ISSN 2308-3840 (online)

World Journal of *Meta-Analysis*

World J Meta-Anal 2023 April 18; 11(4): 79-133

Published by Baishideng Publishing Group Inc

WJMA

World Journal of Meta-Analysis

Contents

Continuous Publication Volume 11 Number 4 April 18, 2023

Contents

Continuous Publication Volume 11 Number 4 April 18, 2023

ABOUT COVER

Editorial Board Member of *World Journal of Meta-Analysis*, Valiollah Dabidi Roshan, PhD, Full Professor, Department of Sport Physiology, College of Physical Education and Sport Sciences, University of Mazandaran, Babolsar 47415, Mazandaran, Iran. v.dabidi@umz.ac.ir

AIMS AND SCOPE

The primary aim of *World Journal of Meta-Analysis* (*WJMA*, *World J Meta-Anal*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality meta-analysis and systematic review articles and communicate their research findings online.

WJMA mainly publishes articles reporting research results and findings obtained through meta-analysis and systematic review in a wide range of areas, including medicine, pharmacy, preventive medicine, stomatology, nursing, medical imaging, and laboratory medicine.

INDEXING/ABSTRACTING

The *WJMA* is now abstracted and indexed in Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Meta-Analysis

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Continuous Publication

EDITORS-IN-CHIEF
Saurabh Chandan, Jing Sun

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2308-3840/editorialboard.htm

PUBLICATION DATE
April 18, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2023 April 18; 11(4): 79-91

DOI: 10.13105/wjma.v11.i4.79

ISSN 2308-3840 (online)

REVIEW

Artificial intelligence ecosystem for computational psychiatry: Ideas to practice

Xin-Qiao Liu, Xin-Yu Ji, Xing Weng, Yi-Fan Zhang

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): E

P-Reviewer: Cabezuelo AS, Spain; Cawthorpe DR, Canada; Morya AK, India

Received: December 26, 2022
Peer-review started: December 26, 2022
First decision: March 9, 2023
Revised: March 18, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: April 18, 2023

Xin-Qiao Liu, Xin-Yu Ji, Yi-Fan Zhang, School of Education, Tianjin University, Tianjin 300350, China

Xing Weng, Huzhou Educational Science & Research Center, Huzhou 313000, Zhejiang Province, China

Corresponding author: Xin-Qiao Liu, PhD, Associate Professor, School of Education, Tianjin University, No. 135 Yaguan Road, Jinnan District, Tianjin 300350, China.
xinqiaoliu@pku.edu.cn

Abstract

Computational psychiatry is an emerging field that not only explores the biological basis of mental illness but also considers the diagnoses and identifies the underlying mechanisms. One of the key strengths of computational psychiatry is that it may identify patterns in large datasets that are not easily identifiable. This may help researchers develop more effective treatments and interventions for mental health problems. This paper is a narrative review that reviews the literature and produces an artificial intelligence ecosystem for computational psychiatry. The artificial intelligence ecosystem for computational psychiatry includes data acquisition, preparation, modeling, application, and evaluation. This approach allows researchers to integrate data from a variety of sources, such as brain imaging, genetics, and behavioral experiments, to obtain a more complete understanding of mental health conditions. Through the process of data preprocessing, training, and testing, the data that are required for model building can be prepared. By using machine learning, neural networks, artificial intelligence, and other methods, researchers have been able to develop diagnostic tools that can accurately identify mental health conditions based on a patient's symptoms and other factors. Despite the continuous development and breakthrough of computational psychiatry, it has not yet influenced routine clinical practice and still faces many challenges, such as data availability and quality, biological risks, equity, and data protection. As we move progress in this field, it is vital to ensure that computational psychiatry remains accessible and inclusive so that all researchers may contribute to this significant and exciting field.

Key Words: Computational psychiatry; Big data; Artificial intelligence; Medical ethics; Large-scale online data

Core Tip: This study reviews and integrates the methods and models in the clinical practice of computational psychiatry and constructs a complete and mature Artificial Intelligence ecosystem. The ecosystem for computational psychiatry includes data acquisition, preparation, modeling, application, and evaluation. This approach allows researchers to integrate data from a variety of sources to obtain a more complete understanding of mental health conditions. Despite the continuous development and breakthrough of computational psychiatry, it has not yet influenced routine clinical practice and still faces many challenges, such as data availability and quality, biological risks, equity, and data protection.

