.0004 | 15.600 | 19 | 0.72 (0.56, 0.92) | 0.001 | 0.80 (0.61, 1.05) | 0.108 | 0.69 (0.25, 1.86) | 0.470 |
| Bread intake | 0.0010 | 20.202 | 7 | 0.77 (0.49, 1.22) | 0.271 | 0.57 (0.36, 0.91) | 0.018 | 0.03 (0.00, 0.25) | 0.022 |

SNPs: Single nucleotide polymorphisms; IVW: Inverse variance weighted; OR: Odds ratio; CI: Confidence interval; WM: Weighted median; GERD: Gastroesophageal reflux disease; NA: Not available.

### *UVMR analysis*

Higher genetically predicted pork intake, beer intake, and non-oily fish intake were associated with an increased risk of GERD. The OR of GERD was 2.83 (95% confidence interval (CI), 1.76, 4.55; $P = 1.84 \times 10^{-5}$) for one standard deviation (SD) increase in pork intake, 2.70 (95%CI: 2.00-3.64; $P = 6.54 \times 10^{-11}$) for a one-unit increase in log-transformed OR of beer intake, and 2.41 (95%CI: 1.49-3.91; $P = 3.59 \times 10^{-4}$) for one SD increase in non-oily fish intake. In addition, dried fruit intake (OR 0.37; 95%CI: 0.27-0.50; $6.27 \times 10^{-11}$), red wine intake (OR 0.34; 95%CI: 0.25-0.47; $P = 1.90 \times 10^{-11}$), cheese intake

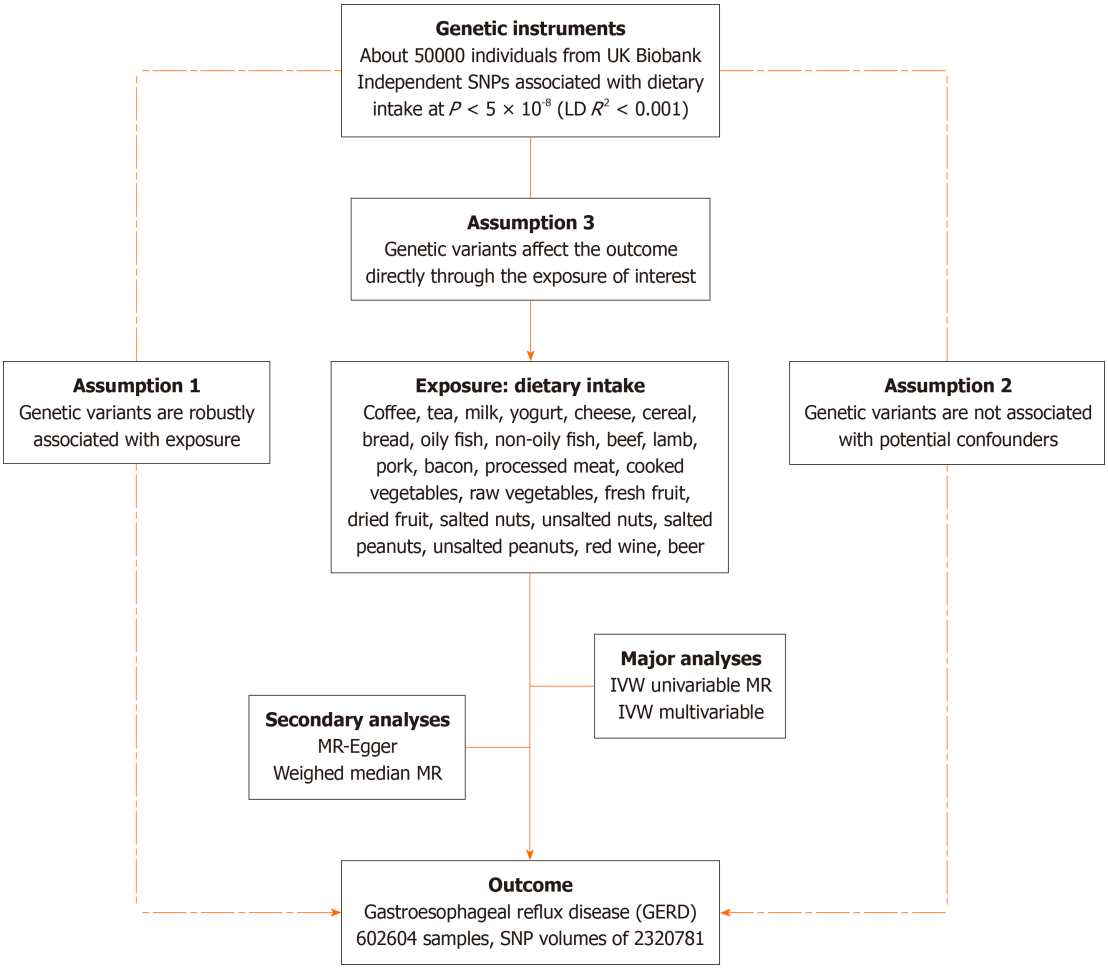


**Figure 1 Overview of mendelian randomization rationale, design, and procedures.** UVMR: Univariate mendelian randomization; MVMR: Multivariate Mendelian randomization; SNPs: Single nucleotide polymorphisms; IVW: Inverse variance weighted; LD: Linkage disequilibrium; UK: United Kingdom.

(OR 0.46; 95%CI: 0.39-0.55; $P = 3.73 \times 10^{-19}$), bread intake (OR, 0.72; 95%CI: 0.56-0.92; $P = 0.0009$), and cereal intake (OR 0.45; 95%CI: 0.36-0.57; $P = 2.07 \times 10^{-11}$) were negatively associated with the risk of GERD. There was a suggestive association for genetically predicted coffee intake (OR per one SD increase, 1.22, 95%CI,:1.03-1.44; $P = 0.019$) (Figure 2). This study also found that tea intake, milk intake, yogurt intake, oily fish intake, beef intake, lamb intake, bacon intake, processed meat intake, cooked vegetable intake, raw vegetable intake, fresh fruit intake, salted nuts intake, unsalted nuts intake, salted peanuts intake, unsalted peanuts intake was not associated with GERD (Figure 2). Table 1 displays the outcomes of three Mendelian methods. The scatter plots of dietary intake on GERD are shown in Supplementary Figures R1-16.

The estimates from other MR methods, including WM and MR-Egger, consistently supported the causal inferences. Furthermore, there is no causal relationship between other dietary intake and GERD. In sensitivity analyses, the MR-PRESSO Distortion Test found outliers in the 16 dietary intakes (Supplementary Table 2-17). After excluding outliers, the nominal association between dietary intakes and GERD remained consistent. An analysis of the relationship between beef intake and GERD showed evidence of horizontal pleiotropy ($P$ for MR-Egger intercept < 0.05) (Table 2). Leave-one-out analysis further supported that any single SNP did not drive the causalities (Supplementary Figures H1-16). Additionally, the funnel plot results indicated a symmetrical distribution of causal association effects when using SNPs individually as instrumental variables, and no potential bias was detected (Supplementary Figures S1-16). The forest plot also demonstrated the causal effect of each SNP on the risk of GERD (Supplementary Figures T1-16).

### *MVMR analysis*

To determine whether the nine dietary intake directly or through common GERD risk factors affect GERD risk, we conducted MVMR analysis. MVMR analysis was performed to adjust for BMI, MDD, smoking, and alcohol drinking in the analysis of GERD. The effect of genetically predicted dried fruit intake, red wine intake, cheese intake, and cereal intake on GERD remained after adjusting for BMI, MDD, smoking, and alcohol drinking. However, the association between genetic predisposition toward Pork intake and GERD was attenuated with adjustment of alcohol drinking. Genetically predicted beer intake was not associated with GERD in the MVMR analysis adjusting for MDD and smoking, respectively. In addition, non-oily fish intake was unrelated to GERD after adjusting to BMI and alcohol drinking separately. The association of bread intake on GERD didn't remain statistically significant after multivariable adjustment for BMI. Notably, after adjustment for BMI, coffee income showed an inverse association with GERD. However, after adjusting for

**Table 2 Heterogeneity and pleiotropy evaluations for genetically causal associations of 24 dietary intake with gastroesophageal reflux disease risk**

| Dietary intake | No. SNPs | Heterogeneity | | Pleiotropy | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Q-MR Egger | Q-IVW | P-MR Egger | P-IVW | Intercept | SE | *P* value | MRPRESSO global test *P* |
| Pork intake | 9 | 10.80 | 14.92 | 0.148 | 0.061 | -0.028 | 0.018 | 0.146 | 0.091 |
| Bacon intake | 0 | NA | NA | NA | NA | NA | NA | NA | NA |
| Processed meat intake | 12 | 22.74 | 25.39 | 0.012 | 0.008 | 0.023 | 0.022 | 0.306 | 0.01 |
| Cooked vegetable intake | 9 | 9.61 | 9.86 | 0.212 | 0.275 | 0.036 | 0.032 | 0.242 | 0.314 |
| Salad / raw vegetable intake | 10 | 7.800 | 9.26 | 0.453 | 0.414 | -0.011 | 0.009 | 0.262 | 0.39 |
| Fresh fruit intake | 37 | 119.23 | 124.00 | 4.05E-11 | 1.35E-11 | -0.007 | 0.006 | 0.245 | < 0.001 |
| Dried fruit intake | 26 | 66.08 | 69.47 | 8.43E-06 | 4.61E-06 | 0.012 | 0.011 | 0.278 | < 0.001 |
| Salted nuts intake | 1 | NA | NA | NA | NA | NA | NA | NA | NA |
| Unsalted nuts intake | 0 | NA | NA | NA | NA | NA | NA | NA | NA |
| Salted peanuts intake | 0 | NA | NA | NA | NA | NA | NA | NA | NA |
| Unsalted peanuts intake | 1 | NA | NA | NA | NA | NA | NA | NA | NA |
| Average weekly red wine intake | 12 | 24.28 | 24.28 | 0.007 | 0.012 | -0.001 | 0.016 | 0.974 | 0.043 |
| Average weekly beer plus cider intake | 11 | 12.74 | 13.36 | 0.175 | 0.204 | -0.008 | 0.012 | 0.525 | 0.32 |
| Coffee intake | 26 | 43.08 | 45.59 | 0.010 | 0.007 | -0.003 | 0.003 | 0.249 | 0.008 |
| Tea intake | 28 | 52.56 | 55.47 | 0.002 | 0.001 | -0.004 | 0.003 | 0.241 | 0.002 |
| Milk intake | 2 | NA | NA | NA | NA | NA | NA | NA | NA |
| Yogurt intake | 1 | NA | NA | NA | NA | NA | NA | NA | NA |
| Cheese intake | 38 | 80.85 | 84.39 | 2.70E-05 | 1.45E-05 | -0.009 | 0.007 | 0.217 | < 0.001 |
| Cereal intake | 27 | 60.22 | 60.77 | 9.74E-05 | 1.32E-04 | -0.004 | 0.007 | 0.638 | 0.003 |
| Non-oily fish intake | 5 | 4.17 | 4.86 | 0.244 | 0.302 | -0.018 | 0.026 | 0.531 | 0.376 |
| Oily fish intake | 37 | 56.19 | 57.51 | 0.013 | 0.013 | 0.004 | 0.005 | 0.369 | 0.015 |
| Lamb intake | 0 | NA | NA | NA | NA | NA | NA | NA | NA |
| Beef intake | 19 | 4.43 | 11.58 | 0.619 | 0.115 | 0.031 | 0.012 | 0.037 | 0.138 |
| Bread intake | 7 | 42.02 | 42.04 | 0.001 | 0.001 | 0.001 | 0.007 | 0.928 | 0.002 |

SNPs: Single nucleotide polymorphisms; IVW: Inverse variance weighted; SE: Standard error.

all four factors, there was no longer a suggestive association between coffee intake and GERD. The results of MVMR are presented in Figure 3. The complementary MVMR analysis results of the causal effects of dietary intake on GERD are shown in Supplementary Table 18.

## DISCUSSION

This MR study found that higher genetically predicted pork intake, beer intake, and non-oily fish intake were associated with an increased risk of GERD. Moreover, we found that dried fruit, red wine, cheese, bread, and cereal have a protective effect against gastroesophageal reflux. Higher genetically forecasted coffee intake was suggestively associated with GERD. In addition, after adjusting for BMI, MDD, smoking, and alcohol consumption, the effects of dried fruits, red wine, cheese, and cereal on GERD still exist.

For dried fruit and GERD, a retrospective study from Maekita T found that daily intake of dried Japanese apricots helped improve GERD symptoms[34]. However, an animal model study found that consuming dried fruits had no effect on the cellular antioxidant status in rats with reflux-induced esophagitis[35]. Our study found a significant protective effect of dried fruits against GERD after adjusting for BMI, MDD, smoking, and alcohol drinking. This strongly indicates that this protective effect is at least unrelated to the common risk factors of GERD. Dried fruits contain a variety of

| Dietary intake | No. SNPs | Method | Odds ratio (95%CI) | *P* value |
|---|---|---|---|---|
| Pork intake | 9 | IVW | 2.83 (1.76,4.55) | < 0.001 |
| Processed meat intake | 12 | IVW | 0.96 (0.69,1.33) | 0.794 |
| Cooked vegetable intake | 9 | IVW | 1.87 (1.28,2.75) | 0.001 |
| Salad/raw vegetable intake | 10 | IVW | 0.84 (0.60,1.18) | 0.309 |
| Fresh fruit intake | 37 | IVW | 0.79 (0.56,1.11) | 0.178 |
| Dried fruit intake | 26 | IVW | 0.37 (0.27,0.50) | < 0.001 |
| Average weekly red wine intake | 12 | IVW | 0.34 (0.25,0.47) | < 0.001 |
| Average weekly beer plus cider intake | 11 | IVW | 2.70 (2.00,3.64) | < 0.001 |
| Coffee intake | 26 | IVW | 1.22 (1.03,1.44) | 0.019 |
| Tea intake | 28 | IVW | 1.12 (0.97,1.29) | 0.119 |
| Cheese intake | 38 | IVW | 0.46 (0.39,0.55) | < 0.001 |
| Cereal intake | 27 | IVW | 0.45 (0.36,0.57) | < 0.001 |
| Non-oily fish intake | 5 | IVW | 2.41 (1.49,3.91) | < 0.001 |
| Oily fish intake | 37 | IVW | 0.88 (0.76,1.03) | 0.122 |
| Beef intake | 19 | IVW | 0.72 (0.56,0.92) | 0.001 |
| Bread intake | 7 | IVW | 0.77(0.49,1.22) | 0.271 |


**Figure 2 Univariate mendelian randomization analysis for genetically causal associations of dietary intakes with gastroesophageal reflux disease risk.** SNPs: Single nucleotide polymorphisms; IVW: Inverse variance weighted.

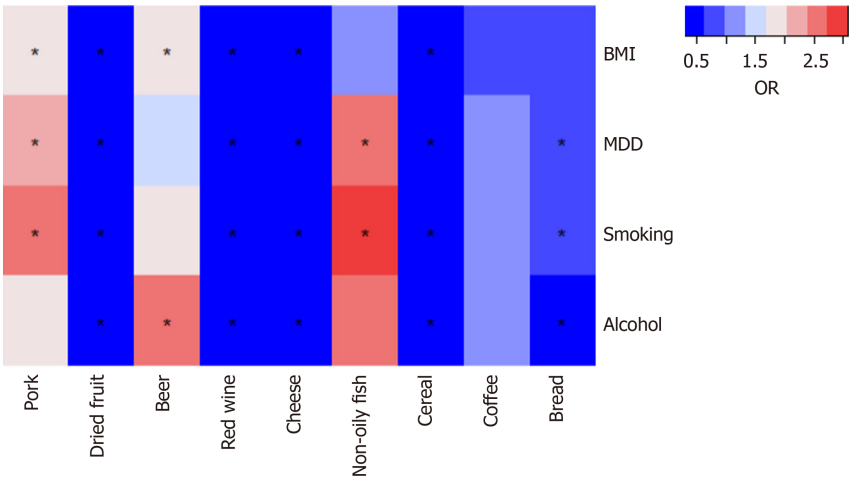


**Figure 3 Associations between nine dietary intakes and gastroesophageal reflux disease after adjusting for each of the four risk factors.** Asterisk represents a significant correlation. OR: Odds ratio; BMI: Body mass index; MDD: Major depressive disorder.

macronutrients, micronutrients, and health-promoting bioactive. These compounds exhibit antioxidant and free radical scavenging activities, which help improve digestive tract disorders[36]. A meta-analysis suggests that dried fruits have preventive value against certain cancers, particularly cancers of the digestive system[37]. Further research is needed on how dried fruits can reduce the increased risk of GERD.

Between alcohol consumption and GERD, the MR study by Yuan *et al*[38] found that genetic prediction of alcohol consumption was not causally associated with the incidence of GERD. The finding may be due to inadequate statistical power or a possible association between heavy alcohol consumption or abuse and GERD. Nevertheless, another observational study suggested red wine does not reduce lower Esophageal sphincter pressure and Retards Gastric Motility[39]. Our MR study found that red wine intake helps reduce the risk of GERD development. This may be related to the lower ethanol content in red wine. Several observational studies have shown that beer causes GERD, consistent with our findings[40,41]. It is worth noting that in multivariate MR, the association between beer intake and GERD became insignificant, which may be explained by the synergistic effect between alcohol and smoking or MDD.

Fermented dairy products are known to be nutritious, high in probiotics, and rich in calcium-quality proteins, bioactive molecules, vitamins, and other ingredients[42]. Their availability can be increased due to the fermentation process[43]. A retrospective study suggests high consumption of milk products and dietary fat is associated with severe GERD symptoms[44]. However, another RCT showed that dairy products do not affect GERD, heartburn, or acid reflux symptoms [45]. The contradictory findings may be due to inherent heterogeneity between studies and residual confounding in ob-

servational studies. Our study found that the MR method is highly effective in mitigating the impact of residual confounding. And our findings indicated a significant correlation between consumption of cheese and heightened susceptibility to GERD. The probiotics found in cheese provide numerous health benefits to the body, including reducing pathological changes, stimulating mucosal immunity, interacting with inflammatory mediators, and strengthening the immune system[46].

Dietary fiber, particularly from cereal sources, has been found to be linked to a lower risk of adenocarcinoma in the esophagus and gastric cardia[47]. A case-control study from M Nilsson showed that the risk of reflux was significantly reduced as the amount of dietary fiber increased[48]. This is highly consistent with our findings. In addition, cereal intake played an independent and significant role after excluding the effects of risk factors. The biological mechanism underlying this discovery remains a matter of speculation. Dietary fibers scavenge nitrites in the stomach, reducing availability for non-enzymatic nitric oxide synthesis. This may potentially lower the concentration of nitric oxide in the gastro-esophageal junction, thereby helping to prevent reflux[49]. The protective effect of bread against GERD demonstrated in our study should be similar to the mechanism of cereal intake. Notably, a cross-sectional data on the dietary fiber content of the main types of bread consumed showed a dose-dependent reduction in the risk of reflux symptoms with increasing fiber content[50]. Besides, MVMR analysis further revealed that the protective effect of bread intake on GERD might be driven by BMI. MR study from Yuan *et al*[38] suggests that a higher genetically predicted BMI is associated with an increased risk of GERD. So, we hypothesized that bread intake reduces GERD risk by controlling obesity.

Our study found pork intake increased GERD risk. This is consistent with the results of several observational studies [51,52]. Further MVMR analysis indicated that the harmful effect of pork intake on GERD might be driven by alcohol assumption. Red meat is rich in hemoglobin and iron, which can catalytically oxidize and cause oxidative stress damage to the body[53]. Then, this can cause wear on the esophageal sphincter and exacerbate reflux. Similar to pork intake, our study found that non-oily fish intake enhances the risk of GERD development. A cross-sectional study in China found that the prevalence of GERD was increased by excessive non-oily fish intake[54]. Additionally, BMI and alcoholic drinking drive the harmful effects of non-oily fish intake on GERD.

There are several observational studies on the effects of coffee on GERD, and their evidence results are inconsistent[55-57]. Hence, there is a lack of high-level evidence to confirm the association. Our MR study suggested that coffee intake has a suggestive association with GERD before adjusting for four risk factors. However, after adjusting for all four elements, there was no longer a suggestive association between coffee intake and GERD. A cross-sectional study found that the effects of coffee exposure were significantly different when analyzed univariately and multivariate, primarily because of positive confounding by smoking[58]. Another MR study from Yuan *et al*[38] found that coffee consumption was associated with an increased risk of GERD symptoms. The confounding factors of GERD may lead to this situation without adjustment. It is worth noting that after adjusting for BMI, coffee intake has a protective effect against GERD. The effect of BMI on the association between coffee intake and GERD deserves further investigation.

One of the advantages of this study is that it comprehensively characterizes the relationship between dietary intakes and GERD through MR analysis. Second, our analysis is superior to previous studies as we used pooled data from GWAS with larger sample sizes and more SNPs, avoiding biases such as unobserved confounding, misclassification, and reverse causation. Third, we also adjusted for the effect of some risk factors for GERD, further validating the second hypothesis of MR.

This study has some noticeable drawbacks. Firstly, horizontal pleiotropy is a major limitation in MR design, where SNPs affect outcomes through alternative pathways rather than exposure[31]. We used the MR-Egger intercept and MRPRESSO global test to detect pleiotropy. After excluding outliers, there was still horizontal pleiotropy for several phenotypes in the MRPRESSO global test. However, we found no evidence of horizontal pleiotropy in the MR-Egger analysis, which is consistent with the results of several sensitivity analyses. Secondly, this study only covered European populations, which may limit its applicability to other ethnic groups. Finally, we found different causal effect estimates for the MR-Egger and other MR methods. Due to its calculation of horizontal pleiotropy, it has weaker statistical efficacy than other MR methods. Our primary approach is to rely on the findings from the IVW method.

To our knowledge, there have been numerous MR studies investigating the risk factors and protective factors of GERD [59-61]. However, there are few studies on the intake of meat, staple foods, fruits, vegetables, and beverages. GERD has a severe impact on the quality of life of patients and lacks an effective treatment. Our conclusions can help clinicians to educate patients about their health and to develop suitable recipes for patients with GERD. For GERD patients, dietary changes can be made to alleviate reflux symptoms and reduce financial burdens.

## CONCLUSION

This study revealed the protective effects of dry fruit intake, red wine intake, cheese intake, bread intake, and grain intake on GERD through genetic prediction, as well as the harmful effects of pork intake, beer intake, and non-oily fish intake on GERD. Furthermore, the effect of genetically predicted dried fruit, red wine, cheese, and cereal on GERD remained after adjusting for BMI, MDD, smoking, and alcohol drinking. Higher genetically forecasted coffee intake was suggestively associated with GERD. However, after adjusting for all four factors, there was no longer a suggestive association between coffee intake and GERD. This study also found that tea intake, milk intake, yogurt intake, oily fish intake, beef intake, lamb intake, bacon intake, processed meat intake, cooked vegetable intake, raw vegetable intake, fresh fruit intake, salted nuts intake, unsalted nuts intake, salted peanuts intake, unsalted peanuts intake were not associated with GERD.

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## FOOTNOTES

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**Institutional review board statement:** The study used public genome-wide association study statistics and did not collect new human data. Hence, ethical approval was not required by the ethics committee of the Hospital of Chengdu University of Traditional Chinese Medicine.

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CASE REPORT

# Clinical review and literature analysis of hepatic epithelioid angiomyolipoma in alcoholic cirrhosis: A case report

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## Abstract

*BACKGROUND*

Hepatic epithelioid angiomyolipoma (HEA) has a low incidence and both clinical manifestations and imaging lack specificity. Thus, it is easy to misdiagnose HEA as other tumors of the liver, especially in the presence of liver diseases such as hepatitis cirrhosis. This article reviewed the diagnosis and treatment of a patient with HEA and alcoholic cirrhosis, and analyzed the literature, in order to improve the understanding of this disease.

*CASE SUMMARY*

A 67-year-old male patient with a history of alcoholic cirrhosis was admitted due to the discovery of a space-occupying lesion in the liver. Based on the patient's history, laboratory examinations, and imaging examinations, a malignant liver tumor was considered and laparoscopic partial hepatectomy was performed. Postoperative pathology showed HEA. During outpatient follow-up, the patient showed no sign of recurrence.

*CONCLUSION*

HEA is difficult to make a definite diagnosis before surgery. HEA has the potential for malignant degeneration. If conditions permit, surgical treatment is recommended.

**Key Words:** Hepatic epithelioid angiomyolipoma; Alcoholic cirrhosis; Magnetic resonance imaging; Computed tomography; Immunohistochemistry; Misdiagnose analysis; Case report

**Core Tip:** Hepatic epithelioid angiomyolipoma (HEA) is rare, with no specific clinical and imaging manifestations, has the potential of malignancy. In the presence of liver diseases such as cirrhosis, it is easily misdiagnosed as a malignant liver tumor. Characteristic imaging may help to diagnose HEA, but the diagnosis must be made by needle biopsy or histopathology. If conditions allow, active surgical treatment is recommended.

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## INTRODUCTION

Hepatitis cirrhosis is an obvious risk factor for the development of malignant liver tumors. The common cause of liver cirrhosis is hepatitis B virus infection and alcoholic liver disease. Hepatic epithelioid angiomyolipoma (HEA) is a special subtype of liver angiomyolipoma. Unlike hepatic angiomyolipoma, HEA contains little or no fat. Its low incidence combined with nonspecific clinical manifestations and atypical imaging findings make diagnosis difficult. Therefore, it is easily misdiagnosed as other liver tumors with a high rate of 40.34% (165/409), especially hepatocellular carcinoma which was wrongly diagnosed in 71 of 409 cases[1]. HEA has the potential for malignant degeneration, and some patients have a poor prognosis[2]. Epithelioid angiomyolipoma of the liver in the background of cirrhosis is a rare clinical diagnosis and easily misdiagnosed as hepatoma. We here report a case of HEA with alcoholic cirrhosis at Lishui Municipal Central Hospital, in the hope of providing a reference for future diagnosis and treatment of such cases.

## CASE PRESENTATION

### *Chief complaints*

A 67-year-old male patient was admitted to hospital with a liver mass found more than 2 months ago.

### *History of present illness*

Three months ago, the patient underwent treatment for abnormal liver function at a nearby medical facility. No associated abdominal pain, diarrhea, or melena was observed. Ultrasound revealed a low echo mass in the left liver. A computed tomography (CT) examination indicated that liver section II was in a circular low-density lesion. Considering the possibility of hepatocellular carcinoma, magnetic resonance imaging (MRI) enhancement was recommended.

### *History of past illness*

The patient was hospitalized 2 years ago due to trauma. During hospitalization an abdominal CT scan showed a low-density lesion in the left intrahepatic lobe. Further examinations were recommended but the patient declined due to personal reasons. A history of other infectious diseases such as viral hepatitis was denied. The patient had a history of alcohol consumption for more than 40 years.

### *Physical examination*

The patient's temperature was 36.8 °C, heart rate was 68 beats per minute, and blood pressure was 137/71 mmHg. There were no obvious positive signs during physical examination.

### *Laboratory examinations*

Laboratory examinations showed that the patient's platelet count was 87 × $10^9$/L (reference range, 125-350 × $10^9$/L), hepatitis B core antibody was positive, glutamic oxaloacetic transaminase was 42 U/L (reference range, 7-40 U/L), glutamyltransferase was 175 U/L (reference range, 7-45 U/L), alkaline phosphatase was 150 U/L (reference range, 50-135 U/L), total bile acid was 57.0 μmol/L (reference range, < 23 μmol/L), and tumor indicators were negative.

### *Imaging examinations*

Two years previously, a CT scan suggested a low density lesion in the left intrahepatic lobe, approximately 1.2 cm × 1.0 cm in size. It was significantly enhanced in the arteriovenous phase of the enhanced scan and significantly decreased in the delayed phase, which was lower than the surrounding liver tissue (Figure 1). Two months ago, ultrasound findings at a local hospital showed a hypoechoic mass in the left liver. CT examination indicated that the liver was abnormal, the envelope was smooth, the liver fissure was widened, and liver section II showed a circular low density lesion. The boundary was clear, approximately 25.5 mm × 26.5 mm in size, and the CT value was about 35 HU. Following contrast

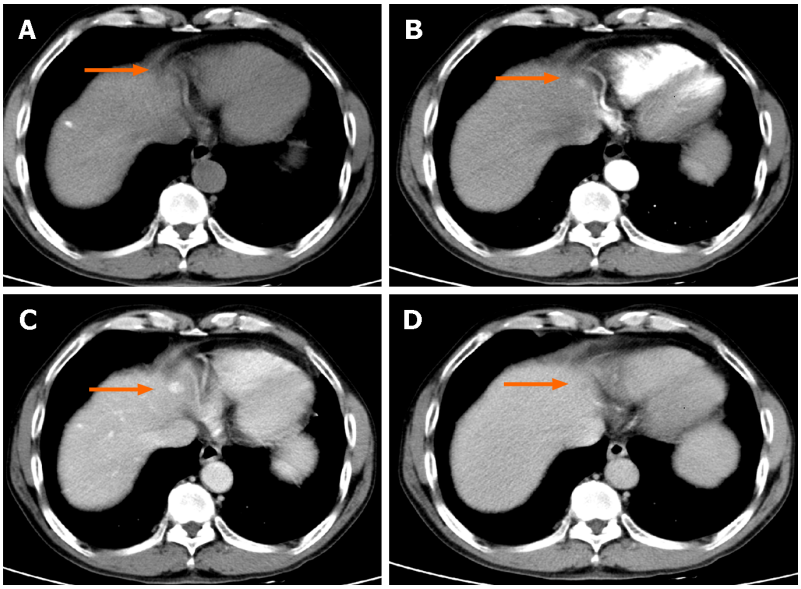


**Figure 1 Abdominal computed tomography.** A low-density nodular lesion near the parietal diaphragm of the left inner lobe of the liver, which was significantly enhanced in the arteriovenous phase of the enhanced scanning, and decreased in the delayed phase, lower than the surrounding liver tissue (the arrow shows the lesion). A: Plain computed tomography scan; B: The arterial phase of the enhanced scan; C: The portal vein phase; D: Delayed phase.

injection, the three-level scan showed that the arterial stage was enhanced, the vein lesions were significantly enhanced, and the density of the balanced period was lower than the normal liver. Considering the possibility of hepatocellular carcinoma, MRI was recommended (Figure 2).

### *Further diagnostic work-up*

MRI showed that the contour of the liver was not uniform, the proportion of the liver lobe was abnormal and the liver cleft was widened. The mass located near the diaphragmatic roof of the left liver lobe was approximately 2.7 cm × 2.8 cm, and showed hyperintensity on T2-weighted imaging (T2WI) and hypointensity on T1-weighted imaging (T1WI). Diffusion-weighted imaging (DWI) showed a hyperintense mass and the corresponding apparent diffusion coefficient (ADC) map showed an increased signal intensity in the mass. Enhanced MRI revealed that the mass was enhanced in the arterial phase and slightly weaker in the delayed phase with a high signal relative to the surrounding liver, suggesting a rich blood supply and cirrhotic nodules (Figure 3).

## FINAL DIAGNOSIS

In middle-aged and elderly male patients with a history of alcoholic cirrhosis, who are hepatitis B core antibody positive, have a gradual increase in left liver rich blood supply to the lesion, and normal tumor serological indicators, a malignant liver tumor cannot be ruled out. Thus, the final diagnosis in this patient was a liver occupying lesion and alcoholic cirrhosis.

## TREATMENT

In patients with liver lesions located in the leaf of the left liver, and no surgical contraindications, treatment is feasible. It was thought that the liver mass in this patient was malignant, therefore, laparoscopic resection of the liver tumor was performed.

## OUTCOME AND FOLLOW-UP

During the operation, free ascites were found in the abdominal cavity, the liver showed nodular cirrhosis, and the tumor was successfully resected. The tumor was located in the left inner lobe of the liver, protruding from the liver surface and was approximately 2.5 cm × 3.0 cm in size, with clear boundaries. Analysis of the mass showed that the tumor envelope was complete and the boundary between the tumor and the surrounding liver tissue was clear. The surface of the liver section was reddish-brown (Figure 4). Microscopy revealed that the tumor under low-power showed a nest-like distribution, a clear boundary, interstroma rich in blood vessels, scattered lymphocyte and plasma cell infiltration, a multinucleated giant cell reaction and local nuclear red cells. Under high-power, some of the tumor cells were round or oval, with

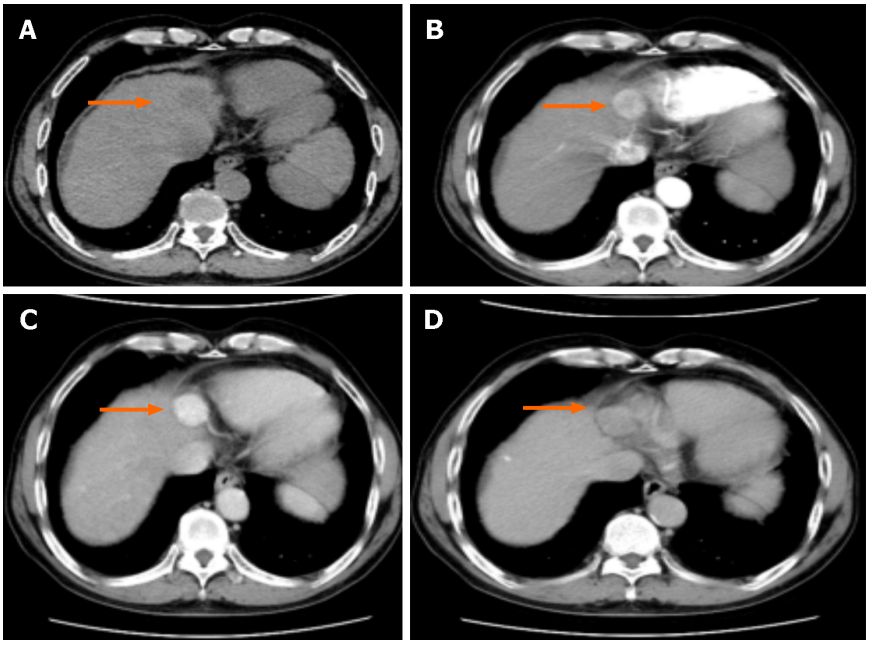


**Figure 2 Computed tomography of the upper abdomen before the operation.** Round low-density foci can be seen in the liver II segment with clear boundaries, enhanced foci can be seen in the arterial phase, significantly enhanced foci can be seen in the portal vein phase, and density in the equilibrium phase is lower than normal liver parenchyma (the arrow shows the lesion). A: Plain computed tomography scan; B: The arterial phase of the enhanced scan; C: The portal vein phase; D: Delayed phase.

large cell bodies, an eosinophilic cytoplasm, large nuclei, and distinct nucleoli. Some tumor cells were fusiform and showed mitosis (Figure 5A and B). Immunohistochemistry revealed the following: S-100-, melanoma marker monoclonal antibody (HMB45) (locally scattered +), MelanA-, smooth muscle cell markers (SMA) locally+, Ki-67 (10%), and anti-human arginase (ARG)-1- (Figure 5B-D). When the immunohistochemistry results were combined with the other test results, the final diagnosis was HEA. The patient was discharged 11 d after surgery. At outpatient follow-up, the patient showed no signs of recurrence.