Citation: Liu XQ, Ji XY, Weng X, Zhang YF. Artificial intelligence ecosystem for computational psychiatry: Ideas to practice. *World J Meta-Anal* 2023; 11(4): 79-91
URL: https://www.wjgnet.com/2308-3840/full/v11/i4/79.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i4.79

INTRODUCTION

Mental illness is a significant threat to human health, which was especially evident during the coronavirus disease 2019 (COVID-19) pandemic[1,2]. In recent years, artificial intelligence has played an increasingly prominent role in the clinical practice of psychiatry. The birth of computational psychiatry represents not only the inevitable choice to conform to the trend of the fourth industrial revolution but also an important means to solve the real dilemma.

Psychiatry mainly studies the causes, symptoms, and clinical diagnosis of human mental diseases. Computational psychiatry[3] uses computational and mathematical techniques to better understand mental disorders and to develop new treatments. Computational psychiatry is an emerging psychiatry approach that integrates various multidisciplinary approaches, such as psychiatry, neuroscience, machine learning, psychology, statistics, and computer science, to develop quantitative models of mental illness and to assess the effectiveness of different treatments[4]. Specifically, computational psychiatry builds computational models of brain function based on the neurological and cognitive phenomena associated with mental illness, predicts the abnormal degree of mental function, and evaluates the efficacy of treatment by using detailed multidimensional computational models[5,6].

Computational psychiatry includes two approaches: Data-driven computational psychiatry and theory-driven computational psychiatry[6]. Data-driven approaches involve machine learning and big data analytics, and they can improve predictive accuracy in clinical diagnosis, prognosis, and treatment by learning clinical and biological data. The theory-driven approach derives from computational neuroscience and focuses more on constructing models to understand the mechanisms of psychosis[7]. Due to the fact that computational psychiatry is based on mathematics, computer science, biological science, and other deep theories, it has the advantage of multidisciplinary integration[3]. One of the key goals of computational psychiatry is to move beyond the traditional "black box" approach to understanding the brain[8], whereby researchers study the symptoms and behaviors of individuals without fully understanding the underlying mechanisms. By introducing computational and statistical approaches, computational psychiatry has opened the "black box" of pathological mechanisms[9]. Moreover, neural computing functions provide precise algorithmic details for the analysis and solution of specific problems.

Computational psychiatry can identify the pathogenesis of mental diseases from both theory-driven and data-driven aspects, which is the result of the fusion of computational neuroscience and psychiatry [10]; in addition, it has a significant contribution to the diagnosis, treatment, and prevention of mental diseases. Overall, computational psychiatry is a rapidly growing and exciting field that has the potential to revolutionize our understanding of mental illness and to allow for the development of new treatments. By using computational and mathematical techniques to build quantitative models of mental illness, researchers in the field are working to identify the underlying mechanisms of mental illness and to develop more effective treatments.

Although various experimental studies have provided valuable information for understanding and explaining the underlying mechanisms of mental illness[11-13], the development of computational psychiatry is challenged by multiple interactions[14]. For instance, one of the biggest challenges faced by computational psychiatry today is the availability and quality of data. Mental health disorders are complex and multifaceted, and it is difficult to collect data that accurately reflect experiences with the disorders. Another challenge is the interpretability of the results. Many techniques that are used in computational psychiatry are highly complex and even difficult for experts in the field to understand, which makes it difficult for researchers to communicate their findings with others and for clinicians to

apply these findings to actual treatment. Many other problems also need to be solved, such as the technical connection between model development and clinical practice and ethical acceptability. Despite these issues, we remain optimistic about the future of computational psychiatry.