## DISCUSSION

Long-term heavy drinking can lead to alcoholic cirrhosis. The cumulative annual risk of liver cancer in patients with alcoholic cirrhosis is approximately 1%-1.5%, and the 5-year cumulative risk is approximately 8%[3]. Epithelioid angiomyolipoma is a member of the perivascular epithelioid cell tumors. It is common in the kidneys and rare in the liver. HEA accounts for 0.4% of primary tumors of the liver[4], and is more common in young and middle-aged women, with a male to female ratio of 1:4.84 and a median onset age of 44 years[1]. There are no specific correlations with hepatitis, cirrhosis, and other underlying diseases. The clinical symptoms of HEA are not typical, most of these tumors are found during physical examination or examinations for other diseases. A few patients present with abdominal pain. Alpha-fetoprotein and other tumor indicators are usually negative[5]. In this case, the patient had been drinking alcohol for a long time and had alcoholic cirrhosis without obvious clinical symptoms. He was admitted to the hospital due to a liver occupying mass. The initial examination indicated liver nodules with a rich blood supply. HEA was not considered before surgery. The patient was shown to have reduced platelets, and increased glutamic oxaloacetic transaminase, glutamyl aminotransferase, alkaline phosphatase, and total bile acid, which may have been related to alcoholic cirrhosis.

Studies have shown that the central vessel sign and the early venous drainage sign are characteristic images of HEA[6, 7]. In addition, the accumulation of $^{18}$F-fluorodeoxyglucose on positron emission tomography/CT can provide clues for diagnosis[8]. As HEA lacks fat, it is difficult to distinguish from other liver tumors on MRI. Furthermore, when its enhanced appearance overlaps with hepatocellular carcinoma, the distinction between the two is particularly difficult[9]. The imaging findings of HEA are mostly single lesions, visible in both the left and right liver. The lesions are circular or oval in shape, with clear boundaries and a false capsule. The CT scan can show a low-density shadow, enhancement of the arterial stage is obvious, and the enhanced shadow of the internal and surrounding vascular enhancement, the portal phase and the delayed phase are mostly seen on the "fast forward and slow out" mode. T1WI shows a low signal or a low hybrid signal, T2WI shows a slightly high signal or mixed signal with bleeding and an uneven signal, and DWI reveals a mostly high signal or slightly high signal. Most ADC signals are equal-signal, mixed high-low signal in some cases, and slightly low signal in rare cases. The MRI enhancement patterns are usually shown as fast wash-in and slow wash-out, and delayed enhancement[10]. In our patient, HEA presented as a round low-density lesion with clear boundaries on plain CT scan, an enhanced vascular shadow was observed around the lesion, and CT enhancement demonstrated a fast wash-in and slow wash-out. MRI showed a low signal on T1WI, a slightly high signal on T2WI, a high signal on DWI, an

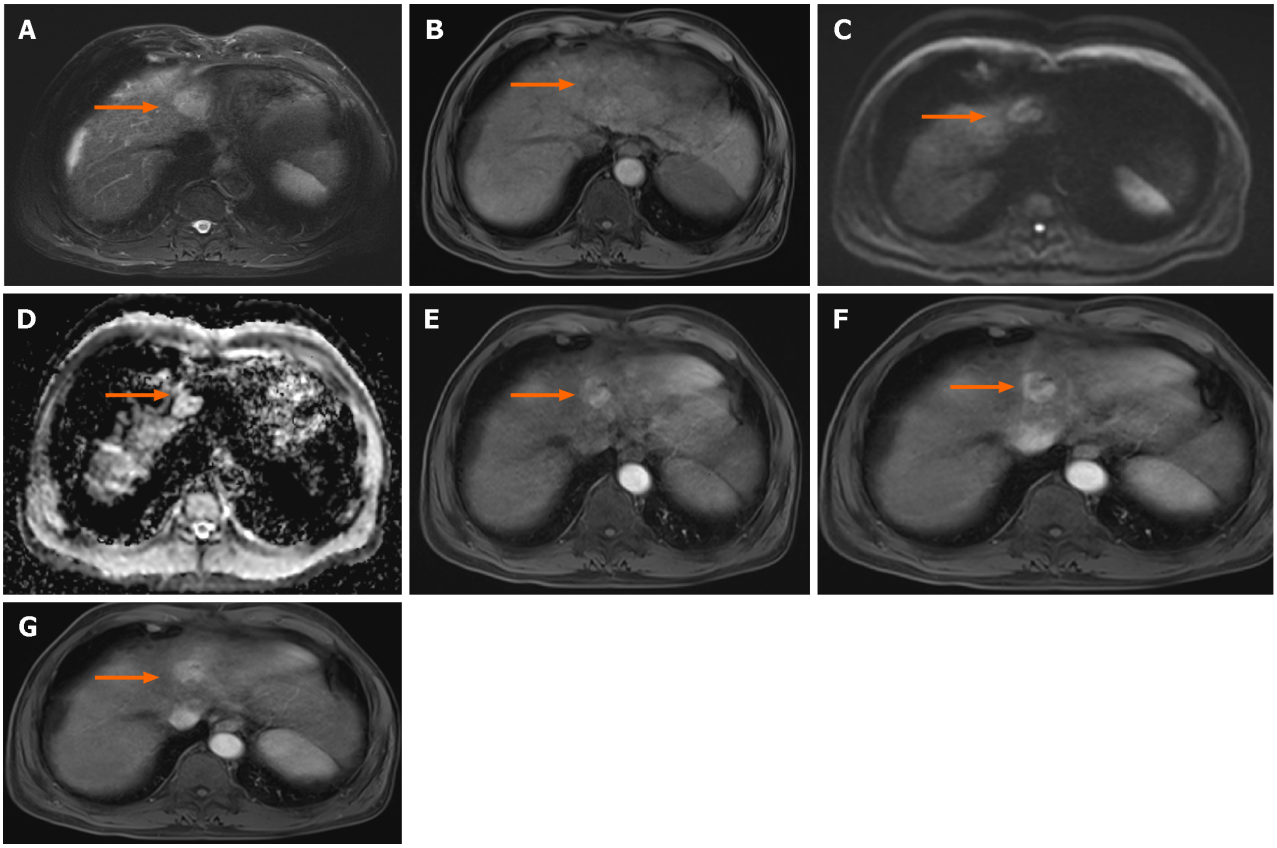


**Figure 3 Magnetic resonance imaging of the upper abdomen before the operation.** A sharp focus of abnormal signals was observed near the roof of the diaphragm of the left lobe of the liver, with a low signal in T1-weighted imaging (T1WI), a slightly high signal in T2-weighted imaging (T2WI), a high signal in diffusion-weighted imaging (DWI), and an increased in the apparent diffusion coefficient (ADC) value.The inproved scan showed obvious enhancement in the arterial phase, and slightly decreased local enhancement in the later period (the arrow shows the lesion). A: T1WI; B: T2WI; C: DWI; D: ADC; E: The arterial phase of the enhanced scan; F: The portal vein phase; G: Delayed phase.

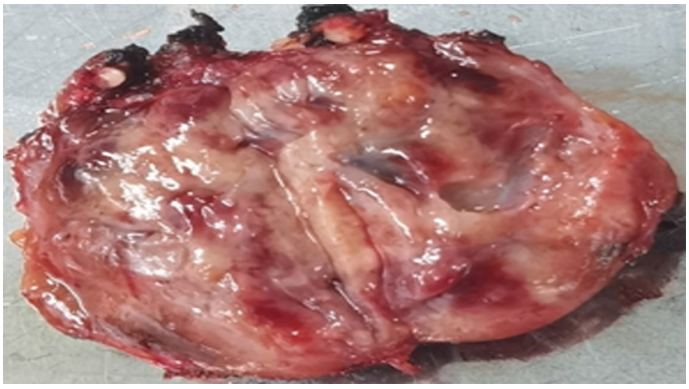

**Figure 4 Gross specimen after operation.** The tumor capsule was complete, the cut surface was reddish brown.

increased ADC value, and enhancement in fast wash-in and slow wash-out.

The tumor morphology of hepatic blood vessels are often circular or oval, with reddish brown slices, no obvious leaf shape, clear boundaries, and some lesions can have a false film. Immunohistochemistry is one of the most important diagnostic methods for HEA. The tumor morphology of liver epithelioid angiomyolipoma is regular, usually circular or elliptic, with a reddish brown section, no obvious lobes, clear boundary, and a pseudocapsule in some lesions. HEA is characterized primarily by the positive expression of melanocyte markers (HMB45, Melan-A) and SMA, with negative epithelial markers (S-100, ARG-1, *etc.*), among which HMB45 positive expression is the most sensitive[11]. Ki-67 is generally low (< 1%-15%), and Ki-67 is highly expressed in malignancy[12]. The immunohistochemistry findings in this patient were HMB45 local +, SMA local +, S-100-, ARG-1-, and Ki-67 (10%), which was consistent with reports in the relevant literature. HEA has an abundant blood supply, which gradually enlarges the tumor, and has the risk of malignancy; the malignancy rate is 3.9%[12]. Most clinicians advocate surgical treatment.

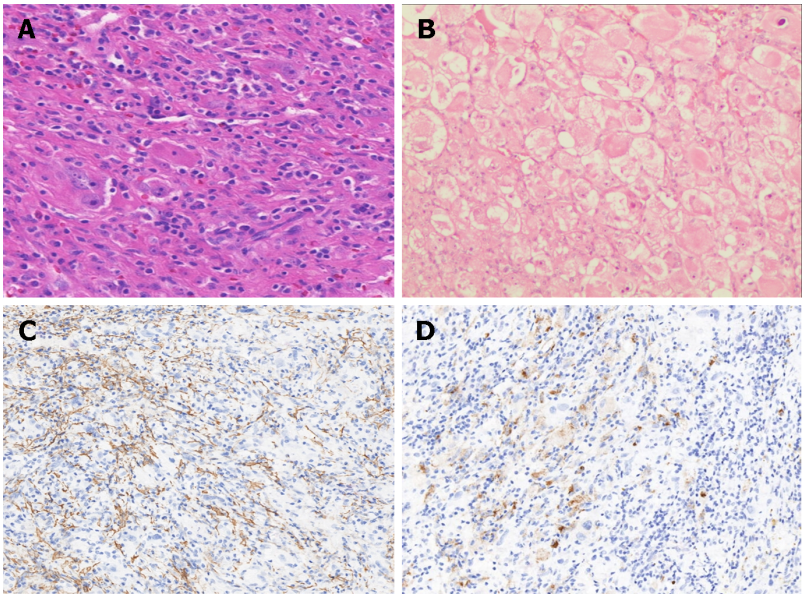


**Figure 5 Postoperative pathology.** A: Tumor cells showed nest-like distribution, clear boundary with liver tissue, rich blood vessels interstroma, scattered lymphocyte and plasma cell infiltration, multinucleated giant cell reaction, and local nuclear red cells (hematoxylin and eosin staining, × 20); B: The tumor cells were round or oval, with large cell bodies, eosinophilic cytoplasm, large nuclei, and distinct nucleoli. Some tumor cells are fusiform and mitotic (hematoxylin and eosin staining, × 100); C: Melanoma marker monoclonal antibody (HMB45) (+) I (immunohistochemical staining, × 100); D: Smooth muscle cell markers (+) (immunohistochemical staining, × 100).

## CONCLUSION

HEA lacks specific clinical manifestations, has variable imaging findings, and preoperative diagnosis is difficult. HEA has the potential for malignant transformation. In the presence of liver diseases such as cirrhosis, it is easily misdiagnosed as a malignant liver tumor. Surgical treatment is recommended. Characteristic imaging may help to diagnose HEA, but the diagnosis must be made by needle biopsy or histopathology.

## FOOTNOTES

**Co-corresponding authors:** Xin-Liang Lv and Chao-Yong Tu.

**Author contributions:** Tu CY and Lv XL contributed equally to the manuscript; Tu CY and Lv XL designed the study; Guo JQ completed the first draft of this manuscript and performed the experiments and data collection; Zhang K was involved in data collection; Zhou JH provided pathological findings; Tu CY revised the manuscript. All authors have read and approved the final version of the manuscript.

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CASE REPORT

# Previously undiagnosed Morgagni hernia with bowel perforation detected during repeat screening colonoscopy: A case report

Said Al Alawi, Alan N Barkun, Sara Najmeh

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## Abstract

*BACKGROUND*

Morgagni hernia (MH) is a form of congenital diaphragmatic hernia (CDH) characterized by an incomplete formation of diaphragm, resulting in the protrusion of abdominal organs into the thoracic cavity. The estimated incidence of CDH is between 1 in 2000 and 1 in 5000 live births, although the true incidence is unknown. MH typically presents in childhood and can be diagnosed either prenatally or postnatally. However, it can also be asymptomatic and carry the risk of developing into a life-threatening condition in adulthood.

*CASE SUMMARY*

A 76-year-old female with no history of prior abdominal surgeries presented for an elective colonoscopy for polyp surveillance. During the procedure, when approaching the hepatic flexure, the scope could not be advanced further despite multiple attempts. The patient experienced mild abdominal discomfort, leading to the abortion of the procedure. While in the recovery area, she developed increasing abdominal pains and hypotension. Urgent abdominal imaging revealed herniation of the proximal transverse colon through a MH into the chest with evidence of perforation. The patient underwent laparoscopic urgent colonic resection and primary hernia repair and was discharged uneventfully 2 d later.

*CONCLUSION*

A MH is a rare condition in adults that can present as a life-threatening complication of colonoscopy, even in patients with a history of uneventful colonoscopies. This case highlights the importance of considering congenital and internal hernias when faced with sudden and unexplained difficulties during colonoscopy. If there is a suspicion of MH, the endoscopist should halt the procedure and immediately obtain abdominal imaging to confirm the diagnosis.

**Key Words:** Bowel perforation; Colonoscopy; Adverse event; Congenital diaphragmatic

hernia; Morgagni hernia; Case report



**Core Tip:** A Morgagni hernia (MH), a congenital gap in the diaphragm, may only become evident later in life. Initially small, this defect enlarges over time due to increased intra-abdominal pressure. Although it usually remains asymptomatic, a MH can lead to severe gastrointestinal or pulmonary complications. We describe the case of a previously asymptomatic 76-year-old woman who underwent a routine follow-up colonoscopy. Unexpectedly, the procedure led to a colonic perforation due to a previously undiagnosed large MH. This rare complication emphasizes the need for endoscopists to be vigilant in suspecting and diagnosing potential intra-procedural complications associated with this condition.

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## INTRODUCTION

A Morgagni hernia (MH) is a diaphragmatic malformation of unknown etiology that typically manifests in the neonatal period[1]. It was first described in 1769 by the Italian anatomist Giovanni Morgagni[2]. MHs constitute a minority, approximately 2%-5%, of all congenital diaphragmatic hernias (CDHs) and typically present as either anterior-retrosternal or anterior-peristernal hernias[1-3] (Figure 1). The remaining cases of CDH include Bochdalek hernias, which are characterized by posterolateral diaphragmatic defects, with central defects being rare. These pathologies can be detected prenatally through fetal ultrasonography, which may reveal herniation of the bowel or liver into the thoracic cavity. This screening method has been found to accurately diagnose the condition in 50%-90% of cases[4]. When symptomatic, a MH commonly presents as acute neonatal respiratory distress or gastrointestinal pathology, usually due to obstruction and incarceration of herniated bowel loops. Pulmonary symptoms are likely attributable to intra-thoracic compression of the lungs by herniated abdominal viscera, resulting in disruptions in pulmonary blood flow during development[4]. Neonatal symptoms associated with congenital MHs include respiratory distress, inadequate oxygenation, an excavated abdomen with sternal protrusion, and displacement of heart sounds to the opposite side. The clinical presentation of a MH can occur at various ages, with individuals exhibiting mild respiratory distress or remaining asymptomatic; in the latter scenario, detection often arises during routine medical examinations for unrelated reasons[2,4]. MHs have been associated with other congenital malformations involving different organs[5].

The patient presented for a routine follow-up colonoscopy. She was asymptomatic prior to the procedure, except for long-standing, very rare sporadic abdominal pain that did not interfere with her daily activities. There is limited literature on delayed presentation of MHs with bowel perforation during colonoscopy in asymptomatic adults. This case study highlights an uncommon manifestation of a MH in adults and the importance of being aware of this condition and maintaining a high level of clinical vigilance.

## CASE PRESENTATION

### *Chief complaints*

A 76-year-old woman reported experiencing increasing abdominal pain approximately 30 min after being transferred from the endoscopy room to the recovery area after a difficult aborted colonoscopy.

### *History of present illness*

The patient was previously healthy with no significant comorbidities. She had been referred for an elective outpatient colonoscopy for post-polypectomy surveillance. The most recent colonoscopy, conducted 5 years prior, was normal and had not presented any technical difficulties. During the index colonoscopy, which was conducted with $CO_2$ insufflation after conscious sedation with 50 μg of fentanyl and 1 mg of midazolam intravenously, the scope could no longer be advanced smoothly upon reaching the hepatic flexure (Figure 2) despite multiple trials and changes in position and technique. There was no abdominal wall or inguinal hernia noted on physical exam during the procedure. An internal hernia was suspected, but there was no history of previous surgery or trauma. During this part of the procedure, the patient experienced mild abdominal discomfort, but vitals remained stable. The procedure was aborted, and it was decided to observe the patient in the recovery area for an extended period of time to exclude a potential perforation. After 30 min in the recovery area, the patient developed increased abdominal pain, rated 8 out of 10 in severity, along with new dyspnea. The patient then mentioned for the first time that she had experienced recurrent pains of a similar nature, although not as severe, for several years; these episodes were infrequent, occurring once every 2–3 years.

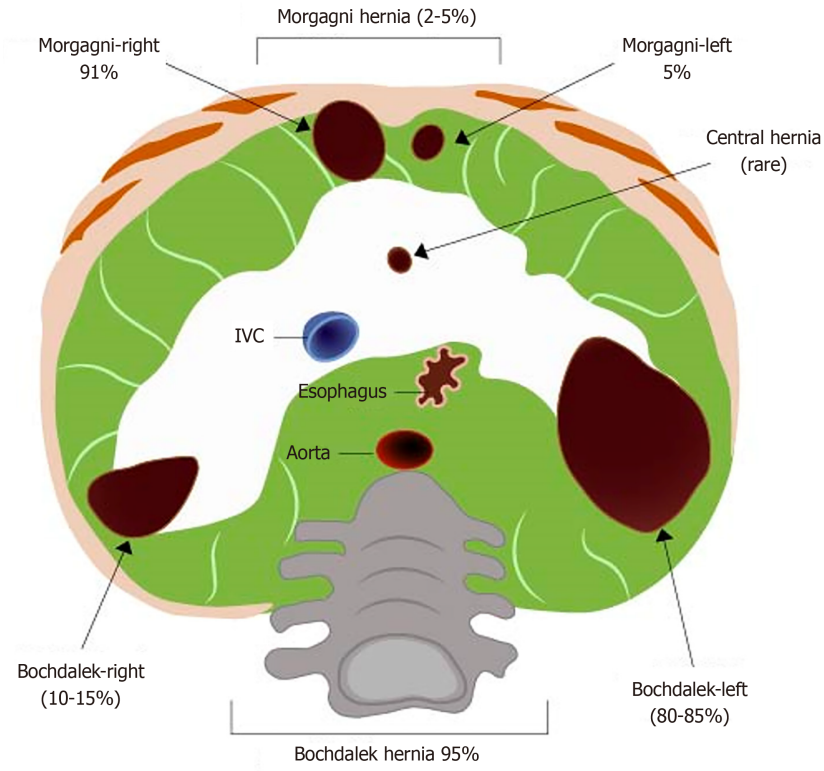


**Figure 1 Sites of congenital diaphragmatic hernia formation.** IVC: Inferior vena cava. Modified from Chandrasekharan *et al*[8].

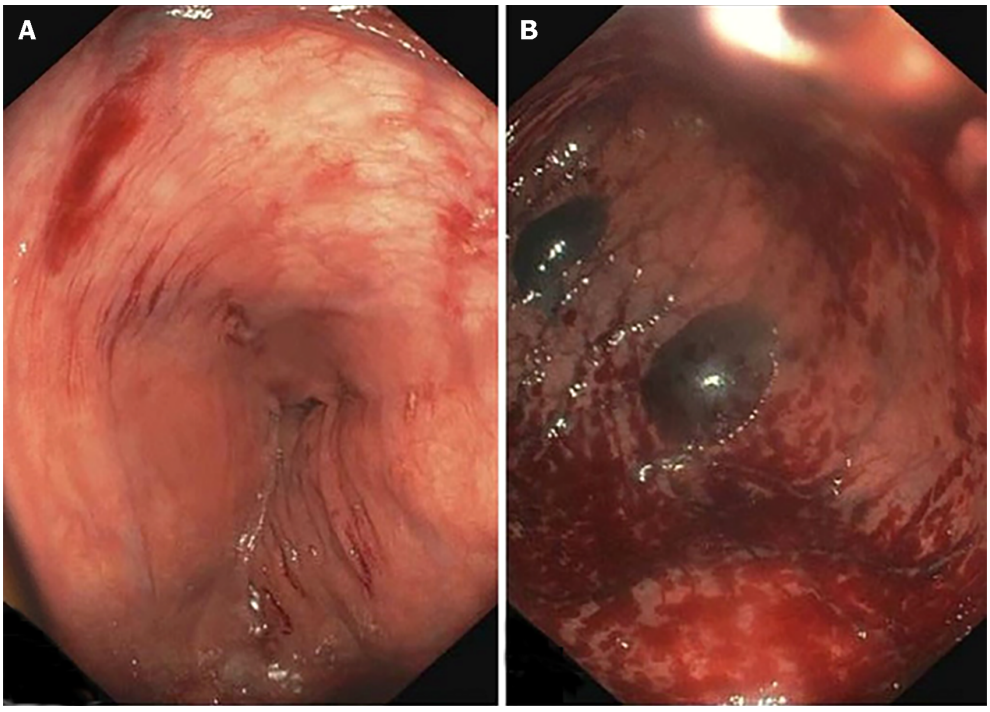


**Figure 2 Colonoscopy appearance of the herniated bowel through Morgagni hernia.** A: Volvulus like appearance; B: Submucosal haemorrhage and evidence of barotrauma.

### *History of past illness*

The patient's medical history included hypertension and a previous transient ischemic attack with no residual neurological deficits. She had undergone three previous colonoscopies. The first, in 1997, was normal. The second, in 2014, revealed a diminutive polyp in the sigmoid colon (tubular adenoma). The most recent colonoscopy, in 2017, showed no abnormalities. In 2002, she also had a sigmoidoscopy and barium enema, both of which were normal.

### *Personal and family history*

Family history was significant for colorectal cancer in her father at the age of 75.

### *Physical examination*

During the episode of abdominal pain, the patient was fully alert and conscious, but appeared uncomfortable and anxious. She exhibited hypotension with a blood pressure of 72/53 mmHg and a heart rate of 68 beats/min. Her oxygen saturation remained above 95% on room air. Abdominal examination revealed no abdominal sounds, a rigid abdomen with diffuse tenderness and guarding, as well as rebound tenderness.

### *Laboratory examinations*

Acute blood tests showed a hemoglobin level of 134 g/L and a white blood count of 7.6 × $10^9$/L. Other lab tests, including liver function, electrolytes, and renal function were all within normal ranges.

### *Imaging examinations*

During the colonoscopy, the colonoscope was able to advance easily into the sigmoid colon but encountered limited progression into the transverse colon and hepatic flexure. The colon appeared tortuous with an intraluminal appearance resembling a volvulus. The procedure was terminated prematurely due to the inability to progress further. Upon scope withdrawal, submucosal hemorrhage and mucosal evidence of barotrauma were observed (Figure 2). A computed tomography (CT) abdomen revealed irregular wall thickening of the hepatic flexure and proximal transverse colon, which had herniated through a large diaphragmatic defect suspected to be a MH into the chest at the level of the right cardiophrenic angle. This herniation extended through the right major fissure to the superior segment of the right lower lobe. Surrounding fat stranding and a few extraluminal air locules were present, indicating a colonic perforation (Figure 3).

## FINAL DIAGNOSIS

Colonic perforation after colonoscopy due to a large MH.

## TREATMENT

The patient was resuscitated with intravenous fluids, resulting in a rapid and appropriate hemodynamic response. The colorectal surgical team was urgently consulted. The patient was started on intravenous antibiotic therapy with cefazolin and metronidazole in preparation for urgent transfer to the operating room (OR). In the OR, a diagnostic laparoscopy revealed that a segment of the transverse colon was incarcerated into a retrosternal diaphragmatic hernia. There was no evidence of fecal peritonitis. Once the hernia was carefully reduced, a small antimesenteric perforation was observed on the serosa of the transverse colon with no significant signs of ischemia. A transverse segmental colectomy was performed with colo-colonic anastomosis. The diaphragm was inspected, confirming a small to moderate-sized MH in the retrosternal position lined by a large hernia sac, which was dissected and removed. Due to the presence of a colonic perforation and a secondary contaminated field, the hernia defect was closed primarily using interrupted non-absorbable sutures without the use of a mesh.

## OUTCOME AND FOLLOW-UP

The patient progressed well postoperatively, tolerating clear liquids on postoperative day one, and was discharged home without any complications two days after the operation, resuming a regular diet. She had follow-up appointments two weeks and four weeks after the surgery, during which was doing very well. Pathology of the transverse colon revealed a small perforation with no signs of ischemia, serositis, polyps, or malignancy.

## DISCUSSION

During the embryonic period and by the eighth week of gestation, the diaphragm undergoes complete development through the fusion of its components, including the septum transversum and the pleuroperitoneal membranes[6]. Failure of appropriate closure of the pleuroperitoneal folds between the fourth and tenth weeks postfertilization results in herniation of viscera into the thoracic cavity, causing disruption to normal development. The causes of unsuccessful diaphragmatic closure remain to be elucidated. One potential explanation is the disruption of normal mesenchymal cell differentiation during the morphogenesis of the diaphragm and other somatic structures by genetic or environmental triggers[7,8]. The occurrence of CDHs is primarily sporadic, with the majority of cases lacking an identifiable familial association.

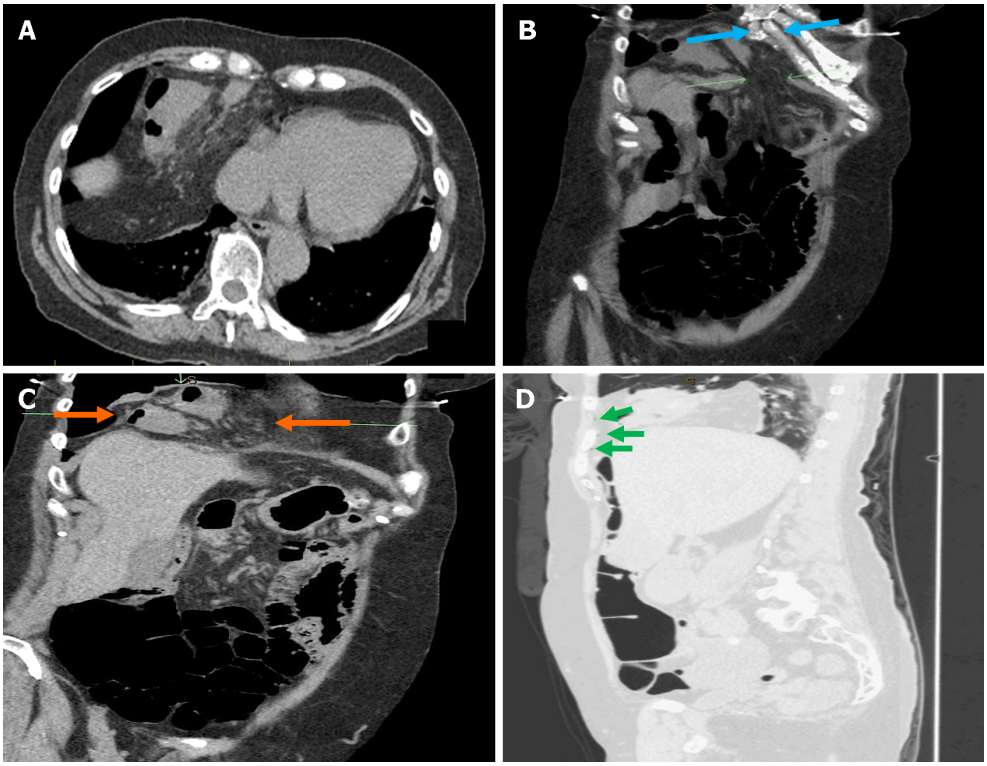


**Figure 3 Non-contrast computed tomography scan.** A: Axial view shows incarcerated bowel loops and fat at right paramedian location just above the hemidiaphragm; B and C: Coronal view shows focal defect in the anteromedial aspect of right hemidiaphragm (blue arrows). The hernia sac is seen at right hemidiaphragm and containing bowel loops and mescentric fat (orange arrows); D: Sagittal view in lung window clearly depicts few extraluminal air locules at the non-dependent part secondary to the bowel perforation (green arrows).

The prenatal diagnosis of a MH can be conducted through detailed prenatal ultrasound or magnetic resonance imaging (MRI). In adulthood, the diagnosis may be made through various diagnostic imaging techniques such as chest X-rays, CT, MRI, or upper gastrointestinal and bowel double-contrast studies. Common imaging findings on a CT scan may include the presence of fat or soft tissue abutting the upper surface of the diaphragm, a distinctive posterolateral position on the hemidiaphragm with consistent density across the defect[4].

The majority of adult cases of MHs are asymptomatic due to the occlusion of the defect by the underlying liver or omentum, which effectively prevents herniation of intra-abdominal organs into the thoracic cavity[9,10]. Several studies have documented its manifestation in an adult population. In a recent review, 310 adult patients were identified with a MH, with 61% being female. The most commonly reported presentation included pulmonary and gastrointestinal tract symptoms. The majority of MHs were located on the right side (84.0%), as in the case of our patient, with the greater omentum and transverse colon being the most frequently herniated viscera[11]. Although there have been some cases of MHs presenting with bowel obstruction or perforation, to our knowledge, there has been only one other reported case of bowel perforation within a MH during colonoscopy[12]. Our patient reported experiencing rare, mild, and self-remitting episodes of abdominal and chest pain of unclear duration over years. These may have been the result of intermittent abdominal content herniation through a narrow hernia neck. The use of increased intra-abdominal pressure, colonic insufflation, and manipulation during colonoscopy may have paradoxically exacerbated the herniation and precipitated bowel perforation. Due to the widespread use of colonoscopy in the field of gastroenterology nowadays, the aim of publishing this case study is to raise awareness of MH when encountering unexpected difficulties during colonoscopies. After navigating the usual challenging sharp angles in the sigmoid colon and splenic flexure, observing a sudden volvulus-like appearance of the transverse colon lumen should prompt the endoscopist to consider a CDH. Presumably, any internal or congenital hernia could present in a similar fashion, and subsequent abrupt onset of abdominal symptoms or respiratory distress during or after the procedure should prompt further investigations. Examining the patient's prior chest or abdominal imaging for incidental findings of CDH and gathering a comprehensive surgical and traumatic history, particularly focusing on the thoracic region, may assist in proactively identifying the presence of a MH. This approach may heighten the suspicion of a diaphragmatic hernia, thus potentially allowing for preventive measures to be taken before the medical procedure, thereby minimizing potential complications.

MHs can be repaired through either transabdominal or transthoracic approaches using either open or minimally invasive techniques. There is a lack of consensus on the preferred approach[13,14]. The hernia defect is often repaired with the use of synthetic mesh due to the size of the hernias, constant tension on the diaphragm muscle, and poor muscle redundancy in that area, which can increase tension on the sutures. However, for smaller defects and increased diaphragmatic redundancy, primary repairs may provide satisfactory results with low hernia recurrence rates[15]. In our patient, we opted for a primary repair due to a colonic perforation and concerns about mesh infection. The defect was repaired with interrupted non-absorbable sutures, with satisfactory results. It has been traditionally advised not to

remove the hernia sac in order to prevent massive pneumomediastinum[16]. However, in our patient's case, we decided to remove the sac to adequately expose the diaphragmatic muscle edge and avoid using the sac for closure. This approach has more recently been found to reduce the likelihood of recurrence, while lowering the risk of fluid collection[17].

## CONCLUSION

A MH is a rare congenital condition that can present in both pediatric and adult populations. While the majority of cases in adults are asymptomatic, some may present with severe, life-threatening symptoms. Thus, surgical correction is recommended for patients with acceptable surgical risk, even if they are asymptomatic. Due to its rarity, there is a lack of awareness in recognizing its clinical presentation. Colonic perforation is a serious complication of colonoscopy that requires both prevention and early detection and intervention if it occurs. The current case report is only the second published description of a MH complicating colonoscopy and leading to perforation. We share this experience along with recommendations to increase the suspicion of such an intraprocedural event, in the hopes that heightened awareness can lead to early diagnosis and the prevention of complications during colonoscopy.

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## FOOTNOTES

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CASE REPORT

# Pleomorphic rhabdomyosarcoma of the vagina: A case report

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## Abstract

*BACKGROUND*

Rhabdomyosarcoma (RMS) of the vagina in postmenopausal women is an extremely rare malignant tumor that was originally described as a unique group of soft tissue sarcomas originating from primitive mesenchymal cells. It was first reported in postmenopausal women in 1970, and fewer than 50 postmenopausal patients have been reported to date.

*CASE SUMMARY*

A 68-year-old multiparous female was admitted to the hospital on October 11, 2023, with the chief complaint of a mass causing vaginal prolapse with incomplete urination that had persisted for 4 months. The vaginal mass was approximately the size of a pigeon egg; after lying down, the vaginal mass retracted. Complete resection was performed, and vaginal pleomorphic RMS was diagnosed based on pathology and immunohistochemical staining features. The patient is currently undergoing chemotherapy. The present study also reviewed the clinical, histological, and immunohistochemical features and latest treatment recommendations for vaginal RMS. Any abnormal vaginal mass should be promptly investigated through pelvic examination and appropriate imaging. The current initial treatment for vaginal RMS is biopsy and primary chemotherapy.

*CONCLUSION*

When surgery is planned for vaginal RMS, an organ-preserving approach should be considered.

**Key Words:** Rhabdomyosarcoma; Vagina; Postmenopausal woman; Pleomorphic; Case report

**Core Tip:** Rhabdomyosarcoma (RMS) of the vagina is an extremely rare malignant tumor in postmenopausal women. Here we describe a 68-year-old female admitted to hospital on October 11, 2023 with the chief complaint of a mass causing vaginal prolapse with incomplete urination that had persisted for 4 months. Complete resection was performed, and vaginal pleomorphic RMS was diagnosed based on pathology and immunohistochemical staining features. The patient is currently undergoing chemotherapy. This study also included review of the current literature to summarize clinical, histological, and immunohistochemical features of the postmenopausal vaginal RMS patients reported to date and latest treatment recommendations.

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## INTRODUCTION

Rhabdomyosarcoma (RMS) is a family of soft tissue tumors that originate from undifferentiated mesenchymal cells, which can differentiate into striated skeletal muscle[1]. The World Health Organization (WHO) has classified RMS into four histologic subtypes, namely embryonic, pleomorphic, spindle cell, and alveolar. Each subtype is linked to a specific genetic mutation profile and prognosis[2].

RMS itself is a rare illness, with an estimated 350 new cases occurring annually in the United States. While it can develop in almost any region of the body, including the head and neck, in up to 29% of cases it has arisen in genitourinary organs such as the bladder, prostate, paratesticular tissues, uterus, cervix, and vagina[3,4]. About 3.5% of all reported cases of RMS occur in the vagina[2]. There is limited information available about RMS of the vagina in the Chinese population, particularly in adult women. Therefore, we report here a case of a 68-year-old postmenopausal woman with early vaginal RMS who underwent precise resection of the tumor using bipolar electrocoagulation with normal saline as the expansion medium.

Treatments for vaginal RMS have evolved alongside advancements in medical research that have improved our overall understanding of RMS. In the past, complete removal of affected organs was often the standard approach. However, currently, more conservative and organ-preserving techniques are increasingly being used; these include local resection, radiation therapy, and chemotherapy. The goal of treatment is to achieve effective tumor control while minimizing impact on the patient's quality of life. According to a study by Andrassy *et al*[5], local resection may be considered an appropriate approach. Indeed, primary chemotherapy following the initial biopsy provides excellent tumor control in these cases. Complete organ removal, such as vaginectomy or hysterectomy, is typically not necessary except in cases of persistent or recurrent disease.

## CASE PRESENTATION

### *Chief complaints*

A 68-year-old multiparous female was admitted to hospital on October 11, 2023, with the chief complaint of a vaginal mass causing prolapse with incomplete urination that had persisted for 4 months. Transvaginal palpitation indicated the vaginal mass to be approximately the size of a pigeon egg. Upon lying in the supine position, the vaginal mass retracted and this was accompanied by incomplete urination. The patient reported some episodes of urinary incontinence upon coughing but denied experiences of frequent urination, urgent urination, or dysuria.

### *History of present illness*

The patient had no history of sexually transmitted diseases nor urinary tract infection.

### *History of past illness*

The patient had a history of bilateral fallopian tubal ligation surgery but no history of cancer, hypertension, or diabetes.

### *Personal and family history*

The patient had given birth to 2 children, had no history of abortion, and was menopausal at the age of 41 years. She had a brother who died of lung cancer.

### *Physical examination*

Gynecological examination of the anterior wall of the vagina and the rear of the urethra revealed a mass of 3.5 cm in diameter with medium texture; the bilateral ovarian fallopian tube area was not in contact with the mass. In addition, cervical and uterine atrophy was observed. The patient indicated no tenderness during the examination. The results of stress test and Bonney test were negative.

### *Laboratory testing*

Tumor marker levels were within normal range, including carbohydrate antigen 125, lactate dehydrogenase, carbohydrate antigen 19-9, α-fetoprotein, β-human chorionic gonadotropin, and carcinoembryonic antigen.

### *Imaging examination*

Pelvic floor three-dimensional color Doppler ultrasound examination showed a solid 3.2 cm × 2.9 cm mass involved the posterior urethra (Figure 1). Further imaging examinations, including color Doppler ultrasonography of the uterus and adnexa, showed no abnormal findings.

### *Genetic testing*

The patient chose to forego genetic testing, citing economic reasons.

### *Biopsy and pathology examinations*

The patient underwent cystoscope examination, complete resection of the anterior vaginal tumor, and vaginal wall repair under general anesthesia on October 12, 2023. Intraoperatively, no other mass was found in the urethra or bladder cavity.

The tumor was not adhered to the urethra and was easily separated from the anterior vaginal wall using normal saline as expansion medium. Resection of the tumor included an adjacent portion of the vaginal wall (1 cm in size) for comprehensive evaluation. Gross examination defined the size of the vaginal mass to be approximately 32 mm × 30 mm × 30 mm (Figure 2A), with no obvious capsule, pale red coloration, medium texture, and resemblance to a uterine leiomyoma (Figure 2B).

Postoperative pathology revealed pleomorphic RMS, chronic inflammation of the vaginal wall tissue, and no tumor infiltration. Microscopic examination revealed various tumor cell morphologies, including round or ovoid nuclei, deep staining, eosinophilic cytoplasm, tennis racket-like or spider-like tumor cells, and a variable number of multinucleated giant cells with deep-stained nuclei and lax interstitium. The rhabdomyoblasts observed in the pathology of our patient's tumor displayed a range of differentiation. The predominant cell type was characterized by small and ovoid to spindled shapes, with limited cytoplasm that stained amphophilic. The nuclei of these cells appeared densely hyperchromatic, with irregular nuclear membranes and frequent apoptoses. Additionally, early differentiating rhabdomyoblasts were identified as elongated, bipolar spindled cells with varying amounts of wavy eosinophilic cytoplasm. It is worth noting that terminally differentiated rhabdomyoblasts were only observed in focal areas, as seen in Figure 3 and in agreement with the literature[6].

Immunohistochemical analysis of the tumor cells showed positivity for vimentin, Brm/Swi2-related gene 1, cluster of differentiation 68 (CD68), myosin, integrase interactor 1, desmin (individual cells), epithelial membrane antigen (individual cells), and cytokeratin (CK AE1/AE3) (individual cells) but negativity for CD34, CK5/6, p63, and myoglobin. The Ki-67 index was more than 30%. P53 was wild-type. Immunohistochemical staining for myogenin and myoblast determination protein 1 (myoD1) in the cellular aggregates were indicated rare to patchy positivity. By contrast, desmin staining was positive in the majority of tested tumors and exhibited more extensive staining compared to myogenin and myoD1, as seen in Figure 4 and in agreement with the literature[7].

Hematoxylin and eosin staining (Figure 3) and immunophenotyping (Figure 4) indicated pleomorphic RMS.

## FINAL DIAGNOSIS

Pleomorphic RMS.

## TREATMENT

The patient is currently undergoing chemotherapy on an administration regimen of once every three weeks for doxorubicin (75 mg/m$^2$ on the 1$^{st}$ day) and ifosfamide (2.5 g/m$^2$/day, from the 1$^{st}$ day to the 3$^{rd}$ day) for a total of six courses of treatment. The main side effects have been II° bone marrow suppression, alopecia, mild nausea, and vomiting, but not to the point of treatment discontinuance. No cardiac toxicity, such as arrhythmia and hemorrhagic cystitis, has occurred, even temporarily.

## OUTCOME AND FOLLOW-UP

Follow-up at 2 months has revealed no signs of recurrence and lifetime follow-up is recommended.

## DISCUSSION

Although RMS is one of the most common soft tissue sarcomas in girls under the age of 5 years, it is an extremely rare malignant tumor of the vagina in postmenopausal women. According to a 4-decade retrospective study conducted in the

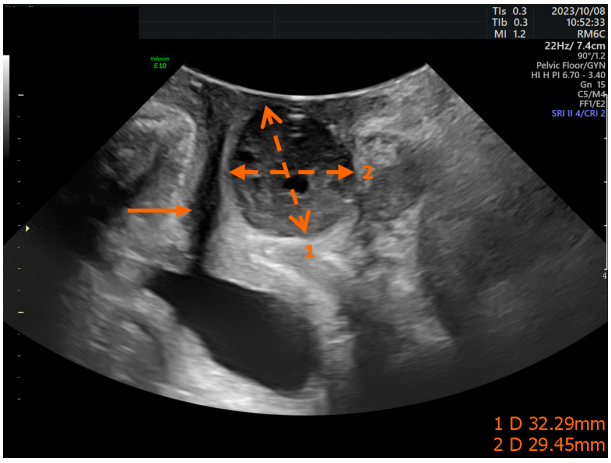


**Figure 1 Ultrasound showing a solid mass of 3.2 cm × 2.9 cm in size involving the posterior urethra (orange arrow).**

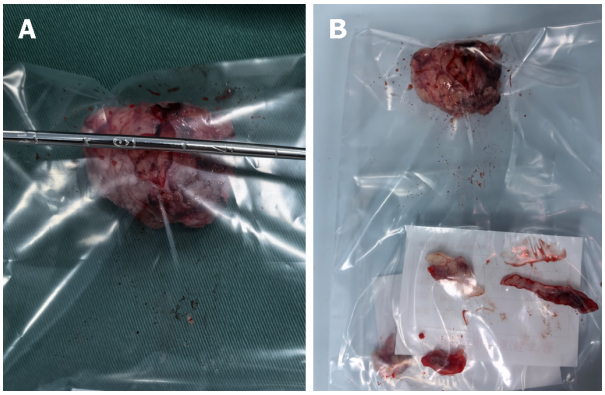


**Figure 2 Gross pathological picture of the patient's vaginal pleomorphic rhabdomyosarcoma.** A: The size of the vaginal mass was approximately 32 mm × 30 mm × 30 mm; B: Gross pathological picture of the vaginal mass, which had no obvious capsule, was pale red with a medium texture, and resembled a uterine leiomyoma. Below, is the 1 cm portion of the vaginal wall that was adjacent to the tumor.

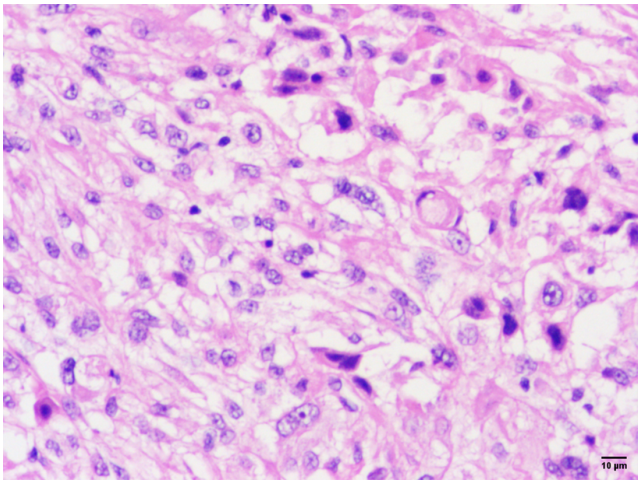

**Figure 3 Hematoxylin and Shuhon stains.** Original magnification of × 200.

United States which analyzed 144 cases of lower genital tract (vulva, vagina, cervix) RMS from 1973 to 2013, the average age of the patients was 16 years. Moreover, it was determined that vulvovaginal RMS was most common in prepubertal girls (89.1%), occurring to a much lesser extent in adolescents (3.0%), premenopausal women (2.3%), and postmenopausal women (4.6%)[2]. Among the four WHO subtypes of RMS, embryonal is the most frequently observed; the relatively uncommon pleomorphic variant tends to occur in adults and that of the spindle cell/sclerosing variant is more commonly seen in children[8]. The pathological diagnosis of our case was pleomorphic RMS.

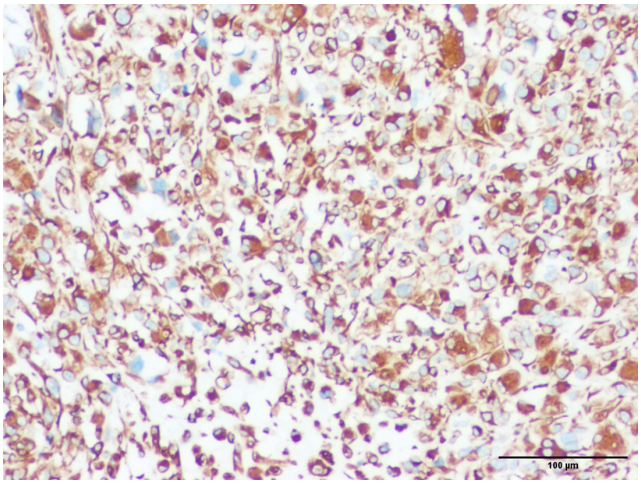


**Figure 4 Immunohistochemical analysis of vimentin.** Original magnification of × 100. Brown indicates tumor cell cytoplasm and blue indicates tumor cell nucleus with Shuhon staining; thus, deeper brown coloration indicates greater expression of cytoplasmic vimentin.

The first report of vaginal RMS in postmenopausal women dates back to 1970 when it was described by Hilgers *et al* [9]. Shy *et al*[10] systematically summarized the cases of vaginal rhabdomyosarcoma before 1995. In 2004, Suzuki *et al*[11] reported a 70-year-old postmenopausal woman with history of endometrial cancer surgery, who was suffering from vaginal RMS. She was given three sessions of intravaginal radiation therapy but at 6 months after the initial treatment, the patient died from progression of the disease. We have founded 6 case reports of postmenopausal women with vaginal rhabdomyosarcoma in English, as is known in Table 1. The 5-year overall survival (OS) rate of women diagnosed with RMS in the lower genital tract is reported to be greater than 90%[12,13]. Several factors are correlated with improved OS, including younger age, lack of distant cancer spread, embryonal histology, absence of lymph node metastasis, and previous cancer-directed surgery[2].

Over the past 30 years, there has been a revolutionary shift in the treatment of vaginal RMS to minimize long-term side effects from the treatment itself and to maintain organ function. This transformation has been driven by a growing awareness of the potential adverse effects of cancer treatments such as those induced by radical surgery and external beam radiotherapy. A more conservative and multidisciplinary approach has been adopted, which involves limited surgical intervention, local radiotherapy (brachytherapy), and chemotherapy. This combined approach has yielded promising results, with an 18% local failure rate and a 5-year OS rate of 91%. Thus, the adopted conservative treatment strategy has effectively reduced the risk of local recurrence and improved the long-term outcome of patients[5,13,14]. According to a retrospective study conducted at a single institution, the survival rate for adult RMS patients was not significantly lower than that for children with RMS if similar treatments were applied[7].

The initial evaluation of vaginal RMS typically involves pelvic magnetic resonance imaging (MRI), cystoscopy, vaginoscopy, bimanual rectovaginal examination, and color Doppler ultrasound. Local biopsy is recommended. When the tumor is small, localized, and well-defined, resection is preferred if it can be completely removed without causing significant damage to nearby normal structures. Routine assessment of surgical lymph nodes is not advised[12]. Complete removal of the tumor is correlated with positive prognosis when the patient receives subsequent chemotherapy [12]. In an international pooled analysis, 33 patients who received chemotherapy after surgical local resection of vaginal RMS but who did not undergo radiotherapy had a 10-year event-free survival of 79% and an OS rate of 97%[13]; thus, radiotherapy is not considered a necessary part of the treatment routine for vaginal RMS. Vincristine, dactinomycin, doxorubicin, and cyclophosphamide are among the most frequently utilized chemotherapeutic drugs, and more recently, iphosphamide and etoposide have also been included in treatment regimens[15].

Intracavitary brachytherapy (BT) was first described by Flamant *et al*[14] as a treatment for RMS of the female lower genital tract. Their patients who had received chemotherapy and BT achieved outcomes that were at least as effective as for those who had undergone radical surgery, such as total vaginectomy and hysterectomy. The BT had been applied alone or in combination with external beam radiotherapy, and the subsequent preservation of gynecological function allowed for fertility preservation with a local control rate of 94%[14]. These findings were later refined by Lautz *et al*[12], who showed that patients with histologically proven complete responses to chemotherapy did not require any further local control, whereas patients with residual disease could be treated effectively with chemotherapy and BT[12,16,17].

Unfortunately, our patient did not undergo a pelvic MRI examination, only Doppler ultrasound imaging evaluation. Postoperative pathology of our case revealed pleomorphic RMS with chronic inflammation of the vaginal wall tissue but no tumor infiltration. Careful and complete local resection of the tumor was possible and allowed for preservation of vaginal function. The patient has tolerated the subsequent chemotherapy well and will continue to attend follow-up.

There are great differences in chemotherapy regimens for different pathological types of rhabdomyosarcomas. Rhabdomyosarcoma can be classified into pleomorphic rhabdomyosarcoma and non-pleomorphic rhabdomyosarcoma, and the treatment approaches differ between the two. Non-pleomorphic rhabdomyosarcoma includes embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, and spindle cell/sclerosing rhabdomyosarcoma. The chemotherapy regimen based on vincristine, actinomycin D, and cyclophosphamide is commonly used for non-pleomorphic rhabdomy-

**Table 1 Summary of vaginal rhabdomyosarcomas in postmenopausal women**

| Ref. | Year | Age | Symptom | Stage | Surgery | Radio-therapy | Chemo-therapy | Survival |
|---|---|---|---|---|---|---|---|---|
| Hilgers *et al*[9] | 1970 | 60 | Bleeding | IV | TV + TAH | No | Yes | DOD at 59 months |
| Davis and Franklin[23] | 1975 | 61 | N | II | TV + TAH + BSO | No | No | NED at 96 months |
| Hays *et al*[24] | 1988 | 72 | N | IV | Biopsy | Yes | Yes | DOD at 32 months |
| Shy *et al*[10] | 1995 | 62 | Bleeding | I | Excision + BSO | Yes | No | NED at 12 months |
| Suzuki *et al*[11] | 2004 | 70 | Mass | IV | Biopsy | Yes | No | DOD at 6 months |
| Present case | 2023 | 68 | Mass | I | Excision | No | Yes | NED at 4 months |

N: Not mentioned; DOD: Died of disease; NED: No evidence of disease; TAH: Total abdominal hysterectomy; TV: Total vaginectomy; BSO: Bilateral salpingo-oophorectomy.

osarcoma. According to the NCCN Clinical Practice Guidelines in Oncology (Soft Tissue Sarcoma, Version 2.2022)[18], doxorubicin-based combination chemotherapy is recommended for the chemotherapy of pleomorphic rhabdomyosarcoma., such as "doxorubicin + ifosfamide", "epirubicin + ifosfamide", "doxorubicin + dacarbazine", "doxorubicin + ifosfamide + mesna", and "mesna + doxorubicin + ifosfamide + dacarbazine". Some studies have shown that postoperative doxorubicin-based chemotherapy can improve recurrence-free survival and OS in patients with soft tissue sarcoma of the extremity and body wall with a median follow-up of 7.7 years[19-21]. Therefore, this case chose a combination chemotherapy regimen of doxorubicin and ifosfamide. Ifosfamide may cause bladder injury leading to hematuria. Protective drug "mesna" should be given when applied, which can effectively reduce the occurrence of such side effects. Doxorubicin and epirubicin have cardiotoxicity, especially when the total amount is large. The protective drug "dexrazoxane" can reduce the occurrence of that side effect.

The prognosis of RMS depends on the patient's age, tumor location in the body, pathological type, tumor size, distant metastasis, and tumor residual size after initial surgery. The incidence of polymorphic RMS increases with age, and the prognosis of adult polymorphic RMS is poor. Studies have shown that polymorphic RMS and growth in poor sites are more common in adults, with an expected 5-year OS of 27% in adults and 63% in children[22]. The good sites of tumor growth were the head and neck (non-meningeal), urogenital tract (non-bladder and prostate), bile duct area, and other adverse sites. Due to the small number of clinical cases, the data is limited. The case reported by our team occurred in postmenopausal women, but the malignant tumor grew in a good location, the tumor was less than 5 cm, the malignant tumor was completely resected, the vaginal wall margin was negative, and there was no distant metastasis. The patient has received doxorubicin-based combined chemotherapy. She is still in the process of continuous follow-up, and we expect her to have a good clinical outcome.

## CONCLUSION

Vaginal pleomorphic RMS is a rare tumor, but good therapeutic effects can be achieved. Early detection of this uncommon malignancy in adult patients can significantly enhance the patient's chances of survival. Any abnormal vaginal mass should be promptly investigated through pelvic examination and appropriate imaging; however, subsequent biopsy and pathological analysis is necessary to obtain a definitive diagnosis of RMS. The current treatment for vaginal RMS following resection is primary chemotherapy. When local treatment is planned, an organ-preserving approach should be considered, which is similar to that used for other primary sites.

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CASE REPORT

# Coexistence of liver abscess, hepatic cystic echinococcosis and hepatocellular carcinoma: A case report

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## Abstract

### *BACKGROUND*

Human cystic echinococcosis (CE) is a life-threatening zoonosis caused by the *Echinococcus granulosus* (sensu lato). Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality in the world. The coexistence of CE and HCC is exceedingly rare, and only several well-documented cases have been reported. In addition to this coexistence, there is no report of the coexistence of CE, HCC, and liver abscess to date. Herein, we aimed to report a case of coexistence of liver abscess, hepatic CE, and HCC.

### *CASE SUMMARY*

A 65-year-old herdsman presented to the department of interventional therapy with jaundice, right upper abdominal distension and pain for 10 d. Laboratory test showed that he had positive results for HBsAg, HBeAb, HBcAb, and echinococcosis IgG antibody. The test also showed an increased level of alpha fetoprotein of 3400 ng/mL. An abdominal computed tomography (CT) scan revealed an uneven enhanced lesion of the liver at the arterial phase with enhancement and was located S4/8 segment of the liver. In addition, CT scan also revealed a mass in the S6 segment of the liver with a thick calcified wall and according to current guideline and medical images, the diagnoses of hepatic CE (CE4 subtype) and HCC were established. Initially, transarterial chemoembolization was performed for HCC. In the follow-up, liver abscess occurred in addition to CE and HCC; thus, percutaneous liver puncture drainage was performed. In the next follow-up, CE and HCC were stable. The liver abscess was completely resolved, and the patient was discharged with no evidence of recurrence.

### *CONCLUSION*

This is the first reported case on the coexistence of liver abscess, hepatic CE, and HCC. Individualized treatment and multidisciplinary discussions should be

performed in this setting. Therefore, treatment and diagnosis should be based on the characteristics of liver abscess, hepatic CE, and HCC, and in future clinical work, it is necessary to be aware of the possibility of this complex composition of liver diseases.

**Key Words:** Cystic echinococcosis; Hepatocellular carcinoma; Liver abscess; Multidisciplinary discussions; Case report



**Core Tip:** This is the first reported case of coexistence of liver abscess, hepatic cystic echinococcosis (CE) and hepatocellular carcinoma (HCC). Transarterial chemoembolization was performed for HCC and percutaneous liver puncture drainage was then performed to relieve the liver abscess. The subtype of CE is CE4, as its blood supply is exceedingly poor, so wait-and-watch can be used in this setting. Individualized treatment and multidisciplinary discussions should be performed in this setting.

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## INTRODUCTION

Human cystic echinococcosis (CE) is a life-threatening zoonosis caused by the *Echinococcus granulosus* (sensu lato)[1]. During the adult stage, the parasite can infect canids, sheep, and other animals before releasing parasite eggs in the environment through their feces. Food and water contaminated by their feces may induce human infection though the ingestion of parasite eggs[2]. With CE, 70% of cases manifest primarily in the liver, while the lung is the second-most common location[3]. The lesions can be asymptomatic for years. As the lesions progress, symptoms such as pain in the upper abdomen, fatigue, and fever can be obvious. Unfortunately, with the appearance of symptoms, the lesions often progress to the late stages. The diagnosis of CE is mainly based on its imaging characteristics rather than its biopsy results, so imaging techniques, such as ultrasound, are important for diagnosing CE[4].

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality in the world, with more than 840000 newly reported cases annually[5]. Hepatitis B virus (HBV) is a major cause of HCC in Asia, and when treating patients with HBV-induced HCC, both anti-cancer and anti-virus measures should be taken[6,7]. The prognosis of HCC is poor, and the treatment of HCC is usually limited because most cases are diagnosed during later stages[8]. The coexistence of hepatic CE and HCC is an exceedingly rare condition and, to date, only a few well-documented cases have been reported [9-13]. Besides, the impact of the coexistence of hepatic CE and HCC is still unknown. The coexistence of liver abscess, hepatic CE, and HCC may be another rare setting. Here, we report clinical data on the diagnosis and treatment of a rare case of liver abscess, hepatic CE, and HBV-induced HCC.

## CASE PRESENTATION

### *Chief complaints*

A 65-year-old herdsman presented to the department of interventional therapy with jaundice, right upper abdominal distension, and pain on January 4, 2021.

### *History of present illness*

The patient started experiencing jaundice and right upper abdominal distension 10 d ago. He took some unrecognizable herbs without any therapeutic effect.

### *History of past illness*

Unremarkable.

### *Personal and family history*

His family history was unremarkable. He had several risk factors for contracting echinococcosis: He was a pastoralist in a rural area, regularly drank water of unknown origin and had contact with dogs.

### *Physical examination*

He had a negative Murphy sign and no history of previous alcohol abuse, smoking, or gallstones. His vital signs were

within normal range (blood pressure, 124/78 mmHg; respiration, 17 breaths/min; and heart rate, 88 beats *per* min).

### *Laboratory examinations*

Laboratory test results were positive for HBsAg, HBeAb, HBcAb, and echinococcosis IgG antibody. The results showed an increase in the levels of direct bilirubin at 4.9 μmol/L and alpha fetoprotein (AFP) of 3400 ng/mL.

### *Imaging examinations*

An abdominal computed tomography (CT) scan revealed an uneven enhanced lesion of the liver that measured 7.25 cm × 6.92 cm at the arterial phase with enhancement, located in the S4/8 segment of the liver (Figure 1A). The CT scan also revealed a 3.2 cm mass in the S6 segment of the liver with a thick calcified wall (Figure 1B). Magnetic resonance imaging (MRI) revealed that lesions can be observed in the S4/8 segment of the liver, with long T1 and mixed with T2 signals (Figure 1C and D).

## FINAL DIAGNOSIS

The diagnosis of CE (at S6 segment, subtype: CE4) and HCC (at S4/8 segment) was established according to the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) PNM classification system[14] and the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for HCC and clinical data.

## TREATMENT

Since the coexistence of CE and HCC was relatively complex, multidisciplinary discussions were performed. Based on the CT scans, CE was considered inactive (CE4 subtype; the blood supply in CE4 subtype cases is exceedingly poor) and the HCC lesion needed to be controlled, so transarterial chemoembolization (TACE) was performed (Figure 2). We used a guide wire for superselective entry into the hepatic artery and infusion of 50 mg of loplatin, 20 mg of epirubicin, and 4 mg of raltitrexed along the catheter for perfusion chemotherapy. We then used a microcatheter for selective entry into the tumor blood supply artery, through which we injected 10 mg of epirubicin, 14 mL of lipiodol suspension, and 10 mL of polyethylene microsphere suspension with a diameter of 150 μm. After embolization treatment, angiography showed lipiodol deposition in the lesion area of the cancer and the disappearance of most of the tumor blood vessels. Considering the positive results for HBsAg, HBeAb, and HBcAb, entecavir was added as an antiviral treatment. When the treatment was completed, the patient was discharged from the hospital.

## OUTCOME AND FOLLOW-UP

On May 7, 2021, the patient presented to our hospital with generalized abdominal pain, nausea, vomiting, and fever for 3 d. His vital signs were within the normal range. An abdominal CT scan revealed that liver abscess appeared in addition to previous HCC and CE lesions (Figure 3). HCC and CE were stable. Blood culture was performed before liver abscess drainage, with no positive results. Percutaneous liver puncture drainage was then performed to relieve the liver abscess (Figure 4); thus, purulent fluid was drained out. The liver abscess was completely resolved, and the patient was discharged with no evidence of lesion recurrence.

During the next follow-up, the HCC lesion and CE were stable, and the liver function was within normal range. The medical images of CE and HCC are shown in Figure 5. Additionally, the AFP level did not show a significant increase in the follow-up (Figure 6). However, this patient was lost to follow-up after his last follow-up in April 2022.

## DISCUSSION

The prevalence of the coexistence of hepatic CE and HCC is rather low. Bo *et al*[15] reviewed 3300 patients with hepatic CE and 815 patients with HCC from an echinococcosis epidemic area, and they found that the coexistence incidence rate of CE and HCC was 0.39%[15]. In addition, in the few reported cases where HCC and CE coexist, there have been no reports of simultaneous liver abscess, leaving evidence-based and standard options of treatments unavailable. Regarding the treatment of this condition, we made multidisciplinary discussions according to the patient characteristics and current guidelines. According to the EASL Clinical Practice Guidelines, when treating HCC, only patients with single lesions with a maximum diameter of less than 5 cm are eligible to receive surgical resection[16], while wait-and-watch can be used when treating the CE4 subtype of CE according to the WHO-IWGE PNM classification system. Thus, during the first period of hospitalization for this patient, we mainly treated him for HCC. TACE is a standard treatment option for intermediate-stage HCC (especially for some subgroups of the barcelona clinic liver cancer-B stage HCC). Compared to open surgery, we used superselective embolization for the tumor supply arteries, which can only intervene in the tumor lesion without causing significant impact on the CE[17]. During the second period of hospitalization, percutaneous liver puncture drainage was performed to relieve liver abscess. The reason for choosing percutaneous liver puncture drainage

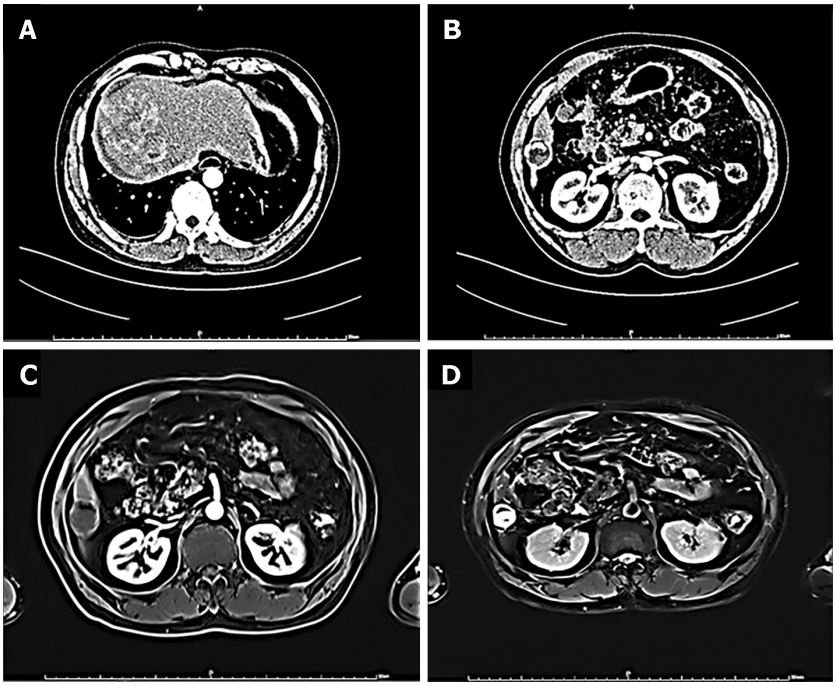


**Figure 1 Medical images.** A: Abdominal computed tomography revealed an uneven enhanced lesion located S4/8 segment of liver; B: Abdominal computed tomography revealed a mass in the S6 segment of the liver with a thick calcified wall; C and D: Magnetic resonance images revealed that lesion can be observed at S4/8 segment of liver, with long T1 and mixed with T2 signal.