Establishing a complete artificial intelligence ecosystem of computational psychiatry is an effective method to solve the challenges in the clinical practice of psychiatry. In this study, we focus on building an artificial intelligence ecosystem for computational psychiatry to better facilitate the elimination of barriers to clinical practice. This review aims to make a fundamental contribution to shaping the ecosystem and for allowing the modules to be smoothly applied. Moreover, it outlines the responsibilities of the different agents and the linkages between them and builds a loop from data collection to modeling, evaluation, and clinical practice. We plan to sort out and integrate the same and different methods and models in the field, overcome the existing limitations, provide full attention to the role of each subject, and eventually form a complete and mature ecosystem. It is believed that as the field continues to evolve, researchers will eventually find ways to overcome the challenges and make greater advances in our understanding and treatment of mental health conditions.

METHODS

In this review, we used "computational psychiatry", "machine learning", "artificial intelligence", "psychiatry", and "deep learning" as keywords and retrieved the English literature in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science. We also manually screened the retrieved literature according to the relevance of the literature content to the topic and narrowed it down to a more accurate scope.

ARTIFICIAL INTELLIGENCE ECOSYSTEM FOR COMPUTATIONAL PSYCHIATRY

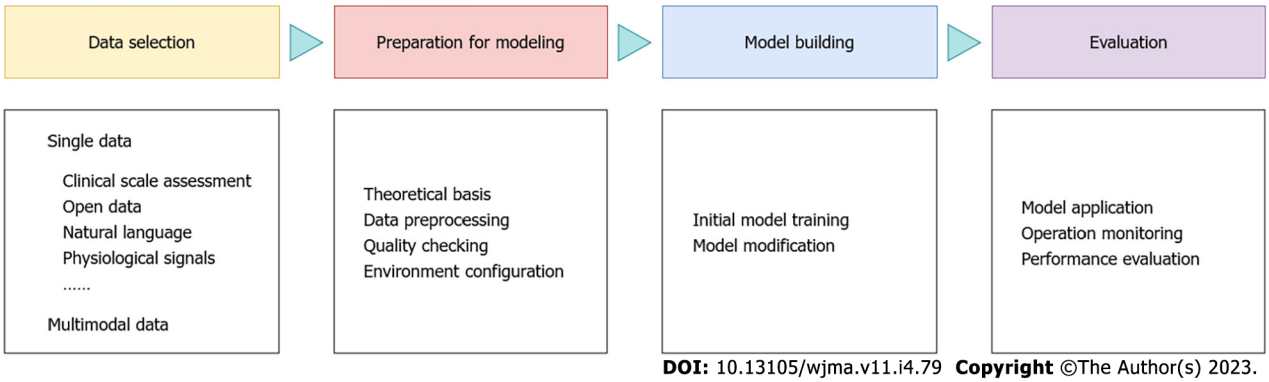
Based on the literature concerning clinical thinking and life cycle management of artificial intelligence projects, we conducted an integrated design of the ecosystem of computational psychiatry. We divided the clinical practice process of computational psychiatry into the following four main stages: data acquisition, modeling preparation, model construction, and application evaluation (Figure 1).

Data collection

One of the strengths of computational psychiatry is its ability to integrate big datasets of various forms to help researchers gain a more complete understanding of a patient's mental health. Thus, the first and most critical step in the artificial intelligence ecosystem for computational psychiatry is data collection. During this process, researchers can select one or more input data that can be measured according to the relevance of the research problem[15]. Common forms include clinical scales, visual data, voice, physiological signals, and Internet of Things data, *etc.* Although there are a wide variety of input data, tool selection should be based on a clear understanding of treatment strategies and the realistic evaluation of clinical effectiveness. Moreover, it should consider the mutual limiting effect of different data acquisition methods and technology operations, as well as the quality of original data and the details of processing methods, which will directly affect the reliability of the tools, and thus affect the effectiveness of clinical application[16,17].