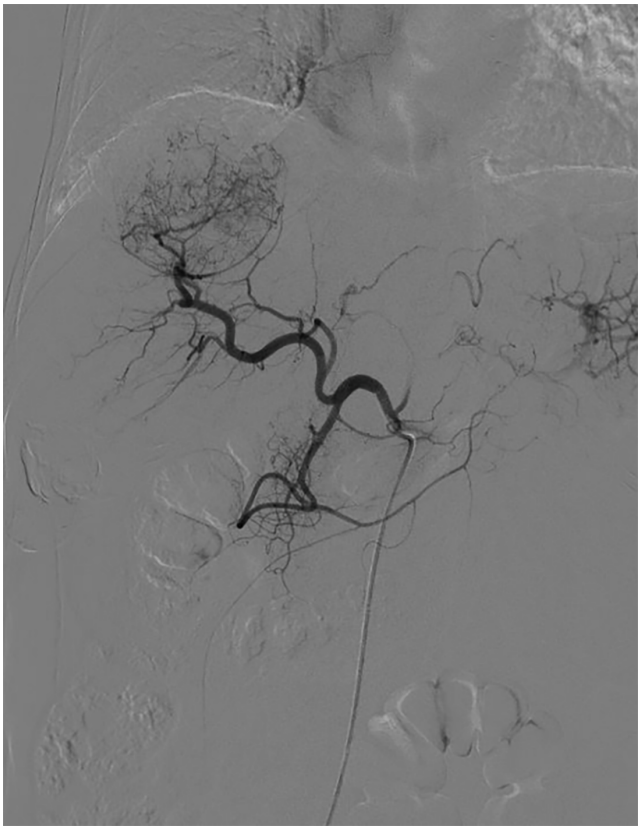

**Figure 2 The procedure of transarterial chemoembolization.**

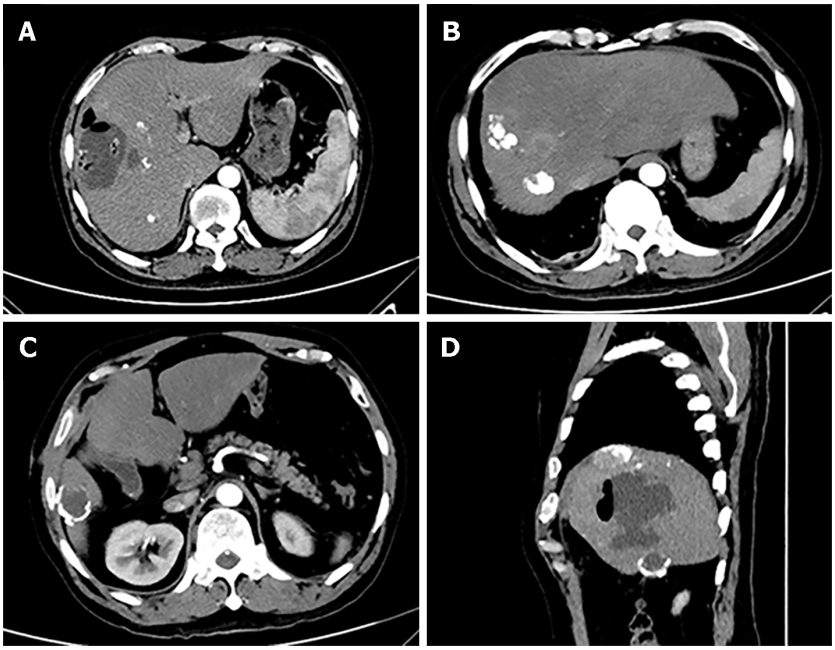


**Figure 3 Abdominal computed tomography scanning in the second hospitalization.** A: The plane of liver abscess; B: The plane of hepatocellular carcinoma; C: The plane of hepatic cystic echinococcosis; D: The reconstruction of computed tomography image.

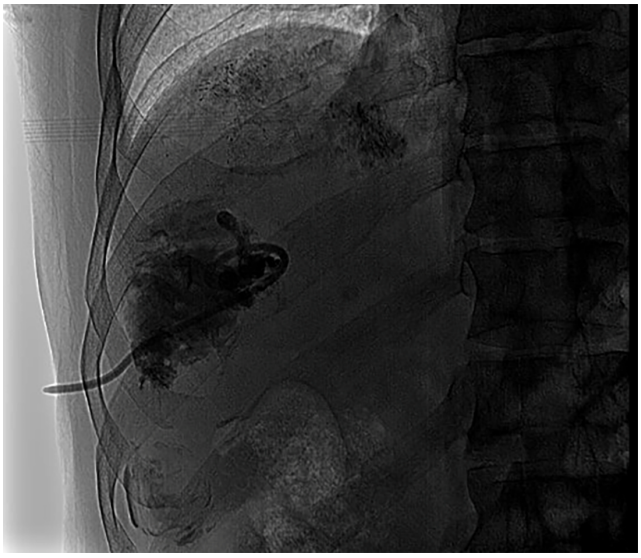

**Figure 4 The procedure of percutaneous liver puncture drainage.**

is that the patient's CE and HCC were in a stable state, and puncture drainage under local anesthesia will not significantly impact the patient's other lesions.

The diagnosis of CE is mainly based on the CT scan or MRI, as CT and MRI could aid in identifying the cyst and assess its location, size, and morphology[18]. CT is the gold standard for the diagnosis of CE, as it could visualize the cystic lesion and walls. Previous studies also found that CT scans could help differentiate between CE and other lesions within the liver, such as abscess and HCC[19]. Serological tests could also help with the diagnosis of CE[20]. In all, the diagnosis of this case was based on the medical image, history, and serological tests.

This case is of a patient with HCC, with HBV infection. HBV showed various mechanisms to accelerate tumor formation, initially by activating various pathways, including the WNT pathway, PI3K/MAPK pathways, and JAK/STAT pathway[21,22]. The culmination of these pathways lead to HBV-related liver disease, which undoubtedly stands as the primary risk factor for the emergence of HCC, so entecavir was added as an antiviral treatment for the patient.

In addition to the coexistence of hepatic CE and HCC, previous studies found that there may be a connection between echinococcosis and cancer[23,24]. Bo *et al*[15] found that echinococcus may have an anti-tumor effect on HCC, reducing tumor progression and improving survival time. In our presented case, we also speculated that one of the reasons why HCC and CE remained stable during the follow-up period may be the anti-cancer effect of CE. It has been reported that the anti-cancer effect of echinococcosis can be found in serum antigens[25,26]. There are also significant differences in

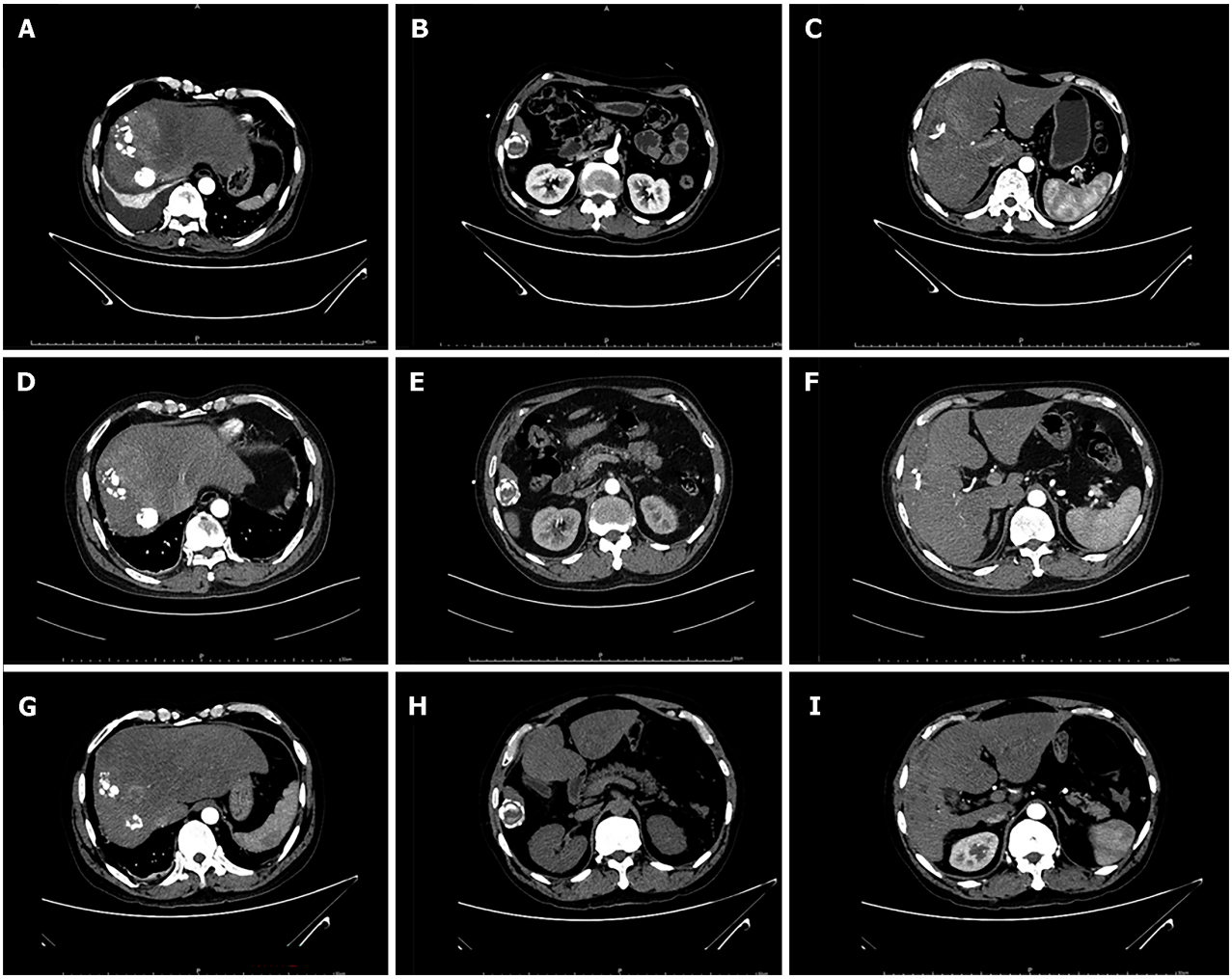


**Figure 5 The medical image in the follow-up.** A-C: The plane of hepatocellular carcinoma (HCC), cystic echinococcosis (CE) and liver abscess in June, 2021; D-F: The plane of HCC, CE and liver abscess in October, 2021; G-I: The plane of HCC, CE and liver abscess in April, 2022.

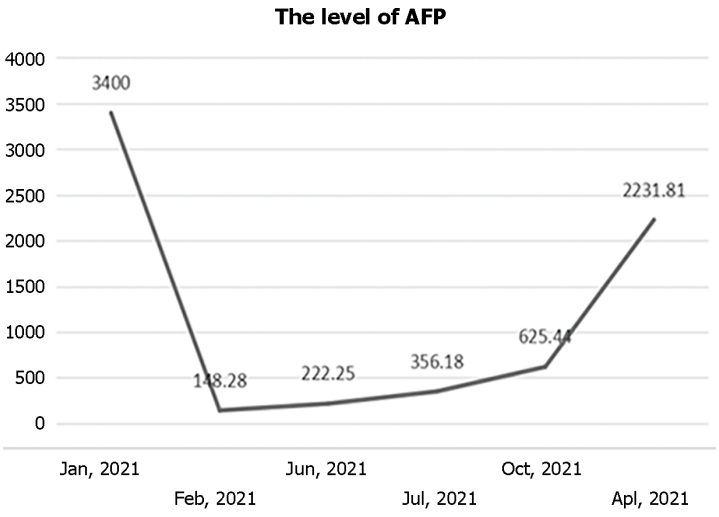


**Figure 6 The level of alpha fetoprotein in the follow-up.** AFP: Alpha fetoprotein.

immune recognition ability for different subgroups of CE and serology is often negative in these cases[27]; hence, we speculated that the anti-cancer effects of different subtypes of CE is different.

Similar to all published cases thus far, HCC and CE in our patient presented as a single lesion. Whether this is a coincidence or is because of the specific mechanisms of the coexistence of CE and HCC still need to be explored in future research. Notably, because no surgical procedures were performed for treatment, our diagnoses were based on imaging

data rather than histological evidence.

Similar to any studies, this study had some limitations. First, although the diagnosis was made according to current guidelines, there is still a lack of histological testing for CE and HCC. Second, this case can only represent the experience of our center. If other clinicians encounter similar cases, personalized treatment still needs to be carried out.

## CONCLUSION

The coexistence of liver abscess, hepatic CE, and HCC is rare. We reported a case of liver abscess that occurred during the follow-up period of a patient with HCC and hepatic CE. Multidisciplinary discussions were performed, and individualized treatment was given. TACE and percutaneous liver puncture drainage were performed for HCC and liver abscess, respectively. Treatment and diagnosis should be based on the characteristics of liver abscess, hepatic CE, and HCC, and in future clinical work, it is necessary to be aware of the possibility of this complex combination of liver diseases.

## FOOTNOTES

**Co-first authors:** Ya-Wen Hu and Yi-Lin Zhao.

**Author contributions:** All authors collected the data from medical records, contributed to the design of the study, and wrote the first draft of the manuscript. Hu YW and Yan JX contributed to the conception and design of the study; Zhao YL and Ma CK provided clinical evaluation and treatment for the patient. All the authors contributed to manuscript revision, and read and approved the submitted version.

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CASE REPORT

# Waist subcutaneous soft tissue metastasis of rectal mucinous adenocarcinoma: A case report

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## Abstract

### *BACKGROUND*

Rectal mucinous adenocarcinoma (MAC) is a rare pathological type of rectal cancer with unique pathological features and a poor prognosis. It is difficult to diagnose and treat early because of the lack of specific manifestations in some aspects of the disease. The common metastatic organs of rectal cancer are the liver and lung; however, rectal carcinoma with metastasis to subcutaneous soft tissue is a rare finding.

### *CASE SUMMARY*

In this report, the clinical data, diagnosis and treatment process, and postoperative pathological features of a patient with left waist subcutaneous soft tissue masses were retrospectively analyzed. The patient underwent surgical treatment after admission and recovered well after surgery. The final pathological diagnosis was rectal MAC with left waist subcutaneous soft tissue metastasis.

### *CONCLUSION*

Subcutaneous soft tissue metastasis of rectal MAC is rare, and it can suggest that the tumor is disseminated, and it can appear even earlier than the primary malignant tumor, which is occult and leads to a missed diagnosis and misdiagnosis

clinically. When a subcutaneous soft tissue mass of unknown origin appears in a patient with rectal cancer, a malignant tumor should be considered.

**Key Words:** Colorectal cancer; Rectal mucinous adenocarcinoma; Cancer metastasis; Subcutaneous soft tissue; Hematogenous; Case report



**Core Tip:** Mucinous adenocarcinoma (MAC) is a relatively rare pathological subtype of colorectal cancer. Patients with rectal MAC are more likely to have abdominal lymph node metastasis, peritoneal metastasis, and abdominal implantation and have a worse prognosis and lower survival rate. Early detection, diagnosis, and treatment of rectal MAC can improve the prognosis of patients. We present a rare case of left waist subcutaneous soft tissue metastasis, hoping to provide some experience for the early clinical diagnosis and treatment of this disease.

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## INTRODUCTION

Colorectal cancer is the third most common malignant tumor in the world, and the incidence and mortality of colorectal cancer in China and the world are increasing. In 2020, the report of China Cancer statistics shows that the incidence and mortality of colorectal cancer rank second and fifth, respectively, among all malignant tumors, with 555000 new cases and 286000 deaths of colorectal cancer occurring in China in 2020[1]. Globally, the fatality rate is the fourth highest among all malignancies[2]. Mucinous adenocarcinoma (MAC) is a relatively rare pathological subtype of colorectal cancer, accounting for only 5%-20%[3]. It has unique clinicopathological features and a relatively low incidence, but it is associated with a poor prognosis. Previous studies have indicated that compared with non-MAC (NMAC) patients, patients with rectal MAC are more likely to have abdominal lymph node metastasis, peritoneal metastasis, and abdominal implantation and have a worse prognosis and lower survival rate[4]. Therefore, early detection, diagnosis, and treatment of rectal MAC can improve the prognosis of patients. Waist subcutaneous soft tissue metastasis of rectal MAC is rare. The clinical and pathological features of rectal MAC were discussed by reporting a case of left waist subcutaneous soft tissue metastasis, hoping to provide some experience for the early clinical diagnosis and treatment of this disease.

## CASE PRESENTATION

### *Chief complaints*

On June 17, 2023, a 49-year-old man was admitted to our hospital with a chief complaint of a mass at the left waist for more than 10 years.

### *History of present illness*

The mass was an approximately 1 cm × 1.5 cm mass bulging from his left waist at the beginning, without pain, rupture, and skin ulceration. Two weeks prior, the mass was approximately 2 cm × 3 cm and caused the patient to have subcutaneous soft tissue pain.

### *History of past illness*

His medical history included radical Dixon resection of rectal cancer (7-9 cm from the anal margin) in April 2019. The diagnosis of postoperative pathology was ulcerative low-differentiated adenocarcinoma and local MAC infiltrating the subserosal fibrous adipose tissue, with 3 of 14 mesorectal lymph nodes involved. A subsequent biopsy and the immunohistochemistry (IHC) findings were as follows: CKI8 (++), CDX2 (++), p53 (++), MUC2 (+), MLHI (+), PMS2 (+), Ki-67 (+ 10%), CD56 (+), p40 (-), Vimentin (-), Syn (-), and CgA (-). The diagnosis of pathology and clinical was reported as stage T3N1M0 and IIIB. The left waist mass became smaller when the patient underwent one cycle of chemotherapy with CapeOx (capecitabine 1.5 g po *bid*) and 7 cycles of oxaliplatin (oxaliplatin 250 mg ivgtt *qd*) in a local hospital after radical Dixon resection of rectal cancer (Figure 1).

### *Personal and family history*

The patient had no relevant personal or family history.

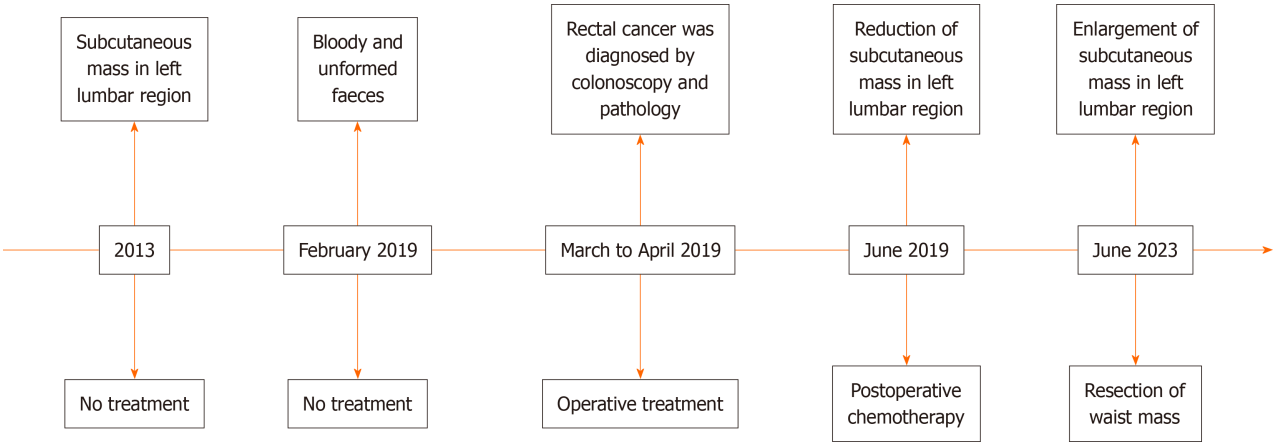


**Figure 1 Timeline of the diagnosis and treatment of the patient.**

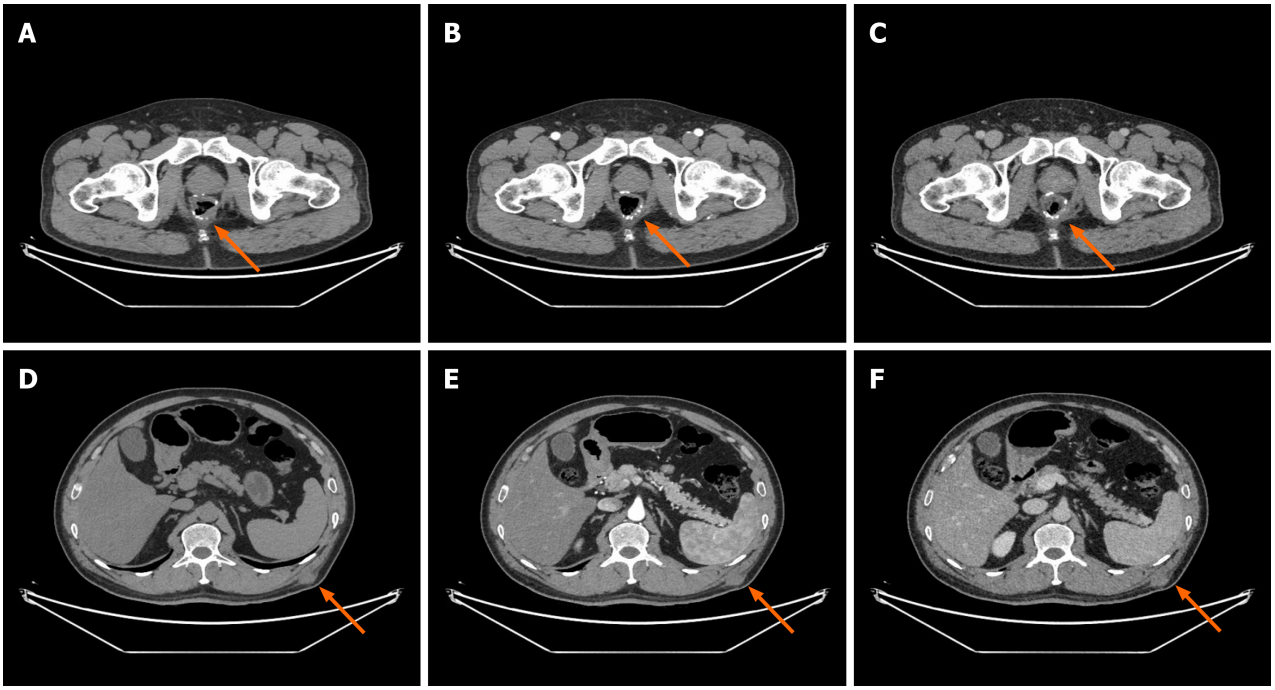


**Figure 2 Contrast-enhanced abdominal computed tomography.** A: Rectal anastomosis plain scan; B: Rectal anastomosis arterial phase scan; C: Rectal anastomosis venous phase scan; D: Plain scan of the soft tissue mass of the left waist; E: Arterial phase scan of the soft tissue mass of the left waist; F: Venous phase scan of the soft tissue mass of the left waist.

### *Physical examination*

Physical examination revealed a firm and relatively clear border subcutaneous tissue mass with a size of approximately 2 cm × 3 cm at the left waist without skin redness, swelling or warming in this patient.

### *Laboratory examinations*

Laboratory examination revealed the following: White blood cell (WBC) 10.49 × $10^9$/L, interleukin-2 (7.05 pg/mL), interleukin-4 (7.33 pg/mL), interleukin-5 (3.96 pg/mL), interleukin-6 (7.10 pg/mL), interleukin-10 (7.09 pg/mL), interleukin-12 P70 (4.86 pg/mL), and tumor abnormal protein (TAP) 160.762 μ$m^2$. The patient's carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), and carbohydrate antigen (CA)19-9 levels were normal.

### *Imaging examinations*

Imaging examination and contrast-enhanced abdominal computed tomography (CT) revealed a soft tissue mass in the subcutaneous tissue plane of the left waist without obvious enhancement in the arterial phase and portal phase, no abnormal strengthening was observed at the anastomosis, and no fluid or enlarged lymph nodes were found in the abdominal cavity or pelvis (Figure 2). The ultrasound revealed a solid mass of 21 mm × 16 mm in size, irregularly bound and without obvious blood flow, located in the subcutaneous soft tissue of the left waist (Figure 3). Colonoscopic exa-

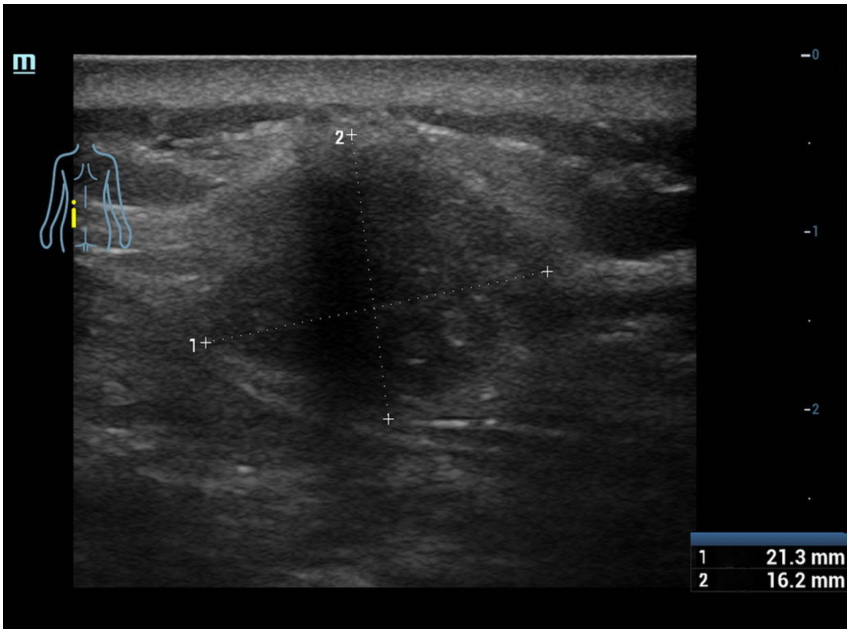


**Figure 3 Ultrasound: A solid mass of 21 mm × 16 mm in size, irregularly bound and without obvious blood flow, located in the subcutaneous soft tissue of the left waist.**

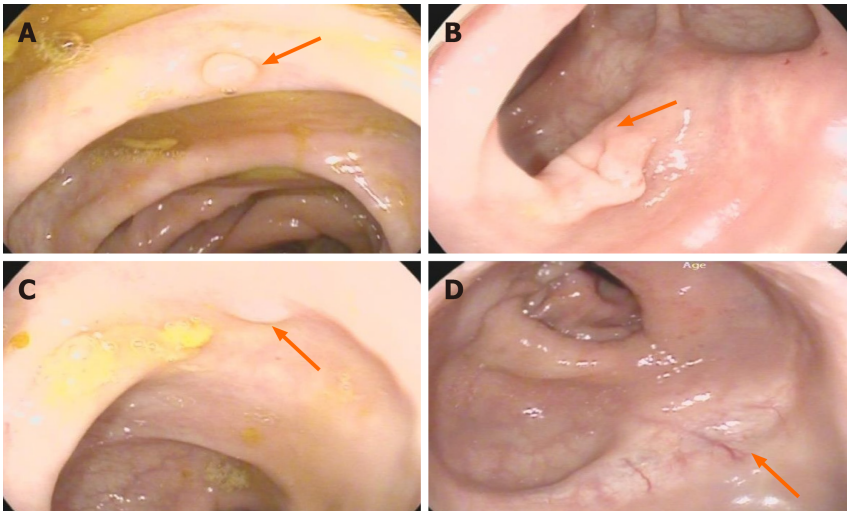


**Figure 4 The colonoscopy results of this admission.** A: Low-grade tubular adenoma (ascending colon); B: Hyperplastic polyp (transverse colon); C: Hyperplastic polyp (sigmoid colon); D: Anastomotic scar.

mination revealed three polypoid lesions approximately 0.2-0.3 cm in size in the ascending colon, transverse colon and sigmoid colon and an anastomotic scar approximately 3 cm from the anal margin (Figure 4).

## FINAL DIAGNOSIS

According to auxiliary examination results and clinical history, skin soft tissue malignancy was considered.

## TREATMENT

The patient underwent left waist mass resection in our hospital on June 21, 2023. The intraoperative discovery was that the tumor was located in the subcutaneous fat and fascia layer, with a size of 2.5 cm × 2 cm and a relatively clear border, and the bottom of the tumor was adhered to the muscle layer. The mass and part of the adherent muscle tissue were completely resected (Figure 5). Postoperative analgesia and anti-infection treatment were given to the patient.

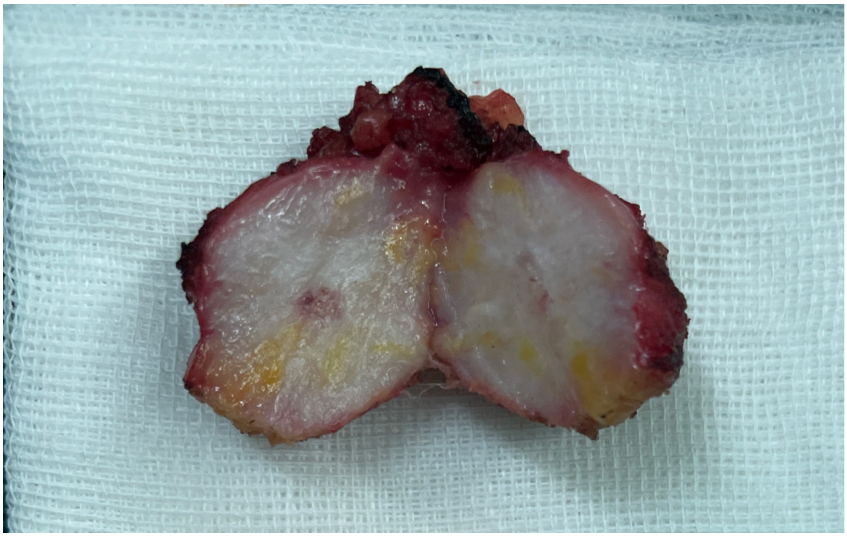

**Figure 5 Soft tissue masses resected from the left waist subcutaneous soft tissue mass during surgery.**

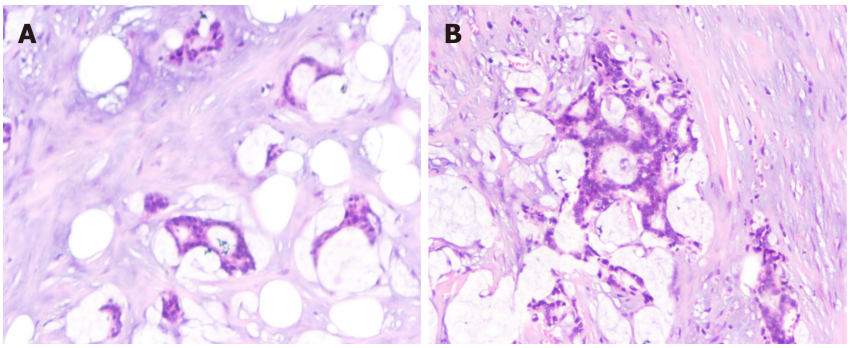


**Figure 6 Pathological examination of the left waist mass.** A: Mucus is visible; B: Mucus is seen around adenocarcinoma cells (hematoxylin and eosin, × 200).

## OUTCOME AND FOLLOW-UP

The postoperative pathologic diagnosis of the left waist mass (hematoxylin and eosin) was MAC, nerve invasion and transfer (Figure 6). Subsequent biopsy and IHC showed the following: MUC2 (+), MUC5AC (+), CK20 (+), CDX-2 (+), CK (P) (+), and Ki-67 (index 80%) (Figure 7). The patient recovered well after surgery with good wound healing and was successfully discharged from the hospital. The patient had no local tumor recurrence or distant metastasis at the 3-month follow-up.

## DISCUSSION

MAC is a relatively rare pathological subtype of rectal cancer. It is frequently diagnosed by pathological paraffin sectioning and IHC. Compared with NMAC, MAC has a larger primary lesion, deeper invasion, higher rates of lymph node metastasis and distant metastasis, and more metastatic sites, so the prognosis is relatively poor[5]. In addition to clinical features, rectal MAC also has unique pathological features, which are also associated with poor prognosis. One of the most important pathological features of MAC is the presence of a large number of mucins outside the tumor cell, including MUC1, MUC2, and MUC5AC. Studies have found that MUC2 and MUC5AC are closely related to colorectal cancer. Research shows that overexpression of MUC2 can form mucous layers in the colon mucosa, which can fight against self-antitumor immunity, thus promoting tumor development[6,7]. Clinical studies have shown that loss of MUC5AC expression can serve as an indicator of more aggressive colorectal tumors, and patients with negative expression of MUC5AC have lower survival rates[8]. Another study has shown that mucoid substances exert mechanical pressure on surrounding tissues, making it easier for tumor cells to invade the intestinal wall and surrounding tissues. At the same time, the phagocytosis of lymphocytes on mucus facilitates the spread of tumor cells in regional lymph nodes, and mucosaccharides in mucus can interfere with the recognition of tumor cells by immune cells around blood vessels and the lymph node cortex and help tumor cells spread[9]. Immunohistochemical results of the waist metastatic lesions in this patient showed MUC2 (+) and MUC5AC (partial +). The results were consistent with the pathological features of

**Table 1 Cases of rectal cancer with cutaneous metastasis**

| Ref. | Age (yr) | Sex | Histology | Stage | Primary cancer treatment | Interval months | Skin mets location | Skin mets morphology | Skin mets treatment | Survival (follow-up time in months) |
|---|---|---|---|---|---|---|---|---|---|---|
| Hayashi *et al* [14], 2003 | 55 | M | Adenocarcinoma mucinous | - | LAR | 4 | Perineum | Nodules | None | - |
| Sarid *et al*[15], 2004 | 60 | F | Adenocarcinoma mucinous | IIIB | NR + LAR + ACR | 16 | Chest | Ulcers | WLE | No (56) |
| Tan *et al*[16], 2006 | 70 | M | Adenocarcinoma mucinous | IIIB | LAR + AC | 24 | Back | Nodules | WLE, C | - |
| Saladzinskas *et al*[17], 2010 | 64 | M | Adenocarcinoma mucinous | IIA | NR + LAR | 42 | Face | Ulcers | WLE | Yes (7) |
| Balta *et al*[18], 2012 | 46 | M | Adenocarcinoma mucinous | IIIB | Colostomy | 12 | Perineum | Ulcers | None | - |
| de Miguel Valencia *et al* [19], 2013 | 55 | M | Adenocarcinoma mucinous | IIIB | NCR + APR + AC | 18 | Multiple | Nodules | None | No (-) |
| Dehal *et al*[10], 2015 | 47 | M | | IV | CR | 1 | Perineum | Nodules | R | Yes (12) |

-: Data not reported; F: Female; M: Male; Mets: Metastasis; LAR: Low anterior resection; NR: Neoadjuvant radiation; ACR: Adjuvant chemoradiation; AC: Adjuvant chemotherapy; NCR: Neoadjuvant chemoradiation; APR: Abdominoperineal resection; CR: Chemoradiation; WLE: Wide local excision; C: Chemotherapy; R: Radiation.

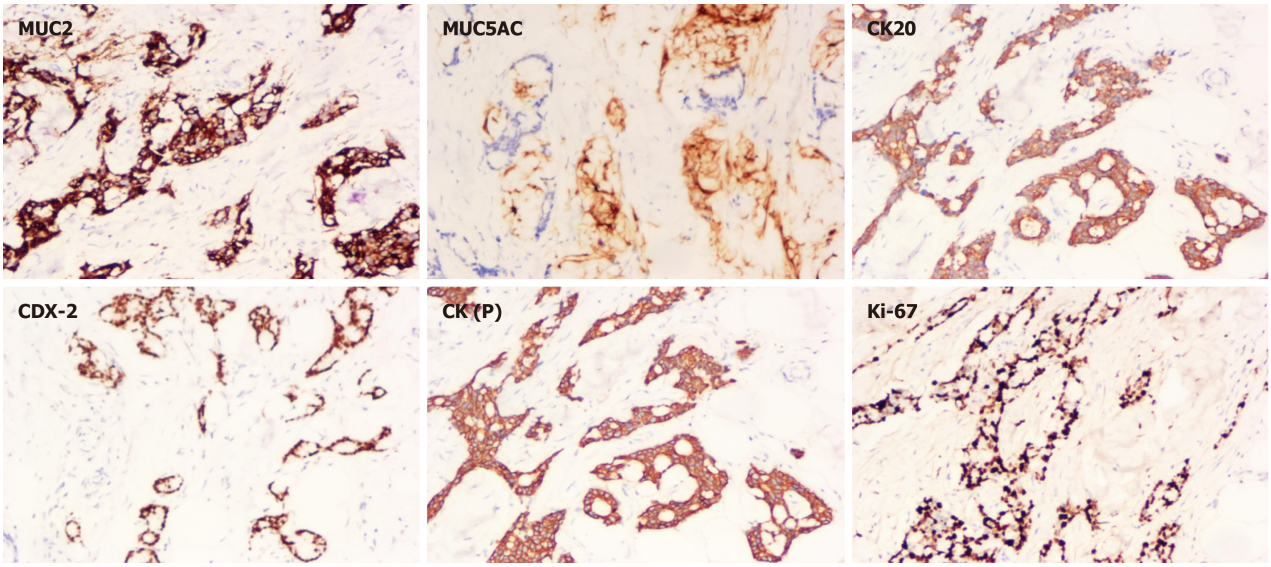


**Figure 7 MUC2 (+), MUC5AC (partially +), CK20 (+), CDX-2 (+), CK (P) (+), Ki-67 (index 80%) (immunohistochemistry, × 200).**

rectal MAC. However, the effect of the proportion and composition of mucous in tumor tissue on the prognosis of patients still needs to be studied further. Colorectal cancer metastasis is more common in the liver and lung, and waist subcutaneous soft tissue metastasis of rectal cancer is rare. We only found 7 cases[10] of cutaneous metastases from MAC of the rectum in the English-language literature (Table 1). The sites where MAC mucinous metastases were reported included the perineum, chest, abdomen and face. It may be related to the biological characteristics of MAC, but the specific mechanism of skin or subcutaneous soft tissue metastases that are far from the primary site is not clear, and these may occur through a blood-derived pathway. Past research has shown that if tumor cells invade blood vessels, skin metastases at distant sites are present, while local recurrence at the site of the primary tumor is more common if the tumor involves lymphatic vessels[11]. The special feature of this patient is that the occurrence time of subcutaneous soft tissue metastases at the left waist may be earlier than the diagnosis time of rectal cancer, and rectal MAC is very likely to develop distant subcutaneous soft tissue metastases through blood origin at an early stage. Because this patient had no early obvious clinical symptoms from this waist subcutaneous mass, the patient did not pay attention to it and was not treated until the tumor was recently found to be larger than before and accompanied by pain, which affected the prog-

nosis of the patient. In addition, the patient's preoperative tests showed that the WBC count, as well as various interleukin indicators, was above the normal range, and combined with the patient's history of rectal cancer, metastasis from rectal adenocarcinoma should have been considered. Many studies have shown that interleukin and other inflammatory factors are closely related to tumor occurrence and development and can promote tumor progression. For example, interleukin-6 is a major cytokine in the tumor microenvironment and is overexpressed in almost all tumors. Interleukin-6 promotes tumor development by regulating all features of cancer and multiple signaling pathways, including apoptosis, survival, proliferation, angiogenesis, invasion, metastasis, and metabolism. In addition, interleukin-6 protects cancer cells from treatment-induced DNA damage, oxidative stress, and apoptosis by promoting repair and induction of counter-signals, leading to treatment resistance[12]. In other aspects, the TAP in this patient was significantly higher than the normal range, and combined with the patient's history of rectal cancer, it also helped us to diagnose tumor recurrence and metastasis. Studies have shown that TAP can be combined with CEA, AFP, CA19-9, and other tumor markers for the early diagnosis of cancer and can also be used for postoperative tumor monitoring[13]. Of course, there are still some deficiencies in this report, such as the failure of the patient to undergo gene detection positron emission tomography (PET)/CT and other examinations, which may affect the overall evaluation of the patient's condition, the implementation of the treatment plan and postoperative treatment follow-up. We will follow up with the patient closely and adjust the treatment plan in time to observe the changes in the patient's condition in the future.

## CONCLUSION

The incidence of rectal MAC is low. However, the malignancy rate is high, the local recurrence and distant metastasis rates are higher, the prognosis is poor, and the survival of patients is affected. Distant subcutaneous soft tissue metastasis of rectal MAC is rare. However, for patients with a history of malignant tumors, these should be considered to be malignant tumors when they appear in the skin and a subcutaneous soft tissue mass without a clear cause. We need to use interleukin, tumor markers, enhanced CT, gastroenteroscopy, PET/CT, puncture biopsy, and other means to evaluate the patient's condition. Finally, it is recommended to surgically remove the lesion and conduct pathological examination IHC and even gene detection to guide follow-up treatment.

## FOOTNOTES

**Co-first authors:** Zi-Xing Gong and Guo-Lei Li.

**Author contributions:** Gong ZX and Li GL contributed equally to this work as co-first authors; Gong ZX, Li GL and Dong WM designed the study and wrote the manuscript; Xu Z and Dong WM collected and analyzed the data; Li R, Lv WX and Yang J prepared figures; Xing W and Li ZX was in charge of patient treatment and designed the paper. All authors have read and approved the final manuscript.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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*CASE REPORT*

# Combined laparoscopic and thoracoscopic repair of adult right-sided Bochdalek hernia with massive liver prolapse: A case report

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## Abstract

### *BACKGROUND*

A Bochdalek hernia (BH) is a congenital diaphragmatic hernia that often develops in the neonatal period. BH typically occurs on the left side of the diaphragm. A right-sided BH in an adult is rare.

### *CASE SUMMARY*

A 45-year-old man was referred to our hospital because of an abnormal shadow seen on chest radiography during a medical check-up. A chest radiograph showed elevation of the right hemidiaphragm. Computed tomography showed prolapse of multiple intraabdominal organs into the right thoracic cavity, corresponding to a right-sided BH. The herniated contents included the stomach, transverse colon, and left lobe of the liver. The left lobe of the liver was enlarged, particularly the medial segment. Laparoscopic surgery was performed. However, the left lobe of the liver was completely trapped in the thoracic cavity. Therefore, thoracoscopic manipulation had to be performed to return the liver to the abdominal cavity. The hernia was repaired with interrupted nonabsorbable sutures and reinforced with mesh.

### *CONCLUSION*

Combined laparoscopic and thoracoscopic surgery was successfully performed for right-sided BH with massive liver prolapse and abnormal liver morphology.

**Key Words:** Bochdalek hernia; Right-sided; Adult; Laparoscopic and thoracoscopic repair; Liver prolapse; Abnormal liver morphology; Case report

**Core Tip:** Bochdalek hernia in adults is rare, especially on the right side. We report an extremely rare case of an adult with a right-sided Bochdalek hernia in which the left lobe of the liver protruded into the right thoracic cavity. We successfully performed a combined laparoscopic and thoracoscopic surgery for an adult right-sided Bochdalek hernia with massive liver prolapse and abnormal liver morphology. The combination of laparoscopic and thoracoscopic surgery enabled safe surgery. To our knowledge, no such cases have ever been reported previously.

**Citation:** Mikami S, Kimura S, Tsukamoto Y, Hiwatari M, Hisatsune Y, Fukuoka A, Matsushita T, Enomoto T, Otsubo T. Combined laparoscopic and thoracoscopic repair of adult right-sided Bochdalek hernia with massive liver prolapse: A case report. *World J Clin Cases* 2024; 12(14): 2420-2425
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## INTRODUCTION

Bochdalek hernia (BH) is a congenital diaphragmatic hernia that typically develops in the neonatal period and presents with severe respiratory and circulatory disorders[1]. Most of these hernias are located on the left side. A BH in an adult may be asymptomatic and discovered incidentally[2,3], and a right-sided one is rare. Management of BH is performed exclusively through surgical treatment[4,5], specifically returning the herniated organs back to the abdominal cavity and repairing the diaphragmatic defect[6-8]. In this report, we describe a rare case of an adult who had right-sided BH with massive liver prolapse and was safely treated with combined laparoscopic and thoracoscopic surgeries.

## CASE PRESENTATION

### *Chief complaints*

A 45-year-old man was referred to our hospital because of an abnormal shadow discovered on chest radiography during a medical check-up.

### *History of present illness*

The patient had no subjective symptoms at the time of the visit.

### *History of past illness*

He had no history of illness.

### *Personal and family history*

There was no relevant family health history.

### *Physical examination*

Routine physical examination revealed no unusual findings. The patient had no complaint of abdominal pain on examination.

### *Laboratory examinations*

Laboratory examinations revealed no abnormal findings.

### *Imaging examinations*

A chest radiograph showed elevation of the right hemidiaphragm (Figure 1). Computed tomography (CT) showed prolapse of multiple intraabdominal organs into the right thoracic cavity through a right-sided diaphragmatic defect (Figure 2A). The herniated contents included the stomach, transverse colon, gallbladder, and liver (Figure 2B). The left lobe of the liver was fitted into the right thoracic cavity in an anticlockwise rotation. The left lobe of the liver was enlarged, particularly the medial segment, and the surface was uneven and irregular (Figure 2C). The hernia measured approximately 10 cm in diameter. No significant organ damage was observed.

## FINAL DIAGNOSIS

The patient was diagnosed with a right-sided BH, and surgery was planned.

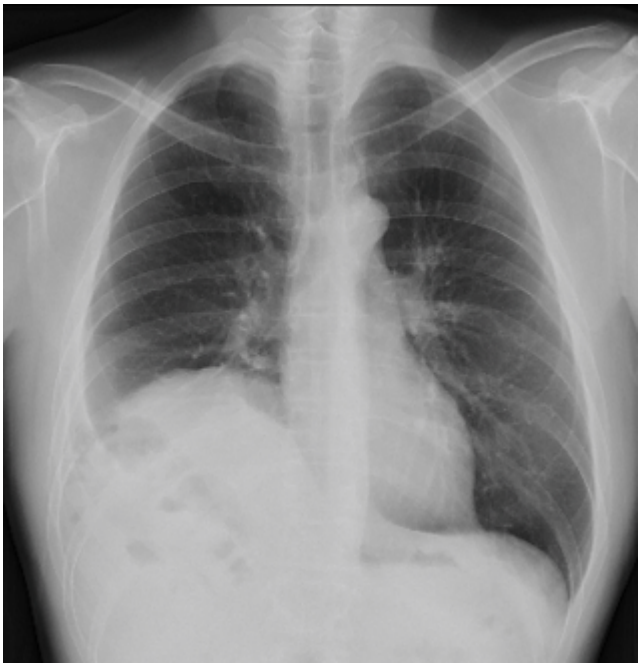

**Figure 1 Chest radiograph.** A chest radiograph showed elevation of the right hemidiaphragm.

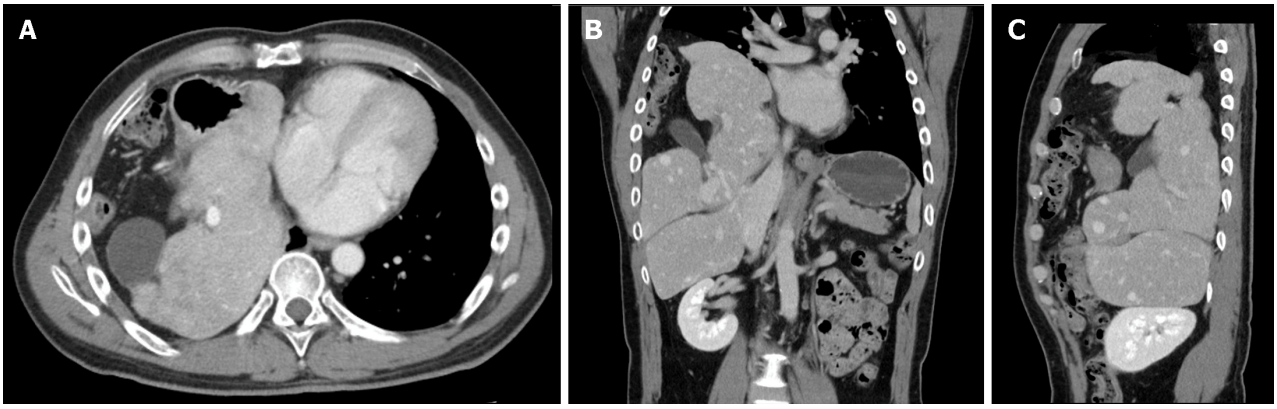


**Figure 2 Computed tomography of the thorax and abdomen.** A: Axial view; B: Coronal view; C: Sagittal view. Computed tomography reveals prolapse of multiple intraabdominal organs into the right thoracic cavity, corresponding to a right-sided Bochdalek hernia. The herniated organs include the stomach, transverse colon, gallbladder, and left lobe of the liver.

## TREATMENT

We performed laparoscopic surgery with the patient in the supine position and the legs spread apart. We inserted a 12-mm camera port at the umbilicus, 5-mm ports into the right upper and left lateral abdomen, and a 12-mm port into the right lateral abdomen. The pneumoperitoneal pressure was 10 mmHg. Intraabdominal observation revealed an approximately 10 cm defect on the posterolateral side of the right diaphragm without a hernia sac. The stomach, transverse colon, greater omentum, liver, and gallbladder were herniated into the thoracic cavity through the diaphragmatic defect (Figure 3A and B). Laparoscopic forceps were used to pull the greater omentum, stomach, and transverse colon back into the abdominal cavity with relative ease. However, the left lobe of the liver was completely lodged in the thoracic cavity, and it was difficult to pull it back into the abdominal cavity, even when the patient was placed in the reverse Trendelenburg position (Figure 3C). Therefore, we decided to approach it thoracoscopically. We inserted an additional 12-mm port into the 7$^{th}$ intercostal space along the right midaxillary line. While pulling the liver toward the abdominal cavity, a tissue exclusion forceps (Endo Retract II®, Medtronic, Tokyo, Japan) was used to push the liver from the thoracic cavity, protecting the liver and allowing it to be returned safely into the abdominal cavity. The diaphragmatic defect measured 10 cm × 8 cm (Figure 3D). The hernia was repaired with interrupted 2-0 Prolene® (Medtronic, Tokyo, Japan) sutures (Figure 3E). In addition, Bard Composix E/X Mesh® (Bard, Tokyo, Japan) was fixed to the diaphragm using an Endo Universal 65 Hernia Stapler® (Medtronic, Tokyo, Japan) (Figure 3F). The operative time was 272 min, and blood loss was 145 mL.

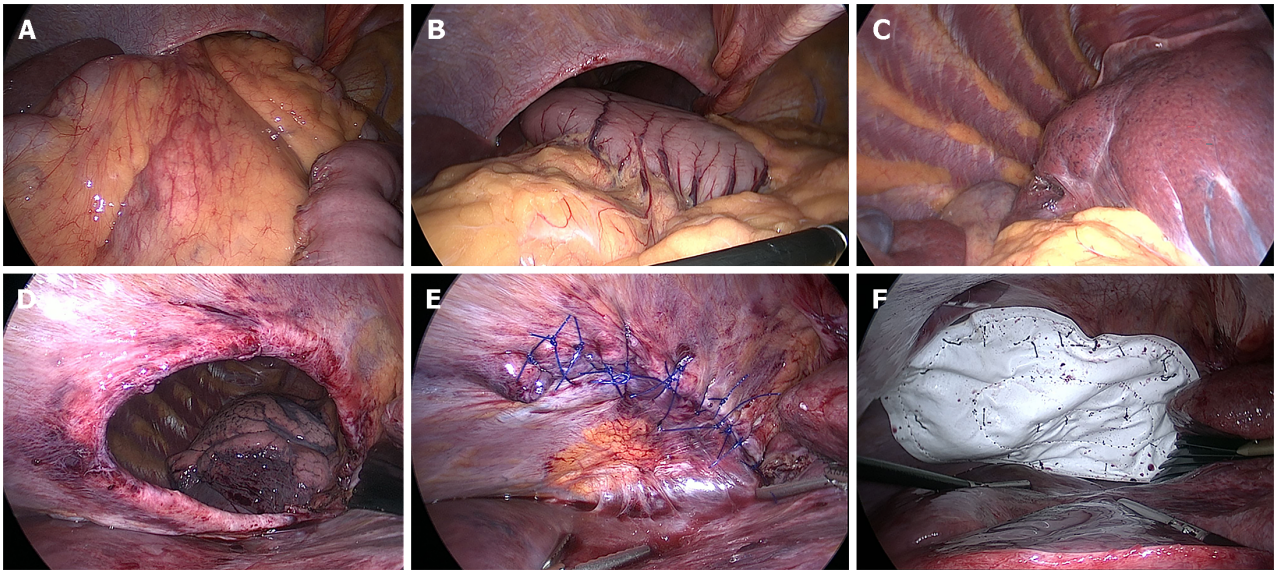


**Figure 3 Surgical findings.** A and B: The stomach, transverse colon, greater omentum, liver, and gallbladder are herniated into the thoracic cavity *via* the diaphragmatic defect; C: The left lobe of the liver is completely trapped in the thoracic cavity; D: The diaphragmatic defect is found to be 10 cm × 8 cm; E: The diaphragmatic defect is closed using interrupted sutures; F: The sutured site is reinforced with Bard Composix E/X Mesh®.

## OUTCOME AND FOLLOW-UP

The patient had an uncomplicated postoperative course and was discharged on the 7th postoperative day. Eight years have elapsed since the surgery, and there has been no recurrence.

## DISCUSSION

A Bochdalek hernia is a congenital posterolateral hernia of the diaphragm that is usually observed during the neonatal period. BH occurs in approximately 1 in 2200-12500 live births but is rare in adults[1-3]. The incidence in adults is estimated to be around 0.17%-6%[9,10]. BH usually occurs on the left-side (80%-90%)[3]. A hernia sac has been reported to be present in 10%-38% of cases[3,11]. In our case, there was no hernia sac. Right-sided hernias are rare because of early closure of the right pleuroperitoneal canal and the location of the liver, which usually acts as a barrier against herniation on the right side[3]. In adults, BH is typically asymptomatic and is an incidental finding[9]. CT is the most useful tool for the diagnosis of BH, and multiple-detector CT is most effective in characterizing diaphragmatic defects[5,9].

Management of BH is performed exclusively through surgical treatment[4,5], specifically returning the herniated organs to the abdominal cavity and repairing the diaphragmatic defect[6-8]. Surgical treatment should be performed whether or not patients have symptoms because perforation or necrosis of the prolapsed organ can cause severe symptoms[12]. In recent years, the number of minimally invasive laparoscopic and thoracoscopic surgeries has increased [6,7,12].

The thoracic approach can be used to easily repair diaphragmatic defects and detach adhesions of the organs that have prolapsed into the thoracic cavity. However, it requires differential lung ventilation, making it difficult to confirm the status of the prolapsed organs. On the other hand, the abdominal approach can be used to easily return the organs if they are not adherent to the thoracic cavity. In this approach, the entire abdominal cavity can be observed, making it possible to confirm and repair damage to the organs. Furthermore, intestinal malrotation, which is often associated with BH, can be easily confirmed and can be repaired and fixed[5,9,10,13]. As there is no established consensus for choosing an approach, the surgical approach should be selected according to the clinical condition of the patient[10,12].

Generally, the diaphragmatic defect is sutured in either an interrupted or continuous manner using nonabsorbable sutures, depending on the size and location of the diaphragmatic defect[5]. The use of mesh reinforcement in the repair of defects depends on the size of the defect. Some reports recommend the use of mesh for defects larger than 20-30 cm, and others use mesh for defects larger than 8 cm or 25 $cm^2$[5].

In this case, the diaphragmatic defect was 10 cm long and 80 $cm^2$ in area; therefore, both direct suturing and mesh reinforcement were performed.

Ramspott *et al*[14] reviewed 44 patients with adult right-sided BH. The mean age was 58 years (22–98 years); 61% of the patients were women and 39% were men. The most common symptom was dyspnea (50%), followed by abdominal pain (43%) and nausea (23%); the condition was asymptomatic in 23% of patients. The most commonly herniated organs were the colon (52%), followed by the small intestine (43%), liver (27%), kidneys (18%), gallbladder (4%), and pancreas (2%). The abdominal approach (laparotomy, 34%; laparoscopy, 34%) was more commonly used than the thoracic approach (thoracotomy, 16%; thoracoscopy, 14%). Thoracoabdominal approaches were also performed in 16% of the cases. Recently, robot-assisted laparoscopic surgery (5%) and robot-assisted thoracoscopic surgery (5%) have also been

reported. The diaphragmatic defect was repaired using direct suturing in 45% of the cases and mesh reinforcement in 43%. A combination of direct suturing and mesh was used in 16% of cases.

BH is frequently associated with other malformations, such as pulmonary hypoplasia, cardiac malformation, and intestinal malrotation. Furthermore, right-sided BHs are generally associated with hypoplasia or atrophy of the right lobe of the liver[13,15,16]. In these cases, atrophy and hypoplasia of the right lobe of the liver can cause herniation of abdominal organs through the defect into the thoracic cavity[13]. In this case, there was marked enlargement of the left lobe of the liver, but no hypoplasia or atrophy of the right lobe, which is considered to be extremely rare. In cases of BH in which the liver protrudes into the thoracic cavity, surgery can be performed safely by combining laparoscopic and thoracoscopic approaches. To our knowledge, no such cases have ever been reported previously.

## CONCLUSION

Right-sided BH in adults with the liver protruding into the thoracic cavity is extremely rare. We successfully performed a combined laparoscopic and thoracoscopic surgery for an adult with right-sided BH with massive liver prolapse and abnormal liver morphology.

## FOOTNOTES

**Author contributions:** Mikami S provided patient information and wrote the manuscript; Mikami S, Kimura S, Matsushita T, Fukuoka A, and Enomoto T are the surgeons who performed the operation and evaluated the patient; Tsukamoto Y, Hiwatari M, and Hisatsune Y prepared the figures and collected the data; Otsubo T supervised the study; all authors have read and approved the final manuscript.

**Informed consent statement:** Informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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CASE REPORT

# Immediate secondary rhinoplasty using a folded dermofat graft for resolving complications related to silicone implants: A case report

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**Specialty type:** Surgery

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## Abstract

*BACKGROUND*

Various surgical techniques have been developed to enhance the nose shapes of Asian patients. Silicone implant augmentation rhinoplasty is widely used because it is relatively easy to perform and often yields satisfactory outcomes. However, this technique may lead to complications, including ischemia, necrosis, and over-augmentation. The most appropriate management of these complications, including infection, is immediate implant removal and revision surgery once the accompanying inflammation has healed. Occasionally, the patient may experience distress from nasal deformities during the intervention period.

*CASE SUMMARY*

Herein, we describe the case of a patient who underwent a secondary dorsal augmentation, with a folded dermofat graft harvested from the inguinal area and simultaneous implant removal, successfully preventing dimpling of the nasal deformity.

*CONCLUSION*

This surgical method can effectively manage implant-related complications following augmentation rhinoplasty using a silicone implant and provide satisfactory patient outcomes.

**Key Words:** Complications; Nose deformities; Acquired; Rhinoplasty; Dermofat; Surgery; Plastic; Case report

**Core Tip:** This case report presents noteworthy findings, as we introduce an innovative secondary rhinoplasty technique using a folded dermofat graft to address complications arising from silicone implant augmentation rhinoplasty. This procedure successfully maintained the nasal contour without complications after silicone implant augmentation rhinoplasty. This approach enhances patient satisfaction and provides a valuable solution to challenges associated with traditional methods, making it a promising option in managing complications following augmentation rhinoplasty.

**Citation:** Kim H, Kim JH, Koh IC, Lim SY. Immediate secondary rhinoplasty using a folded dermofat graft for resolving complications related to silicone implants: A case report. *World J Clin Cases* 2024; 12(14): 2426-2430
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## INTRODUCTION

Various surgical techniques have been developed in Asia to reshape flat, blunt noses into more desired shapes[1,2]. Among these, implant augmentation rhinoplasty has been widely used because it is simple to perform and can produce a wide range of alternative nose shapes[3]. However, this technique can also cause severe complications that require implant removal[4,5]. Correcting a nasal dimpling deformity that occurs following implant removal is challenging when the second procedure is performed following delays owing to complications. Herein, we present an immediate secondary rhinoplasty technique that minimizes dimpling in nasal deformities using a folded dermofat graft harvested from the inguinal area.

## CASE PRESENTATION

### *Chief complaints*

The patient complained of pain and discomfort in the nose.

### *History of present illness*

Forty months after the surgery, the dorsum of the nose became erythematous and slightly inflamed, likely caused by excess pressure from the implant.

### *History of past illness*

A 34-year-old woman without any underlying diseases underwent closed reduction of the nasal bone for a nasal bone fracture and simultaneous augmentation rhinoplasty with a silicone implant.

### *Personal and family history*

The patient had no significant past medical history or family history.

### *Physical examination*

Upon admission, the contour of the implant became more conspicuous as the skin at the tip of the nose became thinner (Figure 1).

### *Laboratory examinations*

All results, including white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level, were within the normal range.

### *Imaging examinations*

Not applicable.

## FINAL DIAGNOSIS

Nasal tip retraction with inflammation after augmentation rhinoplasty using a silicone implant.

## TREATMENT

We highly suspected an infection and a contracture and decided to remove the implant. We scheduled an immediate

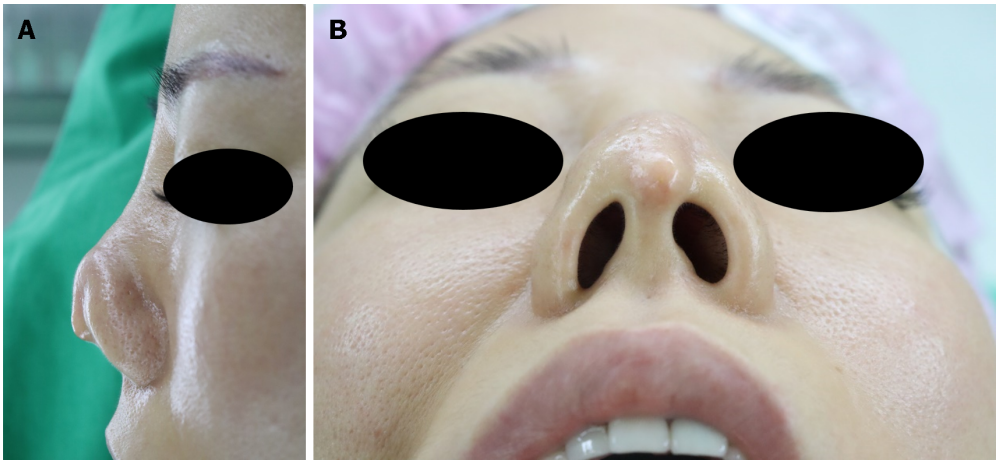


**Figure 1 Photograph taken before the secondary rhinoplasty, 40 months after the initial rhinoplasty.** A: Lateral view; B: Worm's eye view. The skin at the tip of the nose had become thinner, contracture had occurred, and the outline of the implant was visible.

secondary rhinoplasty using a folded dermofat graft harvested from the inguinal area to replace the original implant.

The distance from the nasal root to the nasal tip was 4.7 cm, and a graft double this length was designed for the folded dermofat graft. Using a transcolumellar approach, the implant was exposed by dissecting the cartilage and bone below the cartilaginous plane. The implant and adherent scar tissue were fully removed. The dermofat was harvested from the left inguinal area (approximately 1.0 cm × 9.5 cm) and folded using a 3-0 polydioxanone suture. The folded graft was inserted into the pocket of the nasal dorsum and fixed transcutaneously to the nasal root using a bolster suture (Figure 2). To prevent postoperative infection, a second-generation cephalosporin antibiotic was administered intravenously during the hospital stay for 2 d, followed by a 1-wk course of an oral first-generation cephalosporin antibiotic upon discharge. The columella and bolster stitches were removed on the 5$^{th}$ postoperative day, and those of the intranasal and donor sites were removed on the 12$^{th}$ postoperative day. The wound healed without any complications. Seven months later, the patient presented to our outpatient clinic. The shape of the nose was satisfactory, and no complications were noted (Figure 3).

## OUTCOME AND FOLLOW-UP

Seven months later, the shape of the nose was satisfactory without any complications.

## DISCUSSION

The nose of an Asian person is characterized by a limited projection of the nasal tip and an ala that is wider than the height of the nose[6]. Rhinoplasty is frequently performed on this nose type. Augmentation rhinoplasty is performed to increase the length and height of the dorsal and tip projections of the nose[2]. Augmentation rhinoplasty with silicone implants is the most widely performed procedure of this type because it helps achieve aesthetic goals for nose shapes relatively easily[3]. However, this surgery can sometimes result in complications, such as implant migration, contour irregularity, implant deviation, infection, extrusion, contracture, and skin lesions[4,5]. In particular, thinning of the skin due to foreign body reactions, scarring, and encapsulation around the implant may result in skin contracture, visibility of the contour of the implant, and even extrusion in severe cases[7].

In cases of complications accompanied by infection, the implant must be removed. However, determining the time for revision rhinoplasty can be challenging. A secondary rhinoplasty is recommended several months after implant removal after signs of infection are absent[8]. However, correction can be complex if dimpled nasal deformities, including excessive collapse and contracture, occur following implant removal. In the interim period, patients must tolerate this deformity and may experience psychological discomfort before undergoing a secondary rhinoplasty. Therefore, removing the implant and performing a secondary rhinoplasty concurrently is ideal.

Dermofat grafts have several advantages. For example, the autologous augmentation material comprises a full-thickness dermis and subcutaneous tissues. Since dermofat grafts are autologous tissues, they are relatively more susceptible to infection and foreign body reactions than other implant materials. The degree of volume maintenance at the surgical site may decrease over time. Depending on the location of the donor site, differences may occur between the thickness and fat density of the dermis[9,10]. In this study, we addressed these shortcomings using the "folded" dermofat method, which involves folding the collected dermofat in half. In general, the gluteal fold is the preferred donor site because of the presence of dense fat and a thick dermis[10,11]. However, the operative time may be prolonged when using this approach because the patient must be repositioned during the surgery. In addition to a longer surgical time, the cost burden to the patient is increased owing to the need for a longer duration of general anesthesia, and the patient

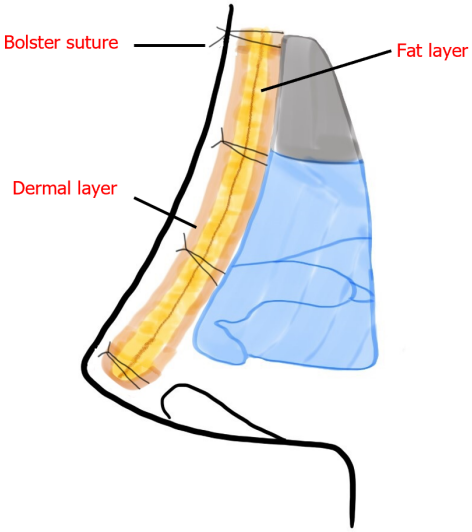


**Figure 2 Schematic diagram of the procedure.** The dermofat graft was folded in half, with the fat layer on the inside and the dermal layer facing outward. The folded graft was inserted into the pocket of the nasal dorsum and fixed transcutaneously on the nasal root using a bolster suture.

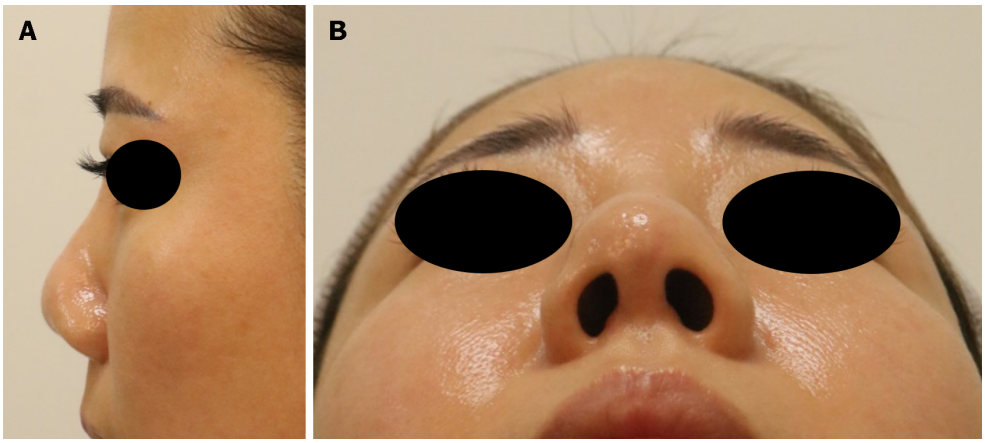


**Figure 3 Photograph taken seven months after the secondary rhinoplasty.** A: Lateral view; B: Worm's eye view. Despite removing the implant, the nasal height was not significantly depressed and severe deformity did not occur as the contracture at the nasal tip was corrected.

may experience additional discomfort. The resultant scars can also be conspicuous if the patient wears a bikini. Because this part of the body continuously bears weight while sitting, wound healing can be slow and the incidence of complications, such as wound dehiscence, is high. When a dermofat graft is performed using the gluteal fold as the donor site, patients often complain of a blunt protruding nose because the dermis is excessively thick. For this procedure, we chose the inguinal area. Relatively large grafts can be obtained from this region, owing to the laxity of the skin, which makes it easier to create a more natural shape. Harvesting and grafting of dermofat can also be performed concurrently with the patient in the supine position, resulting in a very short operative time and high patient satisfaction. Because the dermis of the inguinal area is relatively thin[9], we were able to secure a satisfactory outcome with a sufficient nose height using this approach.

## CONCLUSION

The folded dermofat graft method can be used to effectively manage implant complications following augmentation rhinoplasty with a silicone implant. In our case, a high level of patient satisfaction was achieved using this method.

## FOOTNOTES

**Author contributions:** Koh IC contributed to conceptualization, methodology, software, and validation; Lim SY contributed to conceptualization, validation, manuscript writing and editing, and supervised the study; Kim JH contributed to validation, formal

analysis, investigation, resources, data curation, manuscript writing and editing, project administration, and funding acquisition; Kim H contributed to visualization, manuscript writing and editing, and supervised the study; all authors have read and approved the final manuscript.

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CASE REPORT

# Sustained remission of Cronkhite-Canada syndrome after corticosteroid and mesalazine treatment: A case report

Ya-Lan Chen, Rui-Yao Wang, Ling Mei, Ran Duan

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## Abstract

### *BACKGROUND*

Cronkhite-Canada syndrome (CCS) is a rare disease of unknown etiology. The optimal treatment for CCS remains unknown. Treatment with corticosteroids is considered the mainstay treatment because of its high efficacy, but the therapeutic strategy for steroid-resistant CCS is not yet established.

### *CASE SUMMARY*

This is the case of an 81-year-old woman who was diagnosed with CCS. Given her severe diarrhea, nausea, vomiting, and hypoproteinemia, hormone therapy (40 mg/d) was administered, and the symptoms improved within 1 wk. After 3 mo, the patient had no obvious symptoms. The polyps were significantly reduced on review gastroscopy and colonoscopy, thus hormone reduction gradually began. The hormone level was maintained at 10 mg/d after 6 mo. Despite the age of the patient and the side effects of hormones, the patient had no obvious discomfort. However, hormone drugs were discontinued, and mesalazine was administered orally at 3 g/d. The patient's symptoms continued to improve after a follow-up of 5 years.

### *CONCLUSION*

Corticosteroids and mesalazine are potential treatment options for CCS.

**Key Words:** Cronkhite-Canada syndrome; Corticosteroids; Mesalazine; Gastrointestinal polyposis; Case report

**Core Tip:** Cronkhite-Canada syndrome (CCS) is a rare disease of unknown etiology. The optimal treatment for CCS remains unknown. Treatment with corticosteroids is considered the mainstay treatment because of its high efficacy, but the therapeutic strategy for steroid-resistant CCS is not yet established. The current report describes a case of CCS wherein after the initial therapy with corticosteroids, gastrointestinal symptoms were resolved and polyps were significantly reduced. This was followed by mesalazine monotherapy, which led to long-lasting remission. Thus, corticosteroids and mesalazine are potential treatment options for CCS.

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## INTRODUCTION

Cronkhite-Canada syndrome (CCS) is characterized by gastrointestinal polyposis and ectodermal changes (*i.e.*, to the hair, skin, nails, and tongue)[1]. It was first reported in 1955[2]. Since then, more than 600 cases have been reported[3]. Due to the rarity of the syndrome, evidence-based therapies do not exist. Existing regimens combine multiple therapies, but none of them are consistently effective[4].

Although corticosteroids are routinely used as first-line therapy, many cases have been reported to be steroid-resistant [5]. Furthermore, associated side effects, such as sepsis and thrombosis, may occur after the induction of steroid therapy [6]. The current report describes a case of CCS wherein after the initial therapy with corticosteroids, gastrointestinal symptoms were solved and polyps were significantly reduced. This was followed by mesalazine monotherapy, which led to long-lasting remission.

## CASE PRESENTATION

### *Chief complaints*

An 81-year-old Chinese woman reported a 2-months history of watery diarrhea, severe nausea and vomiting, alopecia, and dysgeusia.

### *History of present illness*

The patient visited a hospital in October 2018 due to a 2-months history of watery diarrhea, described as yellow watery stool, without pus or blood, occurring about 20 times a day. She had frequent nausea and vomiting, followed by reduced taste, poor appetite, and inability to eat. General weakness, bilateral limb edema, severe hair loss, and skin melanosis were also observed. She noted no obvious abdominal pain nor distension, acid reflux or heartburn, panic, or shortness of breath. However, she reported dysgeusia and weight loss of 10.0 kg in the past 2 months. The symptoms did not improve despite treatment with eprazole for acid inhibition, electrolyte correction, and probiotics.

### *History of past illness*

The patient had hypertension and coronary heart disease.

### *Personal and family history*

The patient's family history revealed no cases of gastrointestinal polyposis or colorectal malignancy. The patient had no smoking or drinking habits. She did not use special drugs, nor was she exposed to toxic substances.

### *Physical examination*

The patient's vital signs were stable. Her hair and eyebrows were sparse, and skin pigmentation was noted around the palms, lips, and abdomen on both sides (Figure 1A and B). Her oral mucosa showed no ulcerations or leukoplakia. The cardiopulmonary examination showed no abnormalities. She had a flat abdomen, without gastrointestinal type, peristaltic wave, varicose veins, direct nor rebound tenderness, or muscle tension. The nails of both thumbs were yellow and thick (Figure 1C).

### *Laboratory examinations*

Laboratory data revealed hypoproteinemia (albumin level: 26 g/L). Routine blood and urine tests were normal. Stool examinations were positive for occult blood and three types of parasites. However, stool cultures showed no

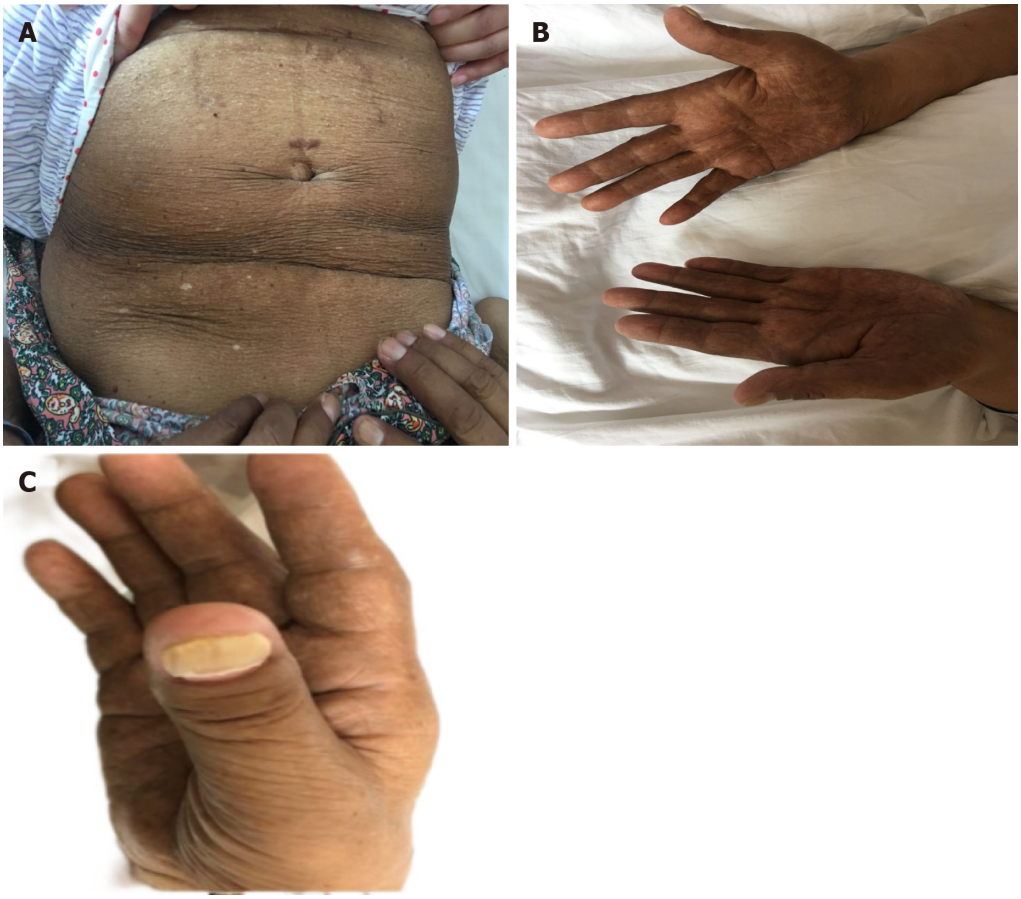


**Figure 1 Before initial treatment.** A and B: Diffuse melanosis of the skin; C: Thickened, brittle, and yellow nails.

abnormalities. Potassium and calcium levels were 2.9 and 1.94 mmol/L, respectively. The erythrocyte sedimentation rate was elevated (73.0 mm/h), but the C-reactive protein level was normal. The routine kidney function tests were similarly normal. An immunological test revealed that the patient was negative for anti-nuclear antibodies, and thyroid function was normal. Epstein-Barr virus and cytomegalovirus were negative, and tumor markers were negative. Adrenocorticoids were within the normal range. A $^{13}C$ breath test revealed that she was negative for *Helicobacter pylori* (*H. pylori*).

### *Imaging examinations*

Endoscopic findings revealed numerous polyps in the stomach (Figure 2A and B) and colon (Figure 2C and D). Polyps were mostly pedunculated or fatty, around 2-5 cm in diameter, with different morphologies: Nodular, grape-like, or coral-like. Histologic findings of the polyps revealed prominent cystic dilation of the crypts and expanded inflamed lamina propria, consistent with inflammatory polyps (Figure 3).

## FINAL DIAGNOSIS

The final diagnosis was CCS.

## TREATMENT

The patient's symptoms were significant, thus methylprednisolone (40 mg/d) was administered. Her symptoms (*i.e.*, nausea, vomiting, and diarrhea) improved within 1 wk and disappeared after 1 mo. The drug was then reduced by 4 mg/d every 2 wk. After review, hormone reduction gradually began, and the hormone level was maintained at 8 mg/d after 6 mo. Despite the age of the patient and the side effects of hormones, the patient had no obvious discomfort. However, hormone drugs were discontinued, and mesalazine was administered orally at 3 g/d.

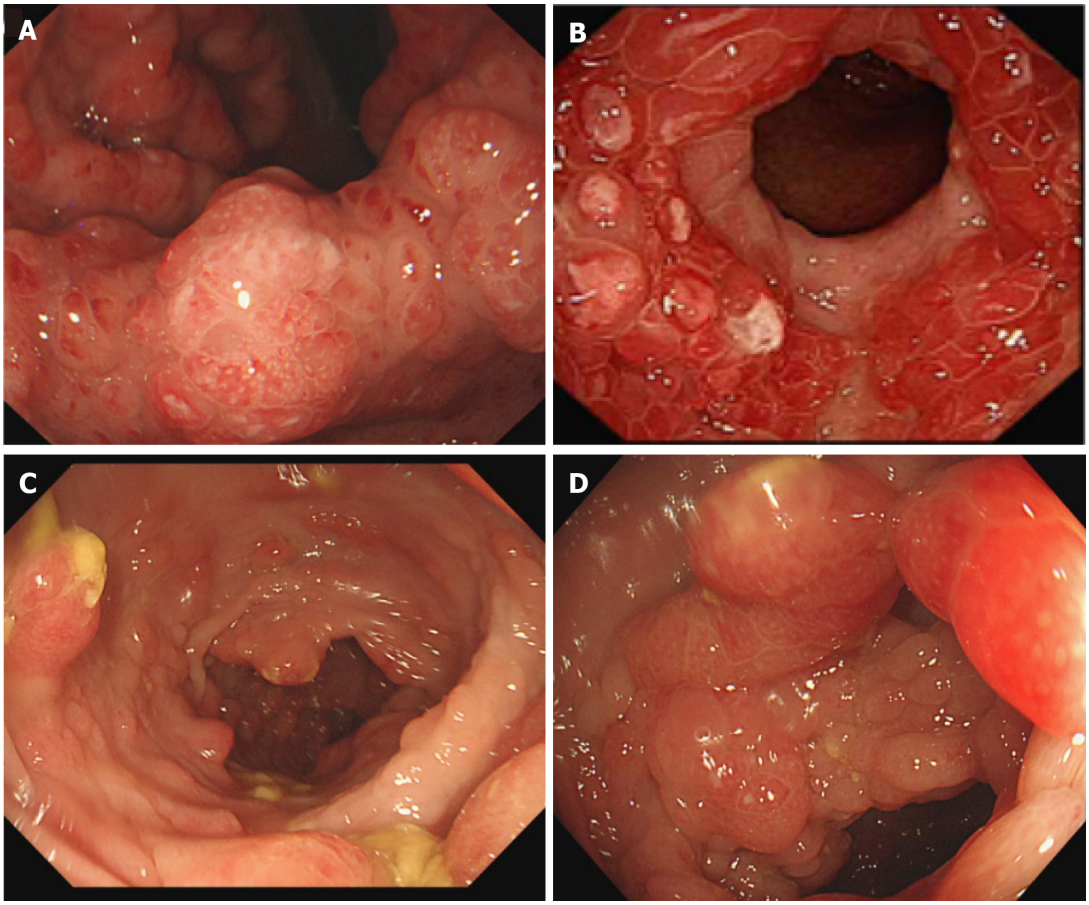


**Figure 2 Endoscopic images before treatment.** A and B: The initial gastrointestinal endoscopy showed multiple reddish inflammatory polyps and edematous adjacent mucosa in the angle and antrum of the stomach; C and D: Preliminary colonoscopy showed multiple red inflammatory polyps and adjacent mucosal edema in the colon and rectum.

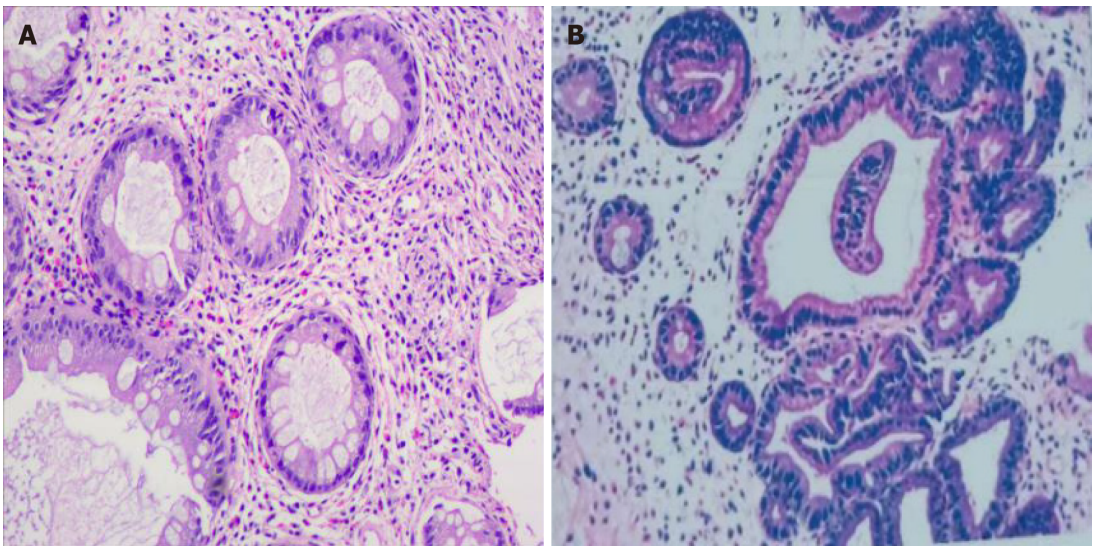


**Figure 3 Polyps revealed prominent cystic dilation of the crypts and expanded inflamed lamina propria, consistent with inflammatory polyps.**

## OUTCOME AND FOLLOW-UP

After 3 mo of hormone therapy, the patient had reduced lower limb edema, normal electrolytes and albumin, and skin color (Figure 4A). Gastrointestinal symptoms were also resolved. However, her nails did not improve (Figure 4B). Polyps were significantly reduced on gastroscopy and colonoscopy (Figure 5), especially since the colon was scattered with

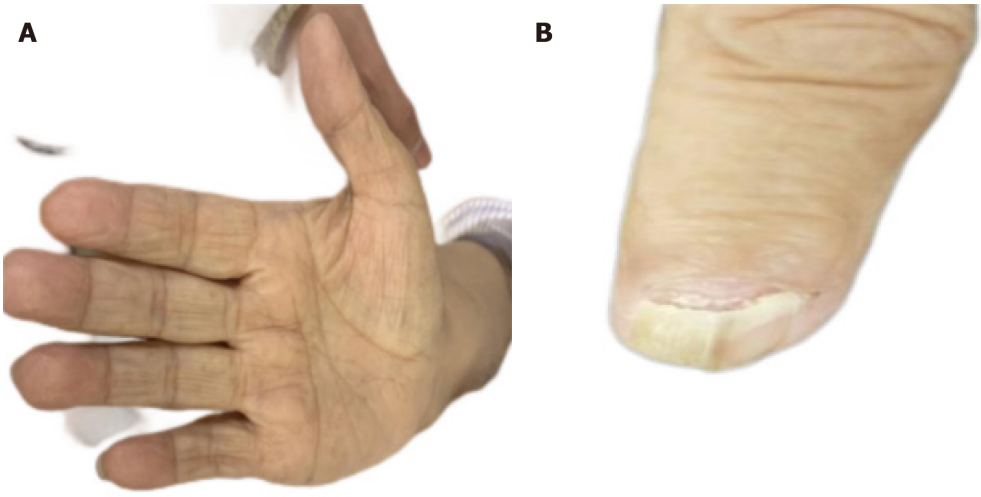


**Figure 4 After 3 mo of initial treatment.** A: Normal skin color; B: No improvement in the nails.

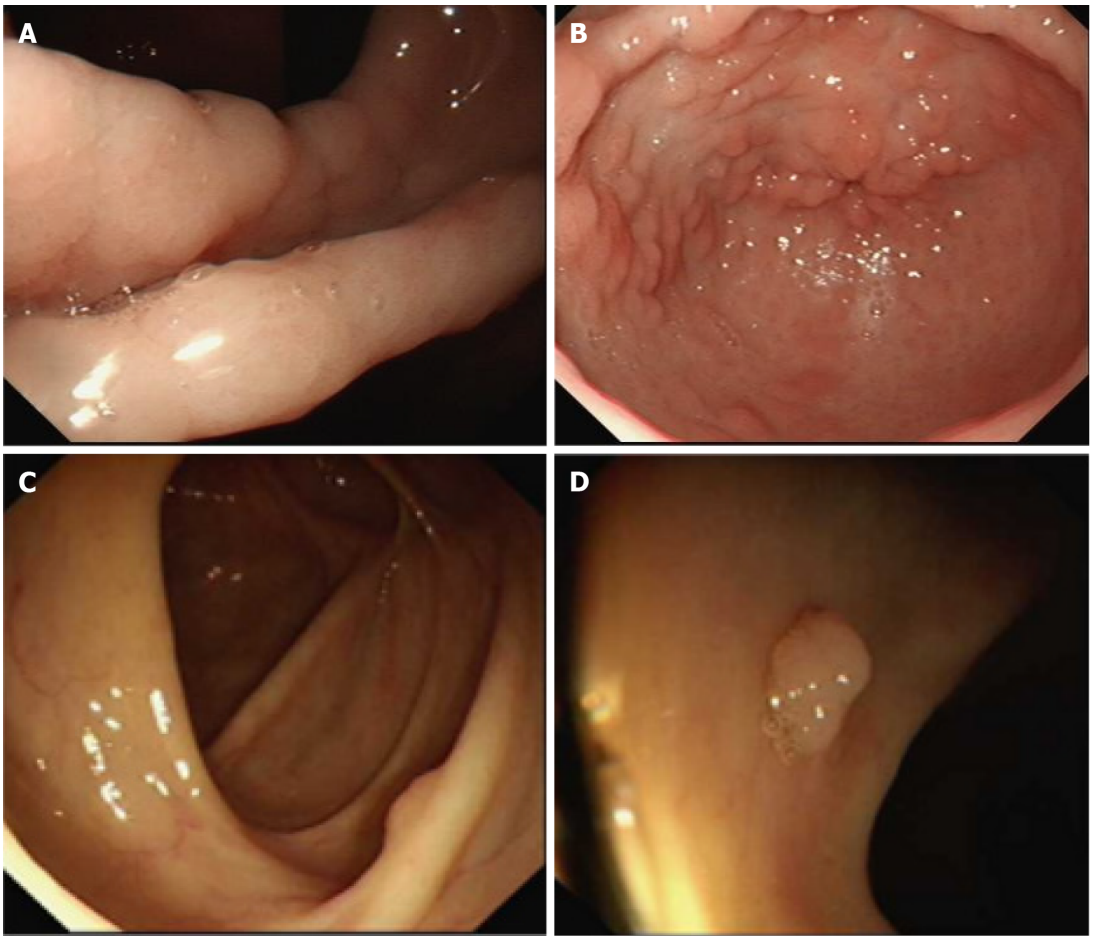


**Figure 5 Endoscopic images after treatment.** A and B: Three months after treatment, there was a marked improvement in polyp number in the angle and antrum of the stomach; C and D: The intestinal cavity displayed scattered polyps.

polyps.

The patient's symptoms continued to improve after a follow-up of 5 years. No obvious nausea, vomiting, or diarrhea occurred after mesalazine administration. However, the patient refused to undergo gastroenteroscopy, thus the effect of mesalazine could not be evaluated more accurately.

## DISCUSSION

CCS is an exceedingly rare clinical syndrome first reported by the American physician Cronkhite and the radiologist Canada in the *New England Journal of Medicine* in 1955[2]. The term "Cronkhite-Canada syndrome" was first identified by Jarnum and Jensen[7] in 1966. The main clinical manifestations of CCS are alopecia, skin pigmentation, finger (toe) nail malnutrition, and gastrointestinal polyps on endoscopy. CCS is also called (gastrointestinal) polyposis-pigmentation-alopecia-finger (toe) nail malnutrition (atrophy) syndrome[8,9].

Over 60 years have passed since CCS was first reported, but its pathophysiology remains unclear. Given its rarity, a standard treatment for CCS has not yet been established. Currently, CSS treatment strategies include corticosteroids, anabolic steroids, proton pump inhibitors, H2 receptor antagonists, nutritional support, sodium glyonate, immunosuppressive agents, antibiotics, surgery, 5-aminosalicylic acid, rituximab, eradication of *H. pylori*, and a combination of these therapies[6]. Corticosteroids are considered the mainstay treatment in CCS because of their high efficacy. To date, no guidelines[6] on the recommended dose and duration of corticosteroids in CCS exist, and the prognosis is unclear[10]. However, not all patients respond sufficiently; some may relapse when steroids are tapered[5], and serious adverse reactions may occur during hormone therapy[6].

In the current case report, the patient showed a favorable initial response to corticosteroid therapy paired with nutritional supplements. However, the risk of severe infection and femoral head necrosis due to long-term, heavy use of hormones was high, given the patient's older age. Therefore, an alternative treatment was required when her symptoms had improved. Mesalazine has been successfully administered for the treatment of inflammatory bowel disease. It can reduce intestinal inflammation and promote mucosal repair. Independent of its anti-inflammatory features, it appears to have an antiproliferative effect on colorectal adenomas[11]. Prior studies[12,13] demonstrated sustained remission after the use of oral mesalazine and corticosteroids. The patient's symptoms were notable at presentation, thus prednisone therapy (40 mg/d) was initiated. After 3 mo, the patient had no obvious symptoms. Polyps were significantly reduced on gastroscopy and colonoscopy, and hormone reduction gradually began. The dose was maintained at 10 mg/d after 6 mo. Thereafter, hormone drugs were discontinued, and mesalazine was administered orally at 3 g/d instead. The patient's symptoms continued to improve after a follow-up of 5 years.

## CONCLUSION

In conclusion, the current study suggests that the 5-year mortality rate of CCS is as high as 55%. It is a rare, non-hereditary disease of unknown origin. The etiology and optimal treatment for this syndrome remain unknown. To date, no standard therapeutic strategies for CCS have been established. Although improvement in gastrointestinal symptoms may result from high-dose corticosteroid treatment, mesalazine has also been shown to maintain remission of intestinal tract lesions. Therefore, mesalazine could be an additional or alternative modality for the treatment of CCS.

## FOOTNOTES

**Co-first authors:** Ya-Lan Chen and Rui-Yao Wang.

**Author contributions:** Chen YL and Wang RY contributed equally to this work as co-first authors; Chen YL, Wang RY, and Mei L contributed to study conceptualization; Chen YL, Wang RY, Mei L, and Duan R contributed to data interpretation; Chen YL and Wang RY wrote the manuscript; Duan R revised the manuscript.

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CASE REPORT

# Type one autoimmune pancreatitis based on clinical diagnosis: A case report

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## Abstract

*BACKGROUND*

Autoimmune pancreatitis (AIP) is a rare form of autoimmune-mediated pancreatitis, which is easily misdiagnosed as pancreatic cancer and thus treated surgically. We studied the diagnosis and treatment of a patient with type 1 AIP recently admitted to our hospital, and reviewed the literature to provide a reference for clinical diagnosis of AIP.

*CASE SUMMARY*

The chief complaint was yellowing of the body, eyes and urine for 21 d. The patient's clinical presentation was obstructive jaundice and imaging suggested pancreatic swelling. It was difficult to distinguish between inflammation and tumor. Serum immunoglobulin G4 (IgG4) was markedly elevated. IgG4 is an important serological marker for type 1 AIP. The patient was diagnosed with AIP, IgG4-related cholangitis, acute cholecystitis and hepatic impairment. After applying hormonal therapy, the patient's symptoms improved significantly. At the same time, imaging suggested that pancreatic swelling subsided, and liver function and other biochemical indicators decreased. The treatment was effective.

*CONCLUSION*

In patients with pancreatic swelling, the possibility of AIP should be considered.

**Key Words:** Autoimmune pancreatitis; Characteristics; Diagnosis; Immunoglobulin G4; Case report

**Core Tip:** Autoimmune pancreatitis (AIP) has a low global incidence. Patients with pancreatic swelling need to differentiate between general pancreatitis and AIP. We report a clinical case and review the diagnosis of AIP in terms of clinical symptoms, physical examinations, laboratory examinations, and imaging examinations. To improve clinicians' ability to diagnose AIP will reduce misdiagnosis and increase the effectiveness of treatment.

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## INTRODUCTION

Autoimmune pancreatitis (AIP) is a rare autoimmune-mediated pancreatitis with an incidence of about 10.1/100000[1], whose pathogenesis is still unclear and is effectively treated with corticosteroids. However, AIP is difficult to differentiate from general pancreatitis or pancreatic cancer. It is important to improve the diagnosis and differentiation ability of clinicians. In this article, we report the medical record data of a representative patient with type 1 AIP recently admitted, to provide a reference for clinicians to diagnose the disease and improve understanding and diagnosis of AIP.

## CASE PRESENTATION

### *Chief complaints*

A 43-year-old Chinese man suffered from yellowing of the skin and mucous membranes of the eyes for 21 d.

### *History of present illness*

A 43-year-old male patient was admitted on July 3, 2023, without any obvious cause. He had yellow coloring of the body and eyes, yellow urine, yellow stool, no itching of the skin, no anorexia, no nausea and vomiting, no chills, no fever, and no abdominal pain. On July 22, 2023, the patient went to the outpatient clinic of the Shunde Hospital of the Guangzhou University of Traditional Chinese Medicine in Guangzhou for diagnosis and treatment. His liver function was checked at the emergency clinic: Alanine aminotransferase 324.0 U/L, alkaline phosphatase 660.39 U/L, γ-glutamyl transferase 1173.96 U/L, total bilirubin 129.60 μmol/L, conjugated bilirubin 50.0 μmol/L, unconjugated bilirubin 27.10 μmol/L, and δ-bilirubin 52.50 μmol/L. White blood cell count was 13.61 × $10^9$/L, absolute neutrophil count was 8.14 × $10^9$/L. Hepatitis A antibody IgM, and five hepatitis B indicators were normal. Ultrasound showed a suspected solid focal lesion in the head of the pancreas (the nature of which was to be determined), dilatation of the upper portion of the common bile duct and intraductal bile ducts, and enlargement of the pancreas. Polyene phosphatidylcholine was given to protect the liver after symptomatic treatment, but without symptom relief. On July 24, 2023, the patient was hospitalized for further diagnosis and treatment.

### *History of past illness*

The patient denied past medical history.

### *Personal and family history*

The patient reported no significant abnormalities in his personal or family history.

### *Physical examination*

Vital signs were stable, the whole body of the skin and mucous membranes showed moderate yellow stain, and the sclera showed mild yellow stain. The whole abdomen was flat, no gastrointestinal type and peristaltic wave, no epigastric pulsation, no varicose veins in the abdominal wall, soft abdomen, no abdominal pressure, no rebound pain, and no palpable mass.

### *Laboratory examinations*

There were no significant abnormalities in carcinoembryonic antigen, carbohydrate antigen 19-9 (CA19-9), α-fetoprotein, hepatitis C immunoglobulin G (IgG) antibody, autoimmune liver disease quantitative test, autoimmune liver disease antibody spectrum, and hepatitis E test.

### *Imaging examinations*

Computed tomography (CT) plain scan, CT enhanced scan and reconstruction of the whole abdomen showed: pancreatic swelling and peripancreatic oozing (inflammatory changes suggestive of AIP); and dilated intra- and extrahepatic bile ducts. Cholecystitis and prostate calcification were considered.

At the time of admission, CT plain scan and enhanced scan of the whole abdomen showed swollen pancreas, and pericardium-like low density shadow at the edge with sheath-like changes. CT enhanced scan showed that the pancreatic ducts were not dilated, and peripancreatic oozing. There was no dilatation of the pancreatic ducts and some peripancreatic exudation. The intra- and extrahepatic bile ducts were dilated and the gallbladder was slightly enlarged (Figure 1).

### *Further diagnostic work-up*

The patient was positive for hepatic schistosomiasis IgG antibody. Magnetic resonance cholangiopancreatography (MRCP) showed widespread dilatation of intrahepatic bile ducts, and proximal middle dilatation of the common bile duct. IG4 level was elevated to 14.7 g/L (normal range: 0.03–2.01 g/L). After admission, he received hepatoprotective, choleretic, anti-inflammatory, anti-infective and supportive symptomatic treatment. Antibodies to hepatitis A, hepatitis B, hepatitis C and hepatitis E viruses and autoimmune liver disease were normal.

## FINAL DIAGNOSIS

Combining the patient's history, signs, laboratory examinations, and imaging examinations, the final diagnosis was: AIP, IgG4-related cholangitis, acute cholecystitis and hepatic impairment.

## TREATMENT

On July 29, 2023, the patient initiated hormonal shock therapy (prednisone acetate tablets, 45 mg/d), and was discharged from the hospital on August 2, 2023. He also received hepatoprotective therapy (diammonium glycyrrhizinate enteric-coated capsules 150 mg *tid*, bicyclol tablets 50 mg *tid*). The bicyclol tablets were changed to glucuronolactone tablets (0.2 g *tid*) on August 10. Ursodeoxycholic acid capsules were added on August 24 (250 mg *qd*), and the dose of prednisone acetate tablets was adjusted to 35 mg/d. The dose of prednisone acetate tablets was adjusted further to 25 mg/d, 15 mg/d and 10 mg/d on September 9, September 23 and October 7, respectively. The treatment was maintained until now. The results of laboratory tests during treatment were significantly improved (Table 1). Ultrasound comparison before and after treatment is shown in Figures 2 and 3.

## OUTCOME AND FOLLOW-UP

The patient's skin mucosa and eye color returned to normal. Liver function and bilirubin returned to normal. IgG4 gradually approached the normal range. The size of the pancreas was close to normal in imaging examination. The patient was recommended to undergo repeat pancreatic ultrasound elastometry.

## DISCUSSION

AIP is a rare form of autoimmune-mediated pancreatitis, which is distributed worldwide, with a predominance of type 1. The clinical presentation is mainly obstructive jaundice and epigastric pain. The pathogenesis of the disease is still unclear, and it often involves extrapancreatic organs, such as the biliary tract, salivary glands and gastrointestinal tract, and hormonal therapy is effective. The imaging manifestations of AIP are diffuse and limited. It is difficult to distinguish from general pancreatitis when it is diffuse, and when it is a mass, it is easy to misdiagnose as pancreatic cancer. It is important to strengthen clinicians' ability to diagnose AIP to avoid delaying treatment or increasing patients' physical, economic and psychological burdens. In this paper, we discuss the diagnosis of AIP in a case admitted to our hospital and retrospectively analyze the relevant data.

We searched for cases in the past 5 years in PubMed with "(autoimmune pancreatitis) and (case report)". In accordance with the 2010 International Association of Pancreatic Diseases (IAPD) diagnostic criteria for AIP, 50 relevant case reports were selected, totaling 51 cases of AIP (Table 2).

The male-to-female ratio was 3.25:1 (39:12) in all age groups. Jaundice and epigastric pain predominated in 33 (65%) and 22 (43%) of the patients, and the tumor index CA19-9 was elevated or normal in a similar proportion of the laboratory tests, while the serological IgG4 test was elevated in 45 (88%) patients. Imaging showed swelling of the head of the pancreas in 30 cases, the tail of the pancreatic body in seven, and the entire pancreas in 14. About 53% of AIP cases were diagnosed primarily by puncture biopsy, but 14 (27%) patients were eventually diagnosed surgically with AIP.

Type 1 AIP is common in middle-aged and older men, and the 50–60 years' age group is common, with no specific clinical manifestations, but mostly obstructive jaundice, epigastric pain and other symptoms. The fifty-one cases of AIP in the literature review were diagnosed with a single symptom of obstructive jaundice, which may be related to the fact that the biliary tract has the highest rate of involvement in AIP.

Serum IgG4 is an important and specific serological marker for type 1 AIP[2], and the IgG4 in the patient diagnosed in our hospital was 14.7 g/L, which was > 7 times the upper limit of normal value. In the literature, 88% of the patients had elevated IgG4, which means that it is an important diagnostic indicator for AIP. In addition, CA19-9 may be elevated in

**Table 1 Laboratory results during treatments**

| Item/time | July 24, 2023 | July 26, 2023 | July 29, 2023 | August 1, 2023 | August 20, 2023 | October 7, 2023 | Reference point |
|---|---|---|---|---|---|---|---|
| WBC (× $10^9$/L) | 10.98 | 12.04 | 12.71 | 14.50 | 14.70 | 12.01 | 3.50-9.50 |
| ALT (U/L) | 231.80 | | 210.80 | 172.10 | 27.50 | 24.70 | 9.00-50.00 |
| AST (U/L) | 138.20 | | 117.90 | 66.80 | 19.90 | 23.00 | 15.00-40.00 |
| TBIL (μmol/L) | 69.40 | | 31.60 | 24.10 | 16.70 | 10.70 | 0.00-26.00 |
| DBIL (μmol/L) | 59.50 | | 29.40 | 23.80 | 10.10 | 4.10 | 0.00-8.00 |
| IgG4 (g/L) | | 14.70 | | | 10.80 | | 0.03-2.01 |

WBC: White blood cell count; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; IgG4: Immunoglobulin G4.

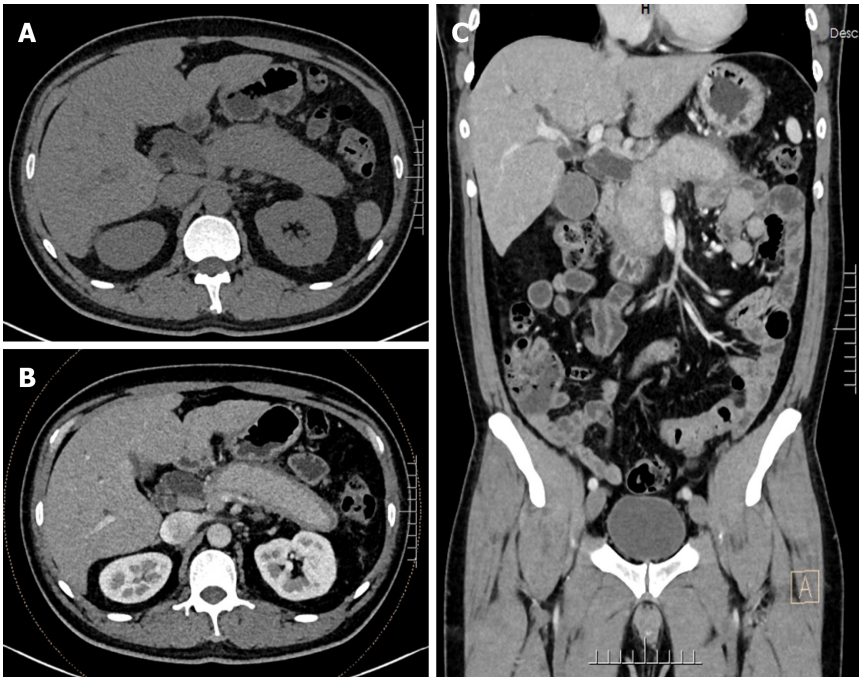


**Figure 1 Computed tomography before treatment.** A: Computed tomography (CT)-plain scan; B: CT-enhanced; C: CT-coronal plane.

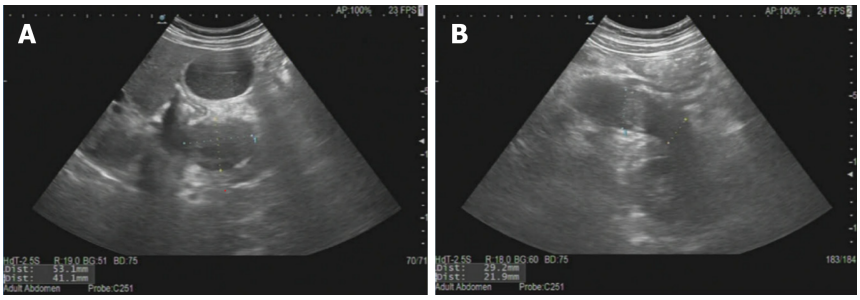


**Figure 2 Pancreatic swelling before autoimmune pancreatitis treatment.** A: Head of the pancreas; B: Body and tail of the pancreas.

patients with AIP, and should be further considered for malignant pancreatic cancer. Some studies have shown that diagnosis of AIP can be improved by combining serum IgG4 (> 280 mg/dL) and CA19-9 (< 85.0 U/mL)[3], and the simultaneous detection of IgG4 and CA19-9 is of practical value in identifying pancreatic cancer.

The typical imaging manifestation of AIP on CT and MRI is diffuse enlargement of the pancreas, which resembles a sausage, commonly known as the sausage sign. Not all cases of AIP have this manifestation. In the present case, ultrasound showed that the head of the pancreas was enlarged and appeared to be a hypoechoic mass. CT of the whole abdomen showed that the pancreas was swollen, with pericardium-like hypodense shadows on the edges, which was a

**Table 2 Summary of case data, *n* (%)**

| | Autoimmune pancreatitis (*n* = 51) |
|---|---|
| Sex | |
| Male | 39 (76) |
| Women | 12 (24) |
| Age (yr) | |
| < 50 | 15 (30) |
| 50-60 | 19 (37) |
| > 60 | 17 (33) |
| Clinical symptom | |
| Jaundice | 33 (65) |
| Abdominal pain | 22 (43) |
| Wasting away, fever etc. | 10 (20) |
| Not have | 4 (8) |
| **Laboratory tests** | |
| CA19-9 | |
| Ascend | 14 (27) |
| Normalcy | 12 (24) |
| Not mentioned | 25 (49) |
| IgG4 | |
| Ascend | 45 (88) |
| Normalcy | 4 (8) |
| Not mentioned | 2 (4) |
| Swollen parts of the pancreas | |
| Head of pancreas | 30 (59) |
| Tail of pancreas | 7 (14) |
| The whole pancreas | 14 (27) |
| Diagnostic methods | |
| Surgical resection | 14 (27) |
| Puncture biopsy | 27 (53) |
| Clinical diagnosis | 10 (20) |

CA19-9: Carbohydrate antigen 19-9; IgG4: Immunoglobulin G4.

sheath-like change, and enhanced CT scan was uniformly strengthened, and the pancreatic ducts were not dilated, and there was a small amount of peripancreatic oozing, which was not the typical diffuse enlargement of AIP. In the literature, 59% of the patients had a mass in the head of the pancreas, which was easily misdiagnosed as pancreatic cancer, and it was difficult to diagnose AIP on the basis of imaging. Another noninvasive imaging technique, MRCP, can show the penetrating duct or icicle sign, which is beneficial to the diagnosis of AIP. However, MRCP failed to provide the basis for diagnosis in the present case, which was probably related to the experience level of the imaging physician. AIP cannot be diagnosed solely based on the imaging manifestations alone,

Histopathological examination is important in the diagnosis of AIP. Type 1 AIP is characterized by a large number of lymphoplasmacytic cells infiltrating around the pancreatic ducts, accompanied by tissue-matted fibrosis, and immunohistochemical staining reveals > 10 IgG4-positive cells per high-power field. Pancreatic tissue can be obtained by minimally invasive and surgical methods, and minimally invasive puncture biopsy, which accounted for about half of the 51 cases reported in the literature. The latest Japanese guideline[4] recommends the collection of histopathological specimens by endoscopic-ultrasound-guided, fine-needle aspiration. Surgical removal of pancreatic tissue is invasive, and AIP was diagnosed in this way in 27% of patients reported in the literature, which often occurs when puncture biopsy is negative and pancreatic cancer is highly suspected, making the accuracy of puncture biopsy important.

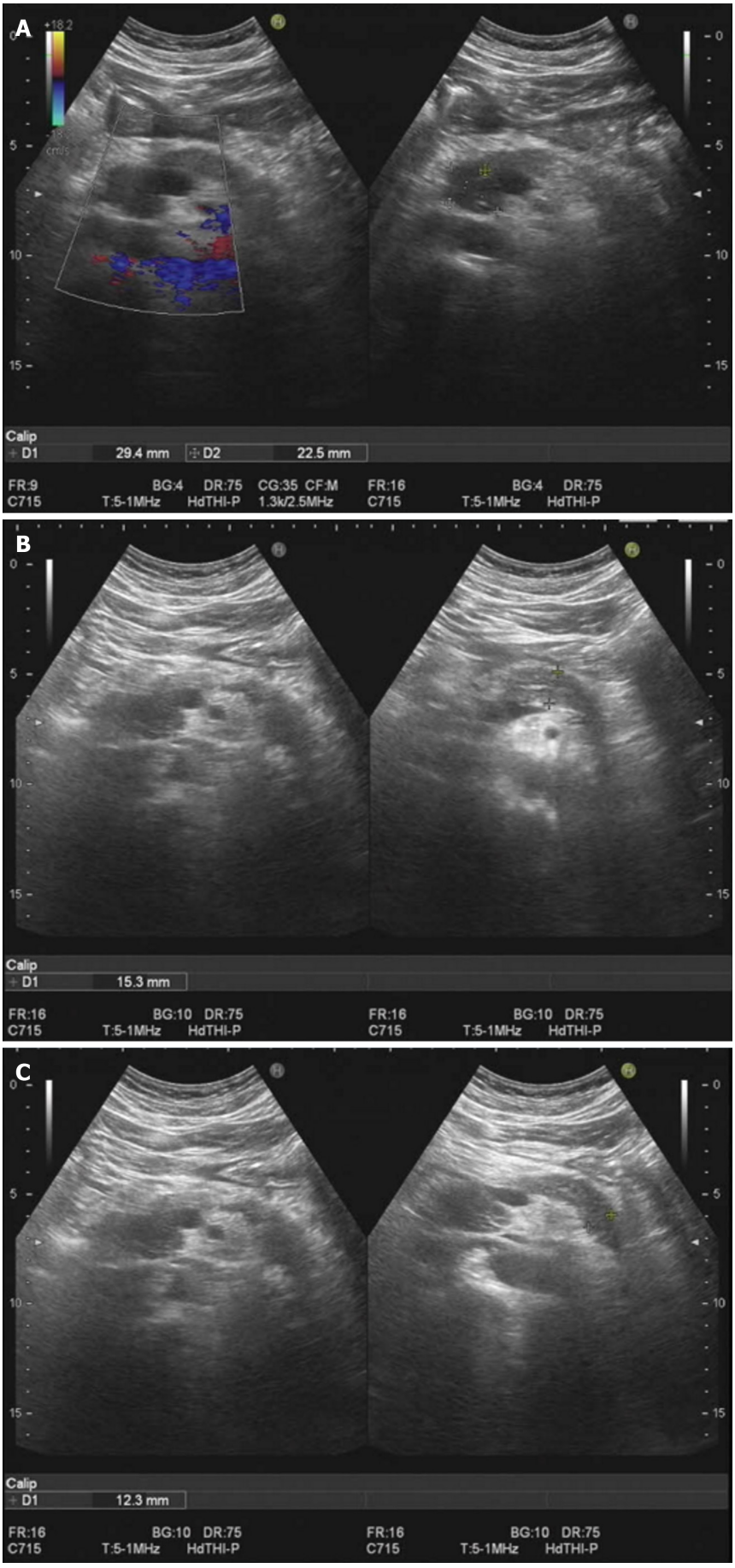


**Figure 3 Pancreatic swelling after autoimmune pancreatitis treatment.** A: Head of the pancreas; B: Body of the pancreas; C: Toil of the pancreas.

## CONCLUSION

Type 1 AIP has no characteristic clinical manifestations, and the imaging manifestations are atypical or similar to those of pancreatic cancer. Therefore, it is easy to misdiagnose, and its diagnosis mainly relies on detection of serological IgG4 levels. Short-term diagnostic treatment with small doses of hormones has a role in identification of AIP, but diagnostic confirmation mainly relies on pathology. However, there are many clinical situations in which pathology is unavailable; for example, if the patient refuses to have a biopsy, as in our case. The cases reported in the literature included some pregnant women with AIP. Pregnant women are a special population that is unsuitable for surgery and biopsy, and these patients require physicians to have sufficient familiarity with AIP and vigilance, and accurate and rapid diagnosis can avoid aggravating the patient's burden and lead to early recovery. At present, the most widely recognized diagnostic standard is that issued by IAPD in 2011[5], which classifies the diagnosis into confirmed and suspected after comprehensive assessment of the diagnostic basis from five aspects, and can provide clinical diagnostic guidance for physicians.

## FOOTNOTES

**Co-first authors:** Bi-Yu Zhang and Mou-Wang Liang.

**Author contributions:** Zhang BY and Liang MW contributed equally to the article; Zhang BY and Liang MW contributed to data collection, data analysis and revised the content of the article; Zhang BY, Liang MW and Zhang SX wrote the paper; Zhang SX revised the article. All authors have read and approved the final manuscript.

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CASE REPORT

# Detection of *LAMA2 c.715C>G:p.R239G* mutation in a newborn with raised creatine kinase: A case report

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## Abstract

### *BACKGROUND*

We report a rare case of primary clinical presentation featuring elevated creatine kinase (CK) levels in a neonate, which is associated with the *LAMA2* gene. In this case, a heterozygous mutation in exon5 of the *LAMA2* gene, *c.715C>G* (resulting in a change of nucleotide number 715 in the coding region from cytosine to guanine), induced an amino acid alteration *p.R239G* (No. 239) in the patient, representing a missense mutation. This observation may be elucidated by the neonatal creatine monitoring mechanism, a phenomenon not previously reported.

### *CASE SUMMARY*

We analysed the case of a neonate presenting solely with elevated CK levels who was eventually discharged after supportive treatment. The chief complaint was identification of increased CK levels for 15 d and higher CK values for 1 d. Admission occurred at 18 d of age, and despite prolonged treatment with creatine and vitamin C, the elevated CK levels showed limited improvement. Whole exome sequencing revealed the presence of a *c.715C>G* mutation in *LAMA2* in the newborn, correlating with a clinical phenotype. However, the available information offers insufficient evidence for clinical pathogenicity.

### *CONCLUSION*

Mutations in *LAMA2* are associated with the clinical phenotype of increased neonatal CK levels, for which no specific treatment exists. Whole genome sequencing facilitates early diagnosis.

**Key Words:** Creatine kinase; *LAMA2*; Gene mutation; Neonate; Case report

**Core Tip:** We analyzed the case of a neonate who appeared with only elevated creatine kinase (CK) and eventually was discharged after supportive treatment. The age of admission was 18 d, and the increased CK did not improve significantly after prolonged treatment with creatine and vitamin C. Whole exome sequencing identified the mutation of *c.715C>G* on *LAMA2* in the newborn, which is associated with clinical phenotype.

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## INTRODUCTION

Creatine kinase (CK), a biomarker of muscle damage, fluctuates within a certain reference range, 40-320 IU/L and 25-200 IU/L for men and women, respectively. Increased CK may be related to muscle damage[1] and it may be asymptomatic [2]. A few similar reports have been found worldwide, and previous reports have shown that increased CK levels in newborns are related to genetic variations. In this article, we describe the clinical manifestations, diagnosis, and treatment of a newborn with increased CK values associated with *LAMA2* gene mutation. The newborn was diagnosed in the term ward of the Children's Hospital of Soochow University. This study aimed to improve our understanding of this disease and advocated that neonatal clinicians should be aware of the serious potential problem of abnormally elevated CK in newborns shortly after birth.

## CASE PRESENTATION

### *Chief complaints*

Identification of increased CK levels for 15 d and higher CK values for 1 d.

### *History of present illness*

The neonate was admitted to Changshu First People's Hospital for 8 d post-birth due to "perinatal infection". During this period, CK value were found to be elevated, peaking at 1348 U/L, with no specific treatment administered. After discharge, CK values continued to increase for 8 d, reaching a maximum of 2111 U/L.

### *History of past illness*

The neonate, born at Changshu First People's Hospital on June 14, 2023, *via* eutocia at a gestational age 39 wk and mother being G2P2, had a birth weight 3700 g and recorded Apgar scores of 10 at both 1 min and 5 min post-birth. Amniotic fluid was clear, with a normal quantity, and no history of rescue suffocation was noted.

However, after birth, the neonate was hospitalised at Changshu First People's Hospital for 9 d due to perinatal infection, clavicle fracture caused by birth injury, neonatal hyperbilirubinemia, atrial septal defect, and neonatal ischaemic hypoxic myocardial damage.

### *Personal and family history*

The mother was diagnosed with hypothyroidism and gestational hypertension at 11 and 26 wk gestation, respectively. Group B strep was a potential concern at 36 wk gestation, while the parents of the newborn had no significant medical history, were physically healthy, and were not close relatives.

### *Physical examination*

Upon examination, the newborn displayed a body temperature of 36.5 °C, a pulse rate of 170 beats/min, a respiratory rate of 40 breaths/min, and an oxygen pulse of 99% under hood oxygen. Physical measurements included a body weight of 4.04 kg, a length of 52 cm, a head circumference of 35 cm, and a chest circumference of 34 cm. The newborn exhibited a full term appearance with a ruddy complexion, a flat anterior fontanel, measuring about 1.5 cm × 1.5 cm, and soft neck. The newborn experienced no shortness of breath, no obvious inspiratory trifossa sign, the lungs indicated rough breathing sounds without rales. Additionally, a grade 2/6 systolic murmur was audible at the left margin of the sternum and between the 2$^{nd}$ and 3$^{rd}$ ribs. The abdomen was soft, the extremities were warm, and the primitive reflexes were elicited, with normal muscular tone.

### *Laboratory examinations*

Peripheral blood examination revealed a CK value 2155.10 U/L. Myocardial enzyme levels indicated CK-MB at 7.70 ng/mL, troponin-T 42.81 ng/mL, myoglobin < 21 ng/mL. White blood cell count 9.77 × $10^9$/L, red blood cell count 4.08 × $10^{12}$/L, hemoglobin 138 g/L, platelet distribution width 12.90%, and blood gas analysis showed $Na^+$ 134 mmol/L, $Ca^{2+}$ 1.15

mmol/L, $Cl^-$ $10^2$ mmol/L, base excess 1.9 mmol/L, lactic acid 1.60 mmol/L, blood pH 7.496, oxyhemoglobin saturation 99.10%, oxygen partial pressure 119.0 mmHg, carbon dioxide partial pressure 31.70 mmHg, aspartic transaminase 42.30 U/L, alanine aminotransferase 44.10 U/L, total bilirubin 131.30 μmol/L, direct bilirubin 12.60 μmol/L, indirect bilirubin 118.70 μmol/L. Triiodothyronine, thyroxine, thyroid-stimulating hormone, free triiodothyronine, and free thyroxine levels showed no obvious abnormalities, and inflammatory markers showed no significant increases. Newborn screening results were unremarkable.

### *Imaging examinations*

Chest and abdominal imaging demonstrated an increase and blurring of the lung texture alongside changes indicative of aright clavicle fracture. Echocardiography suggested atrial septal defect, categorised as a secundum type with a size of 3.1 mm.

### *CK-related gene test*

The patient (*chr6:129465121*) showed a heterozygous mutation of *c.715C>G* in the gene *LAMA2*; while the father (*chr6:129465121*) had a heterozygous mutation of *c.715C>G:p.R239G*; No mutations were detected in the mother (*chr6:129465121*) (Figure 1). Large fragment variations in *LAMA2* were absent (Figure 2).

## FINAL DIAGNOSIS

Elevated CK levels; perinatal infection; fracture of the collarbone due to birth injury; atrial septal defect; neonatal pneumonia.

## TREATMENT

After the newborn's hospitalisation, CK levels continuously increased, stabilising at approximately 2000 U/L. Upon active treatment with vitamin C and creatine phosphate sodium, the CK values decreased from 2155.1 U/L to 1803.1 U/L in 15 d, and remained significantly higher than the normal values. Therefore, an investigation into CK-related genes was undertaken, resulting in the diagnosis of elevated CK levels in the neonate. Throughout the hospitalisation period, apart from the increased CK levels, no notable clinical manifestations were observed. The liver function index and bilirubin levels did not exhibit significant increases. The patient did not experience breathing difficulties, digestive system abnormalities, cardiac dysfunction, or disruption in normal milk intake. Additionally, all inflammatory markers remained within the normal range. Genetic problems were also considered in this study. Gene examination was performed and supportive treatments were administered. However, CK values showed no discernible decline. Eight days after admission, the child developed a lower respiratory tract infection caused by respiratory syncytial virus (RSV). Following comprehensive therapy, including creatine phosphate sodium and vitamin C, the neonate was discharged after 19 d of hospitalisation. Healthcare-associated infections related to RSV occurred during the disease course, with administration of antiviral and anti-inflammatory treatments, expectorant drugs, and probiotics to alleviate symptoms of cough. Vitamin C and creatine phosphate sodium were administered for 11 d during hospitalisation but were discontinued upon discharge. Subsequently, CK levels gradually subsided. After a 180-d follow-up period, the child's exhibited normal growth and development, with neurologic evaluations revealing no abnormalities in motor development, limb weakness stiffness, or sitting ability to. The patient weighed 8 kg, and CK levels remained at approximately 400 U/L.

## OUTCOME AND FOLLOW-UP

Gene mutation analysis revealed a heterozygous mutation in the exon5 region of the *LAMA2* gene: *c.715C>G* (with nucleotide 715 in the coding region changing from cytosine to guanine), resulting in the amino acid change *p.R239G* (No. 239), characterised as a missense mutation[3]. This change led to replacement of amino acid arginine with glycine. Interpretation of multiplex ligation-dependent probe amplification indicated absence of large fragment variations in the *LAMA2* gene, with the population exhibiting a low frequency of morbidity associated with this gene. Upon verification within the family, the father showed a heterozygous variation at the same site, while the mother of the neonate showed no variation, suggesting a suspected mutation. Had the father exhibited similar symptoms, it might have implicated diseases theoretically caused by the mutation site, or conversely, the mutation site might have been very small. However, no significant fragment variations were observed at the exon level, and gross motor development was normal during the 180-d follow-up.

## DISCUSSION

Increased CK levels in neonates can be attributed to various factors, including both physiological and pathological factors. Physiologically, elevated CK levels may arise from compression injury of the skeletal muscle and transient hy-

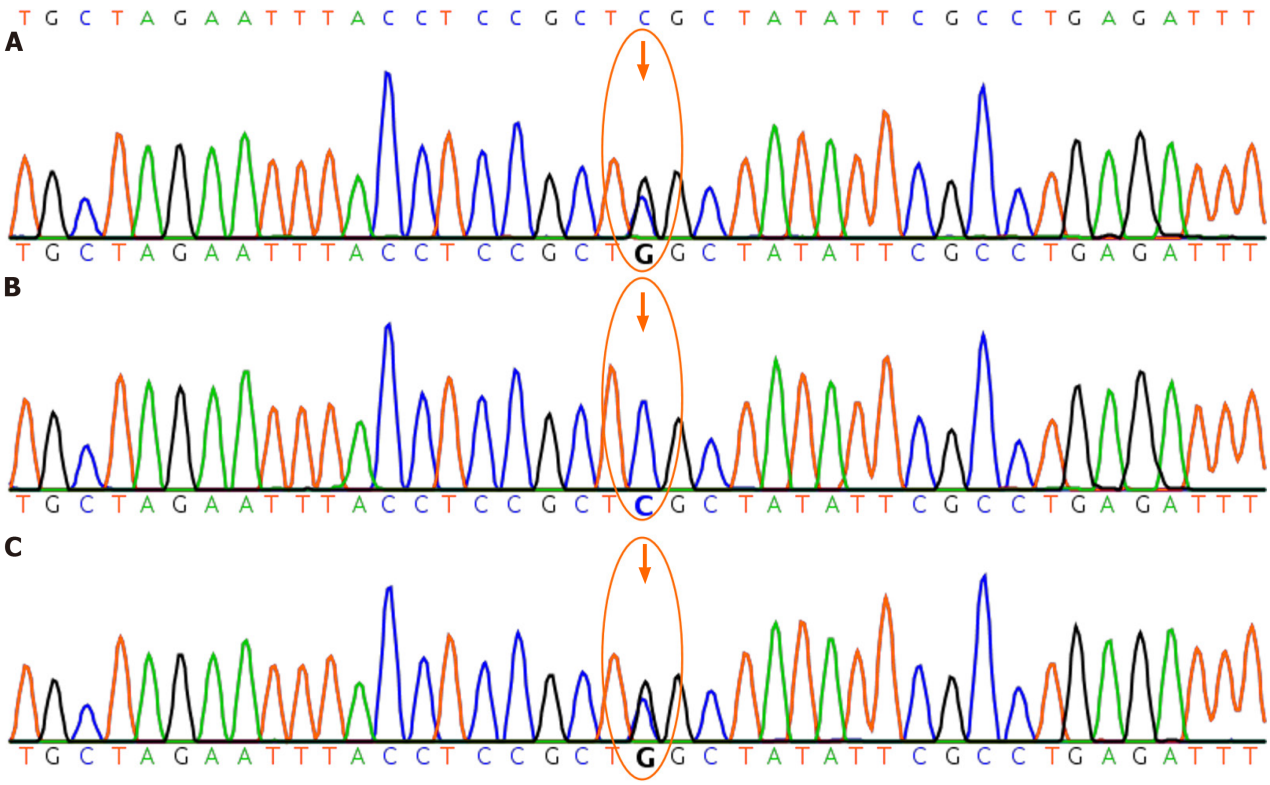


**Figure 1 Creatine kinase-related gene test.** A: The patient, *chr6:129465121* had a heterozygous mutation of *c.715C>G:p.R239G* in the gene *LAMA2*; B: The father, *chr6:129465121* had a heterozygous mutation of *c.715C>G:p.R239G*; C: The mother, *chr6:129465121* had no mutations.

poxia during vaginal birth[4,5]. Pathologically, elevations in CK levels can stem from cardiogenic diseases, endocrine and genetic metabolic diseases, inflammatory myopathies, autoimmune diseases, and drug interactions between metabolised pharmaceuticals[6,7]. Additionally, surgeries, other injuries, seizures, or direct drug toxicity from medications can induce muscle damage affecting CK values[6,7]. Understanding the multifaceted etiology of elevated CK is complicated. CK elevations can occur at birth due to compression damage to skeletal muscles and temporary hypoxia. Data indicate that in normal newborns, CK values increased rapidly after birth, stabilising within normal ranges within a week[8]. However, in our case, despite the neonate being delivered full-term normally, a peripheral blood examination indicated a significant increase in CK levels one day after birth, persisting for 16 d. Therefore, physiological factors are excluded. Despite receiving creatine and vitamin C supplements for 11 d during hospitalisation, the neonate's CK values remained unchanged, indicating that supplementation did not reduce elevation. Echocardiography revealed an atrial septal defect, 3.1 mm in size, and it was a secundum type. However, no significant increase in pulmonary hypertension or myocardial enzymes such as CK-MB and cardiac troponin T was observed. Moreover, clinical manifestations of circulation failure or heart failure were not obvious. Thus, cardiogenic diseases were excluded. The child's mother had a history of hypothyroidism triiodothyronine. Nevertheless, thyroxine, thyroid-stimulating hormone, free triiodothyronine, and free thyroxine of the child were all normal, and the thyroid gland exhibited normal functioning with no obvious manifestations of thyroid dysfunction; thus, thyroid problem was excluded. Therefore, other potential factors contributing to elevated CK levels were considered.

Monitoring increased CK levels in newborns can facilitate early detection of CMD before symptom onset[5]. Notably, a nonsense mutation, *c.4048C>T* (*p.Arg1350**) in exon 27 may contribute to severe CMD[9]. A small percentage of individuals with elevated CK levels receive a diagnosis of hereditary myopathy[10,11]. While the mutational site lacks sufficient evidence for clinical pathogenicity, it remains linked to the phenotype observed in this case. According to the guidelines[12-15], the mutation of *c.715C>G* in the *LAMA2* gene is classified as a site of unknown significance. This variation is absent in various databases, including the human thousand genome (1000G), Chellonese genome database, human exon database (ExAC), and human genome mutation frequency database (gnomAD). After 180 d of clinical follow-up, the newborn's condition gradually improved. Comprehensive phenotypic information and genetic testing of family members can aid in further evaluating the correlation between variation sites and this case. An unexplained and repeated rise in CK warrants genetic testing. In our patient, genetic testing revealed a heterozygous mutation in the CK-related gene *LAMA2*, inherited from the father. In this case, despite elevated CK levels, the newborn in this case displayed no unusual facies, suggesting that the *c.715C>G* mutation may be related to the features of increased CK. This child had no special clinical manifestations other than exceptionally high CK levels, in which case Early treatment, genetic testing, and infection prevention are crucial in such cases. These results expand our understanding of genetic diseases associated with CK and highlights the significance of linkage analysis in gene discovery studies.

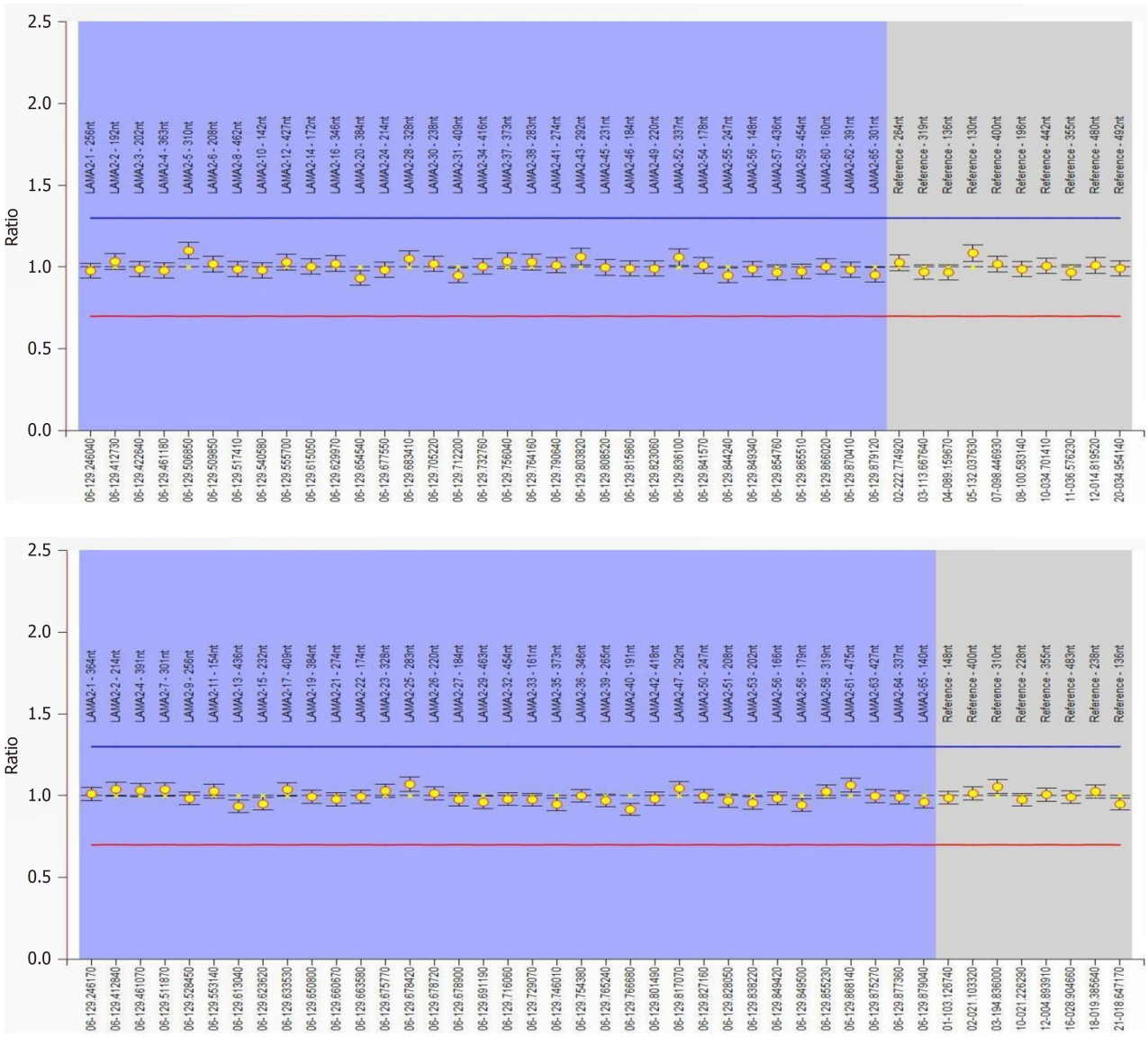


**Figure 2 Creatine kinase-related gene test.** No large fragment variation of the patient was found in *LAMA2* gene.

## CONCLUSION

Increased CK caused by a heterozygous mutation of the *LAMA2* gene has no specific treatment and can be self-limiting. Neonatal diseases can be diagnosed early through increasingly advanced genetic diagnostics. Monitoring and discovery of resymptomatic patients during the neonatal period will contribute to clinical research and measurable treatment procedures to observe therapeutic effects. In view of this case, neonatologists should observe an unexplained increase in CK and implement pathological analysis and whole-exome sequencing to make an early conclusive diagnosis and treatment.

## FOOTNOTES

**Author contributions:** Yuan J analyzed the data and wrote the paper; Yan XM checked and audited the paper.

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CASE REPORT

# Ultrasound-guided sphenopalatine ganglion block for effective analgesia during awake fiberoptic nasotracheal intubation: A case report

Hangil Kang, Seongjae Park, Yehun Jin

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## Abstract

*BACKGROUND*

Awake fiberoptic nasotracheal intubation (AFNI) is the preferred airway management strategy for patients with difficult airways. However, this procedure can cause significant physical and psychological distress. This case report explores the application of a sphenopalatine ganglion (SPG) block as an alternative analgesic modality to mitigate the discomfort associated with AFNI.

*CASE SUMMARY*

A 63-year-old female with a history of right maxillary osteosarcoma underwent craniotomy for a suspected malignant brain lesion. The patient's medical history included prior surgery, chemotherapy, and radiation therapy, resulting in significant jaw impairment and limited neck mobility. Considering the anticipated airway challenges, AFNI was planned. A SPG block was performed under real-time ultrasound guidance, providing effective analgesia during nasotracheal intubation.

*CONCLUSION*

The SPG block represents a promising analgesic approach in AFNI, offering potential benefits in alleviating pain involving the nasal and nasopharyngeal regions as well as improving patient cooperation.

**Key Words:** Sphenopalatine ganglion block; Nerve block; Regional anesthesia; Analgesia; Awake fiberoptic nasotracheal intubation; Case report

**Core Tip:** This is the first clinical case report of the application of a sphenopalatine ganglion (SPG) block for awake fiberoptic nasotracheal intubation (AFNI). The SPG block provided sufficient analgesia during AFNI. This case report suggests that an alternative analgesic modality for AFNI is the most reasonable option for airway management.

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## INTRODUCTION

Patients with malignant oral tumors who undergo surgical intervention and chemoradiotherapy often experience progressive physiological and pathological changes at the surgical site. These changes lead to structural alterations in the upper airway, resulting in severe airway compromise during procedures requiring general anesthesia[1]. To prevent potential ventilatory challenges and hypoxia arising from difficulties in securing the airway during the induction of general anesthesia, awake fiberoptic nasotracheal intubation (AFNI) has emerged as the most reasonable option for airway management[2].

AFNI is considered a safe and effective alternative approach for patients with significant airway compromise owing to oral surgery[2]. This method enables the preservation of spontaneous breathing, thereby minimizing potential complications such as critical desaturation due to difficulties with mask ventilation[3]. However, AFNI causes considerable physical and psychological distress. In addition, reflexive movements triggered by stimulation can occur, necessitating an appropriate response. Nerve blocks aimed at alleviating pain in the vocal cords and lower airways have been developed and widely used in clinical settings[4].

Blocks of the superior and recurrent laryngeal nerves have been used to alleviate discomfort in the laryngeal region during intubation[4]. Transcricothyroid membrane blocks have been used to induce anesthesia in the subglottic region. However, challenges have arisen during AFNI, particularly regarding the associated pain and discomfort in the upper airway and nasopharyngeal regions. This case report proposes that using an ultrasound-guided sphenopalatine ganglion (SPG) block when performing AFNI is effective in alleviating pain and discomfort, particularly in the upper airway and nasopharyngeal regions.

## CASE PRESENTATION

### *Chief complaints*

A 63-year-old female (height, 153 cm; weight, 42 kg) was scheduled for craniotomy for a suspected malignant brain lesion.

### *History of present illness*

The patient was diagnosed with right maxillary osteosarcoma 28 years ago and underwent radical orbitomaxillectomy, chemotherapy, and radiotherapy. However, disease recurrence prompted further surgical interventions, including mandibulectomy, right eye enucleation, and facial reconstruction.

### *History of past illness*

The patient's past medical history revealed only hypertension.

### *Personal and family history*

She denied any other medical history or family history of medical issues.

### *Physical examination*

The patient presented with persistent complications secondary to her prior treatments, including significant jaw impairment, posterior maxillary constriction, and facial asymmetry, culminating in Mallampati classification IV and a mouth opening of < 1.5 cm. The patient also exhibited limited neck mobility associated with prior radiation therapy. On neurological examination, she exhibited an alert mental status and proper orientation, with no signs of focal neurological deficits.

### *Laboratory examinations*

The patient's arterial blood gas analysis showed mild respiratory acidosis with $CO_2$ retention, as follows: pH, 7.37; Pa$CO_2$, 47.3 mmHg; Pa$O_2$, 87.0 mmHg; $HCO_3$ concentration, 25.7 mmol/L; base excess, 1.5 mmol/L; and oxygen saturation, 96.7%. Considering the patient's general condition, pulmonary function tests were not performed. The results of all other laboratory tests, including blood and urine analyses, were within acceptable ranges.

### *Imaging examinations*

Preoperative brain computed tomography (CT) revealed osteosarcoma recurrence along the inner cortex of the right frontotemporal craniotomy site, accompanied by chronic otomastoiditis on the right side. In addition, CT findings included an asymmetrical hypoplastic mandible with erosions on the right side of the condylar head (Figure 1). Chest radiography revealed no significant abnormalities.

## FINAL DIAGNOSIS

Due to restricted mouth opening and limited neck extension, difficulty in airway management or ventilation was anticipated, thus, AFNI was performed.

## TREATMENT

Informed consent regarding the potential risks of anesthesia was obtained from the patient and her family. The patient was admitted to our hospital without premedication. Upon entering the operating room, routine monitoring measures, such as pulse oximetry, electrocardiography, noninvasive blood pressure measurements, bispectral index, and capnography were initiated.

The patient's vital signs measured immediately after admission were as follows: Blood pressure, 126/73 mmHg; heart rate, 73 beats/min; and oxygen saturation, 97% on room air. To prevent hypoxemia, oxygen was administered for several minutes through a high-flow nasal cannula (Optiflow, Fisher & Paykel Healthcare). An intravenous injection of 0.2 mg of glycopyrrolate was administered, as a form of premedication, to decrease saliva production. Additionally, 2 mg of midazolam were administered intravenously for conscious sedation.

Using an out-of-plane approach with a 25-gauge, 2-inch needle, a left SPG block was performed under real-time ultrasound guidance. With the patient's head inclined to the right, a linear probe was placed in the infrazygomatic region and directed upward at an angle of approximately 45°. The sonographic view was bound anteriorly by the maxilla and posteriorly by the shadow of the mandibular coronoid process, which lies over the greater wing of the sphenoid process [5,6]. The needle was introduced approximately 1 cm behind the posterior orbital rim and 1 cm above the upper edge of the zygomatic arch. The needle was angled 30° caudally and 10° anteriorly and advanced 4 cm through the pterygomaxillary fissure into the pterygopalatine fossa (PPF). We administered 6 mL of 1% lidocaine, and the spread of the local anesthetic was observed using ultrasonography (Figure 2).

Through the cricothyroid membrane puncture, we administered a 5 mL bolus of 2% lidocaine into the trachea. Oral gargling was performed with 10 mL of 4% lidocaine. Nasal intubation was performed using a 6.5 mm nasal endotracheal tube with a preloaded flexible bronchoscope. The nasotracheal tube was seamlessly inserted into the left nostril without the patient coughing or gagging. The patient did not complain of pain or discomfort as the nasotracheal tube passed through the left nostril. We verified the accurate positioning of the nasotracheal tube by observing the carina and its tips and subsequently withdrawing the bronchoscope.

Once the presence of an end-tidal carbon dioxide waveform was confirmed, anesthesia was induced using propofol and remifentanil, followed by the intravenous administration of 40 mg of rocuronium. Propofol and remifentanil-based total intravenous anesthesia with target-controlled infusion was administered to maintaingeneral anesthesia. The patient received mechanical ventilation with a fresh gas flow of 3 L/min consisting of 50% oxygen mixed with ambient air. Arterial cannulation of the right radial artery and central venouscannulation of the right internal jugular vein were performed.

## OUTCOME AND FOLLOW-UP

The surgery was extended over a 6 h duration while maintaining stable vital signs. Although spontaneous breathing resumed postoperatively, nasotracheal intubation was maintained for half a day as a precaution against the anticipated airway edema. On the following day, the patient was extubated. She did not complain of nasopharyngeal pain or epistaxis.

## DISCUSSION

SPG block is commonly used to alleviate pain in the nasopharyngeal region. Its effectiveness has been demonstrated in the treatment of post-dural puncture headaches, migraines, and various facial pain syndromes, as well as in the setting of endoscopic sinus surgery[5,7-9]. The application of this procedure during AFNI proved beneficial, such that the effective reduction of patient discomfort and pain in the nasal cavity and pharynx facilitated tube insertion without compromising airway integrity.

SPG, also referred to as the pterygopalatine ganglion, is located within the cranial division of the autonomic nervous system and has distinctive features[7]. It interconnects with three main neural pathways, the somatosensory, sympathetic,

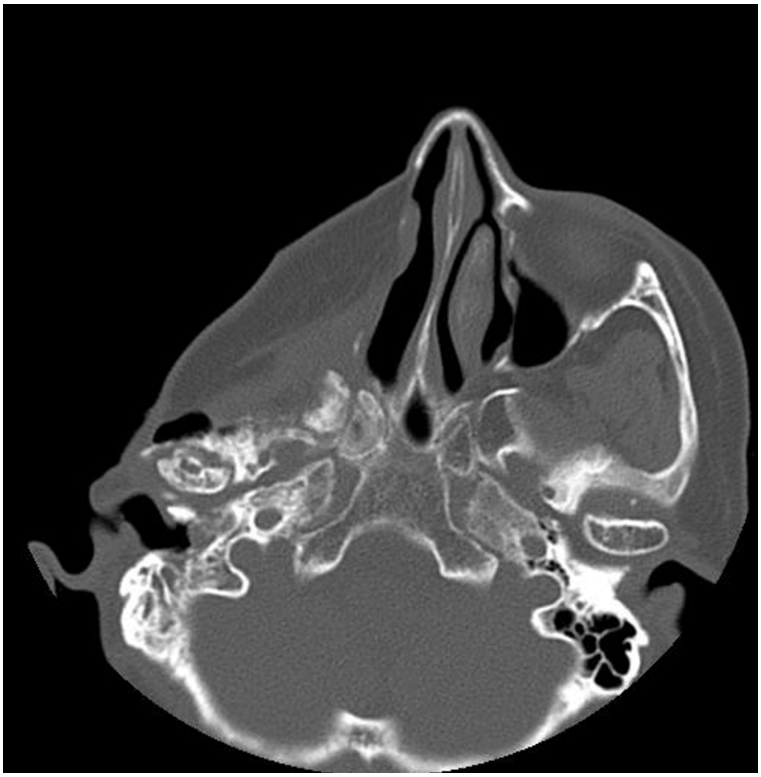

**Figure 1 Computed tomography revealed a rim-enhancing cystic lesion in the right mandibular ramus, which corresponded to a periosteal abscess.** Computed tomography also showed the prior maxillectomy on the right side.

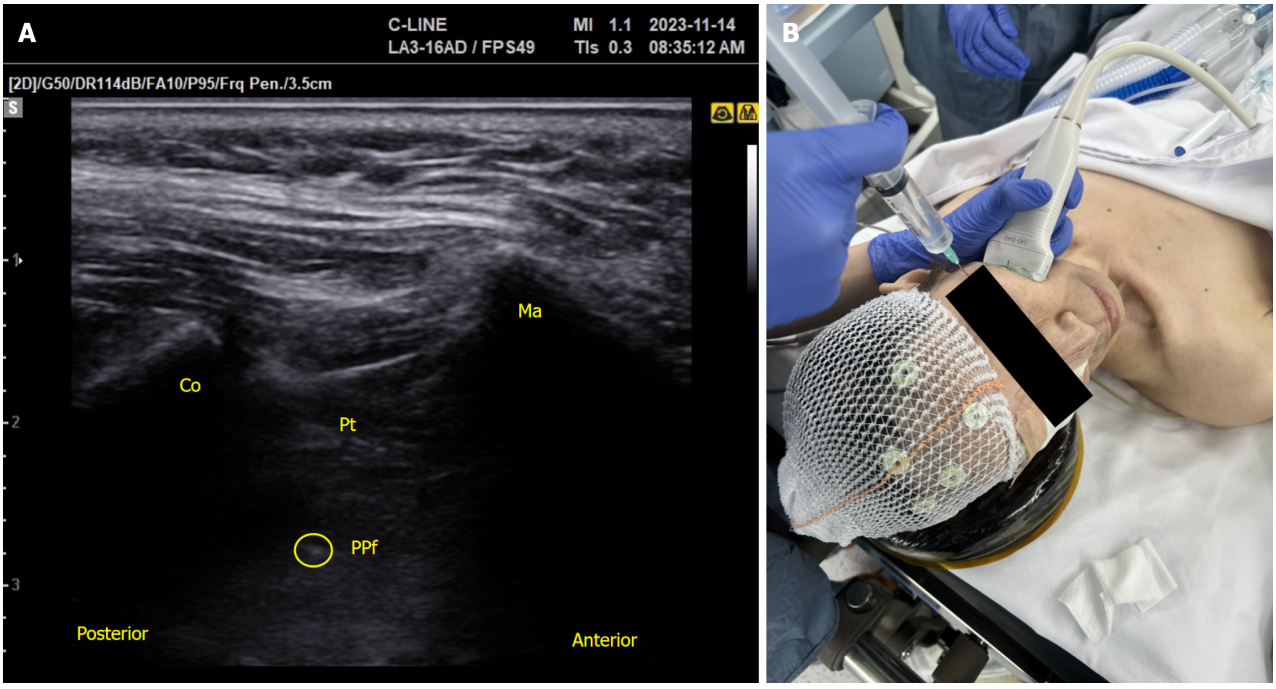


**Figure 2 Sphenopalatine ganglion block guided by ultrasonography.** A: Ultrasound image visualizing the surrounding anatomical structures; B: Ultrasound-guided needle placement to perform the sphenopalatine ganglion block. Co: Coronoid process of the mandible; Ma: Maxilla; Pt: Pterygoid muscles; PPf: Pterygopalatine fossa; Yellow circle: Needle tip.

and parasympathetic systems, making it well-suited for addressing various painful conditions affecting the facial and cranial regions[7].

Anatomically, the maxillary division of the trigeminal nerve courses through the foramen rotundum and proceeds anteriorly through the PPF[10]. The efferent branches of the SPG form the nasopalatine nerve, the posterior, superior, and inferior lateral nasal branches, and the pharyngeal nerves; additionally, the SPG is directly connected to the greater and

lesser palatine nerves. Sensory nerve fibers arising from the maxillary nerve traverse the SPG, facilitating the sensory innervation of the nasal mucosa, palate, and pharyngeal areas. SPG blocks modulate the transmission of pain signals by suppressing the activity of these sensory nerves.

The sympathetic pathway of the SPG originates from the superior cervical ganglion, following a trajectory through the internal carotid plexus as the deep petrosal nerve. This nerve merges with the greater petrosal nerve, forming the pterygoid canal nerve, also known as the vidian nerve[10]. Vasoconstrictive innervation of the nasal cavity, upper pharynx, and palate is supplied by the postganglionic sympathetic fibers that pass through the SPG[10]. The parasympathetic pathway originates from the superior salivatory nucleus (SSN) within the brainstem and extends towards the SPG. Efferent fibers from the SSN traverse *via* the nervus intermedius, combining to form the greater petrosal nerve, which contributes to the parasympathetic innervation of the SPG[8,10]. This pathway stimulates the secretory function of the nasal cavity, pharyngeal mucosa, and lacrimal and palatine glands[8]. Therefore, through its effects on the sympathetic and parasympathetic nervous systems, SPG block can be an effective method to facilitate the smooth execution of AFNI.

SPG block is commonly performed using transnasal and percutaneous approaches. In contrast to the transnasal approach, the percutaneous approach offers the advantage of delivering medication directly to the SPG without encountering barriers such as the nasal mucosa, sphenopalatine foramen, and fat tissue before reaching the PPF[7,11]. The transnasal method results in inconsistent coverage of the contents within the PPF, leading to fewer enduring outcomes [11].

A superior laryngeal nerve block was not performed in this case, which could be considered a limitation. The superior laryngeal nerve innervates the cricothyroid muscle, whereas the recurrent laryngeal nerve innervates the remaining muscles[12]. Although we can reduce reflective contractions by performing a translaryngeal block targeting the recurrent laryngeal nerve, this may be inadequate as the cricothyroid muscle of the larynx would remain unaffected. Overall, this was not deemed essential for awake intubation, and no disruptive reflexes were observed in our patient during the procedure.

## CONCLUSION

In conclusion, when performing AFNI, the implementation of a nerve block strategy such as the SPG block improves patient cooperation and minimizes physical and mental pain without compromising airway integrity. Further clinical studies are needed to investigate the comparative outcomes and establish optimized protocols.

## FOOTNOTES

**Author contributions:** Jin Y designed the research; Kang H, Park S and Jin Y performed the research; Kang H and Jin Y analyzed the data and wrote the paper.

**Informed consent statement:** All study participants have read and understand the information in this form. I have been encouraged to ask questions and all of my questions have been answered to my satisfaction. I have also been informed that I can withdraw from the study at any time. By signing this form, I voluntarily agree to participate in this study.

**Conflict-of-interest statement:** The authors have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript

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CASE REPORT

# Appendiceal bleeding caused by vascular malformation: A case report

Qin Ma, Jin-Jie Du

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## Abstract

*BACKGROUND*

Acute lower gastrointestinal bleeding (LGIB) is a common occurrence in clinical practice. However, appendiceal bleeding is an extremely rare condition that can easily be overlooked and misdiagnosed. The preoperative detection of appendiceal bleeding often poses challenges due to the lack of related guidelines and consensus, resulting in controversial treatment approaches.

*CASE SUMMARY*

We presented a case of a 33-year-old female who complained of hematochezia that had lasted for 1 d. Colonoscopy revealed continuous bleeding in the appendiceal orifice. A laparoscopic appendectomy was performed immediately, and a pulsating blood vessel was observed in the mesangium of the appendix, accordingly, active bleeding into the appendicular lumen was considered. Pathological examination revealed numerous hyperplastic vessels in the appendiceal mucosa and dilated capillary vessels.

*CONCLUSION*

The preoperative detection of appendiceal bleeding is often challenging, colonoscopy is extremely important, bowel preparation is not routinely recommended for patients with acute LGIB or only low-dose bowel preparation is recommended. Laparoscopic appendectomy is the most appropriate treatment for appendiceal bleeding.

**Key Words:** Lower gastrointestinal bleeding; Appendiceal bleeding; Colonoscopy; Vascular malformation; Laparoscopic appendectomy; Case report

**Core Tip:** Acute lower gastrointestinal bleeding (LGIB) is common, however, appendiceal bleeding is extremely rare. The diagnosis of appendiceal bleeding is challenging because of its rarity and lack of related guidelines and consensus. Colonoscopy is extremely important, and bowel preparation is not routinely recommended for patients with acute LGIB. Laparoscopic appendectomy is the most appropriate treatment for appendiceal bleeding.

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## INTRODUCTION

Lower gastrointestinal bleeding (LGIB) is defined as hemorrhage originating from the gastrointestinal tract segment below the Treitz ligament[1]. Various diagnostic modalities, including digital subtraction angiography (DSA), computed tomography angiography (CTA) and colonoscopy, are used for appropriate diagnosis. However, pinpointing the source of bleeding remains a significant challenge[2]. Only a few guidelines and a consensus on LGIB, especially, no major guidelines for appendiceal bleeding. Appendiceal bleeding is extremely rare, and easily missed and misdiagnosed[3]. Here, we report a case of appendiceal bleeding in which the clinical manifestation was hemafecia, and the cause of the appendiceal bleeding was vascular malformation.

## CASE PRESENTATION

### *Chief complaints*

A 33-year-old female presented to our hospital with hematochezia that had lasted for 1 d.

### *History of present illness*

The patient reported a prior episode of passing approximately 300 mL of bloody stool before presenting to the hospital. There were no accompanying gastrointestinal symptoms, such as nausea, vomiting, or abdominal pain. Following the administration of 4 L of polyethylene glycol (PEG)-based bowel preparation, the patient experienced another episode of bloody stool, amounting to approximately 300 mL. The patient denied any previous history of hematochezia.

### *History of past illness*

The patient had no history of acute or chronic infectious diseases, heart disease, hypertension or diabetes, or surgery.

### *Personal and family history*

The patient had not recently taken any medicine, such as corticosteroids or nonsteroidal anti-inflammatory drugs. There was no family history of similar cases or bleeding disorders.

### *Physical examination*

There were no signs of anemia, her blood pressure was 100/54 mmHg, and her heart rate was 96 beats per minute. The patient did not have any pathological signs.

### *Laboratory examinations*

Her hemoglobin level was 134 g/L (normal range: 130-175 g/L), her leucocyte count was 15.87 × $10^9$/L, and her percentage of neutrophils was 83.4%. Other routine relevant examinations, such as platelet counts and coagulation function tests, yielded normal findings.

### *Imaging examinations*

An emergency colonoscopy was performed, and the endoscope was extended to the terminal ileum. Continuous bleeding was observed at the appendiceal orifice (Figure 1A). In addition, a contrast-enhanced abdominal computed tomography scan revealed structural disorder in the ileocecal area, and the appendix was not clear (Figure 1B).

## FINAL DIAGNOSIS

Appendiceal bleeding.

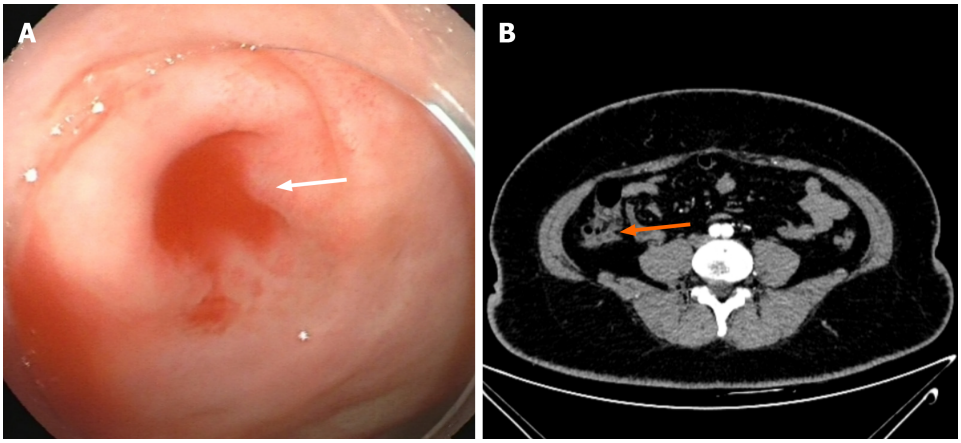


**Figure 1 Colonoscopy and contrast-enhanced abdominal computed tomography scan.** A: Continuous bleeding was observed at the orifice of the appendix; B: Structural disorder in the ileocecal area, and the appendix was not clear.

## TREATMENT

An emergency laparoscopic appendectomy was performed. During the surgery, the appendix was 90 mm × 5 mm in size and the appendix was swollen 3-5 cm from the appendicular root (Figure 2A). A pulsating blood vessel was observed in the mesangium of the appendix (Figure 2B). Active bleeding into the appendicular lumen was considered, and a large number of blood clots were observed in the lumen. Pathologically, a large number of hyperplastic vessels were observed in the appendix mucosa and capillary vessels were dilated (Figure 3).

## OUTCOME AND FOLLOW-UP

The patient had no recurrent hematochezia or melena, and was discharged from the hospital 5 d after the surgery. One month later, no evidence of rebleeding was observed.

## DISCUSSION

Acute LGIB is not an uncommon condition, with an incidence of approximately 0.02%, and it is more common in men and older people. Approximately 80% of cases are of colorectal origin, and appendiceal bleeding is extremely rare[4,5]. A search of the PubMed/MEDLINE database for literature published between 2010 and August 2023 regarding "appendiceal bleeding" or "appendiceal hemorrhage" identified 16 patients (Table 1). Appendiceal bleeding was more common in males than in females (male:female = 15:1), and the average age of the included patients was 54.75 years (range: 25–90 years). The causes of appendiceal bleeding mainly include vascular malformation, ulcers, inflammation, neoplasms, mucosal erosion and Dieulafoy's lesions. In addition, the causes of appendiceal bleeding in 40% of patients are unknown.

The diagnosis of appendiceal bleeding mainly includes CTA, DSA and colonoscopy. CTA is suitable for patients with active bleeding (bleeding rate ≥ 0.3 mL/min). Additionally, DSA is affected by the bleeding rate. When the bleeding rate is greater than 0.5 mL/min, the detection rate reaches 50%–72%, but if the bleeding rate is lower than 0.5 mL/min, the detection rate decreases significantly[6]. Colonoscopy plays an irreplaceable role for LGIB, at least to the terminal ileum [7].

No consensus exists regarding on bowel preparation before emergency colonoscopy for LGIB. Some scholars believe that adequate bowel preparation and clear exposure under the scope are the basis for discovering and treating all lesions, and recommend 4-6 L of PEG-based bowel preparation; in addition, split-dose preparation and/or the use of low-volume preparations can also be considered[8]. However, some scholars believe that oral laxatives can aggravate gastrointestinal bleeding and shock[9]. According to our case, the patient experienced massive hematocheia again after receiving oral laxatives. We believe that bowel preparation is not routinely recommended for patients with acute LGIB or that only low-dose bowel preparation is recommended for the following reasons: (1) Aggravation of gastrointestinal bleeding; (2) The equipment used for colonoscopy is more advanced, and which can be observed while washing, therefore, it is helpful to find and treat the lesion site; and (3) The blood in the intestinal lumen itself has a cathartic effect.

No standard treatment is available for appendiceal bleeding, and it has been reported that local spraying of hemostatic drugs can successfully stop bleeding. Hemostasis can also be achieved by endoscopic clamping of part of the appendiceal orifice or appendiceal artery embolization[4,10,11]. The choice for most scholars is appendectomy[3]. In our case, the site of bleeding in the patient's appendix was approximately 3 cm from the orifice, and the appendix was slender. The hemostatic effect of spraying hemostatic drugs alone may be poor. Partial occlusion of the appendiceal orifice with colonoscopic clipping or appendiceal artery embolization increases the risk of acute appendicitis, and there is the possibility of rebleeding[11]. Therefore, Laparoscopic appendectomy is the most appropriate treatment for appendiceal bleeding, and

**Table 1 Case of appendiceal bleeding**

| Case | Age (yr)/sex | Techniques | Treatment | Complications | Pathology | Ref. |
|---|---|---|---|---|---|---|
| 1 | 32/male | Colonoscopy | Endoscopic appendectomy | None | Appendiceal ulcer | [2] |
| 2 | 90/male | Colonoscopy | Laparoscopic appendectomy | None | Unknown | [3] |
| 3 | 70/male | Colonoscopy | Endoscopic clipping | None | None | [4] |
| 4 | 25/male | Colonoscopy | Appendectomy | None | Appendiceal mucosal erosion | [5] |
| 5 | 54/male | Colonoscopy | Appendectomy | None | Unknown | [10] |
| 6 | 32/male | Colonoscopy | Laparoscopic appendectomy | None | Dieulafoy's lesion | [10] |
| 7 | 72/male | Colonoscopy | Laparoscopic appendectomy and cecum wedge resection | None | Vascular malformation | [11] |
| 8 | 73/male | Colonoscopy | Appendectomy | None | Appendiceal mucosal erosion | [12] |
| 9 | 32/male | Colonoscopy | Appendectomy | None | Appendiceal ulcer | [13] |
| 10 | 72/male | Colonoscopy | Right hemicolectomy | None | Appendiceal mucinous adenocarcinoma | [14] |
| 11 | 49/male | Colonoscopy | Appendectomy with partial cecal resection | None | Acute appendicitis | [15] |
| 12 | 88/male | Colonoscopy | Appendectomy | None | Low-grade mucinous neoplasm of appendix | [16] |
| 13 | 42/male | Colonoscopy | Laparoscopic appendectomy | None | Appendiceal mucosal erosion | [17] |
| 14 | 44/male | Colonoscopy | Colonoscopic clipping | None | None | [18] |
| 15 | 34/female | Colonoscopy | Colonoscopic clipping | None | None | [19] |
| 16 | 67/male | Angiogram | Embolization the appendiceal artery | Acute appendicitis | None | [20] |
| Our case | 33/female | Colonoscopy | Laparoscopic appendectomy | None | Vascular malformation | |

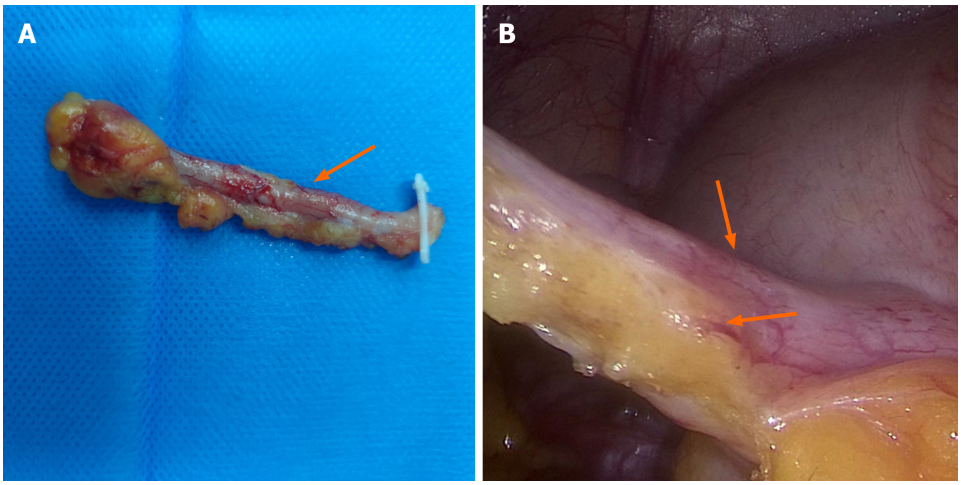


**Figure 2 Specimens of the appendix and intraoperative images.** A: The appendix was swollen 3-5 cm from the appendicular root; B: A pulsating blood vessel could be observed in the mesangium of the appendix.

colonoscopy is performed during the operation when necessary.

## CONCLUSION

The number of reports on appendiceal bleeding is limited, and there is a lack of corresponding guidelines and consensuses on standardizing the clinical diagnosis and treatment. We eagerly await more large-scale research to provide evidence for evidence-based medicine in clinical practice.

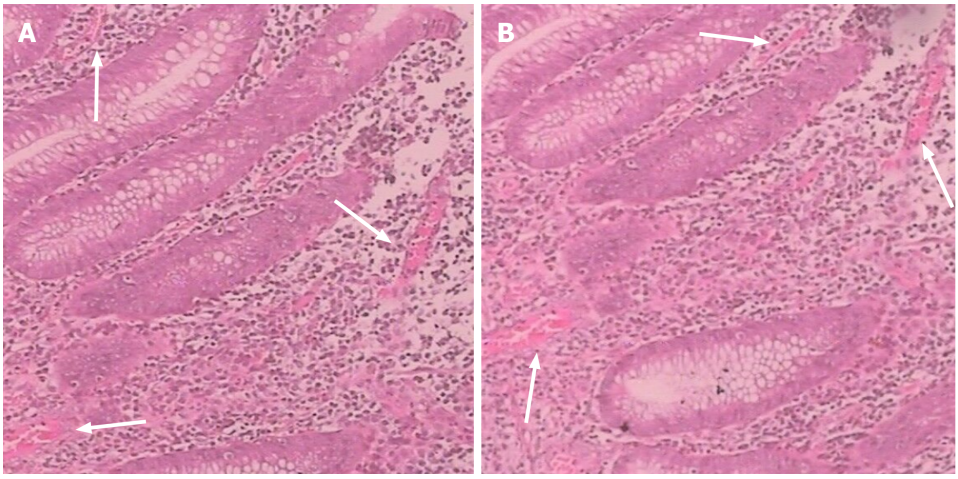


**Figure 3 The pathology of the appendix.** A and B: A large number of hyperplastic vessels were observed in the appendix mucosa and capillary vessels were dilated.

## FOOTNOTES

**Author contributions:** Ma Q and Du JJ contributed to manuscript writing, data analysis, and editing. All authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

# Early diagnosis of pancreatic cancer: Shedding light on an unresolved challenge

Cristian Lindner

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## Abstract

Diagnosing early-stage pancreatic cancer (PC) remains a clinical challenge. Hence, studying novel imaging aspects that could enhance the diagnostic accuracy of malignant pancreatic precursor lesions is imperative. This article aims to underscore the promising role of emerging imaging aspects that may facilitate the earlier diagnosis of PC, thereby improving its management and prognosis.

**Key Words:** Pancreatic cancer; Pancreatic intraepithelial neoplasm; High-grade pancreatic intraepithelial neoplasm; Pancreatic ducts; Cancer; Early diagnosis



**Core Tip:** The description and validation of novel imaging findings that could enhance the diagnosis of pancreatic cancer (PC) at early stages remain a challenge for radiologists. However, recent studies have suggested emerging radiological signs that may facilitate the early diagnosis of PC and its malignant precursor lesions.

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## TO THE EDITOR

In their recent article titled "High-grade pancreatic intraepithelial neoplasia diagnosed based on changes in magnetic resonance cholangiopancreatography findings: A case report", Furuya *et al*[1] reported and described the pre-operative diagnosis and

surgical treatment of high-grade pancreatic intraepithelial neoplasia (PanIN) based on the evaluation of indirect imaging findings and their evolution over time. I commend this novel and intriguing report, which may contribute to emerging insights into imaging aspects relevant to the early diagnosis of pancreatic cancer (PC).

According to the Globocan observatory database, PC ranks as the fifth most common gastrointestinal malignancy and the seventh leading cause of global cancer deaths[2]. Nevertheless, current epidemiological studies over the past decade have consistently reported an increasing trend in both its incidence and mortality rates[3,4]. Given that many patients are diagnosed at advanced stages due to the absence of specific symptoms, the detection of PC heavily relies on imaging studies. However, despite continuous advancements in abdominal imaging techniques, accurately detecting PC at early stages remains challenging[5,6].

At present, approximately 50% of patients present with locally advanced or distant metastatic disease at the time of diagnosis, resulting in a 5-year survival rate ranging from 3% to 15%[7]. Notably, the poor survival rate observed in pancreatic PC is attributed not only to its extremely aggressive biological behavior but also to the challenges in achieving accurate diagnosis during the early stages[8,9]. Therefore, it is imperative to further investigate diagnostic findings that enable suspicion and detection of early-stage PC.

High-grade PanIN is a type of preneoplastic lesion originating from pancreatic ducts, characterized by low-papillary progression, and considered a potentially curable stage of PC[10]. However, the absence of specific imaging findings suggesting the diagnosis of high-grade PanIN complicates the detection of this intra-epithelial malignant lesion, which is primarily detectable only under a microscope. Consequently, the emergent description and development of indirect radiological features that may allow for the detection of high-grade PanIN could play a promising role in the early diagnosis of PC[11].

An observational and retrospective multicenter study conducted by the Japan Study Group on the Early Detection of Pancreatic Cancer[12] examined the clinical, imaging, and pathological features of 200 patients with early-stage PC. The study suggested that the evaluation of several findings on ultrasound, computed tomography (CT), and magnetic resonance imaging, such as main pancreatic duct (MPD) dilation, MPD stenosis, focal pancreatic parenchymal atrophy, and local fatty changes, could be useful for detecting early-stage PC.

Another interesting study recently published by Toshima *et al*[13] also aims to investigate indirect imaging findings that could be useful in detecting early-stage PC. In this study, the authors analyzed CT examinations conducted before the diagnosis of PC, revealing that 53.4% of patients with early-stage PC exhibited focal pancreatic abnormalities at least 1 year before diagnosis. These abnormalities included focal pancreatic atrophy, faint focal enhancement, and focal changes in the MPD. These findings may represent secondary structural changes in the ductal parenchyma underlying prolonged disease progression among malignant precursor lesions and progressive early tumoral desmoplasia.

In summary, the accurate diagnosis of PC in early stages remains a challenge for radiologists. Continuous research into emerging imaging aspects that could be useful for diagnosing early PC is imperative. In this context, the study published by Furuya *et al*[1] sheds light on this unresolved challenge, highlighting emerging aspects that could facilitate earlier diagnosis of PC, thereby improving management and prognosis.

## FOOTNOTES

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