Preparation for modeling

Modeling relies on different theoretical traditions[18]. For example, algorithm engineers are required to follow industry practice rules and conference content, articles, or implicit guidelines related to machine learning, and psychiatrists are bound by rules in the legal and medical fields, such as the National Institute for Health and Clinical Excellence guidelines or the American Psychiatric Association Practice guidelines. In addition, judgments are often made differently depending on the unique personality of the model builder. For example, clinicians' decision-making styles and willingness to take risks have a direct impact on their treatment paths and diagnostic strategies, and conservative and adventurous engineers also exhibit differences in aesthetic awareness and modeling styles. Therefore, the theoretical basis is worth fully preparing before building the model. The second is data preprocessing and quality checking. Since the collected data are often incomplete, as well as the fact that data from heterogeneous data sources may need to be collected, the raw data need to be preprocessed and quality checked to ensure the quality of the data. Only after data cleaning, data integration, data reduction, data transformation, and other processing can standardize data for model construction. The establishment of the compilation environment is also one of the preparatory works of model construction. There are several open source platforms that can be used for training, testing, and benchmarking algorithms based on different design requirements, such as OpenAI Gym[19], which provides a range of tasks, including some classic arcade games including Doom, as well as models, tests, and diagnostic paradigms that can be used for mental illness.



DOI: 10.13105/wjma.v11.i4.79

Figure 1 Framework for modeling artificial intelligence ecosystems.

Model building

The first two steps in the computational psychiatry ecosystem both serve the third step; specifically, after collecting and processing the corresponding data in the theoretical context, the next step involves normative model building[20-22]. This step is divided into two parts: initial model training and model modification. Machine learning[23-27] is often used in model training to recognize emotional states[28], to detect mood swings[29], and to diagnose mental diseases[30]. There are two main types of machine learning: supervised learning and unsupervised learning. Supervised learning uses categorization and regression to learn from examples of existing labels. This method is often used to build classifiers to distinguish healthy people from sick people or to build predictive models. Washington *et al*[31] designed Guesswhat, which is a smartphone game for emotional data collection. They trained a pediatric emotion classification convolutional neural network classifier to recognize children's expressions, such as sadness, surprise, disgust, happiness, and neutral expressions. Their results demonstrated the value of mobile digital health. Although mood classifiers have made remarkable progress in automatic emotion recognition, the computational cost of existing models is too high. Banerjee *et al*[32] optimized the design of the machine learning model. The MobileNet-V2 network that they trained on ImageNet achieved a balanced accuracy rate of 65.11% and an F1 score of 64.19% on CAFE. Through optimization techniques, machine learning models can achieve greater accuracy and lighter weight. Unsupervised learning[33,34] is a classification method that does not require human data classification but automatically divides the structure based on the inherent distribution characteristics of datasets. In addition, clustering methods are often used in unsupervised learning. Regardless of which training method is used, professional school education and clinical training are needed. For example, clinicians require training in psychiatric education based on clinical case studies (fictional or nonfictional), and machine learning engineers require systematic schooling and professional experience. Finally, the initial model is reasonably built.

Computational psychiatry seeks to develop quantitative, mechanistic models of psychiatric disorders [35] that can help researchers better understand the biological and cognitive processes that lead to these disorders. A key benefit of computational models is that they can help researchers generate testable hypotheses about the underlying mechanisms of mental disorders. For example, reinforcement learning models of addiction[36,37] can be used to generate hypotheses about specific brain regions and pathways associated with addiction, as well as types of interventions that may be effective in treating addiction. The model, which is based on principles of neuroscience and psychology, suggests that addiction is caused by a disorder in the brain's reward system, which leads to obsessive behavior and a loss of control over behavior. Another benefit of computational models in psychiatry is that they can help researchers assess the effectiveness of different treatment options. For example, the cognitive-affective neural circuit model of depression[38] can be used to evaluate the efficacy of different antidepressants or psychotherapy based on predictions of their effects on basic brain circuits associated with depression. The model, which is based on evidence from neuroscience and psychology, proposes that depression is caused by the disequilibrium of the brain's emotional and cognitive processing systems, which leads to symptoms such as low mood, reduced negative thinking, and reduced motivation. However, regardless of how good the model is, there is room for improvement. As more theoretical background is accumulated in clinical practice, updated data will be incorporated into the model[39, 40]. Moreover, the model will expose more practical problems in clinical application; thus, it needs to be constantly adjusted and modified to adapt to new challenges.

Evaluation

Computational psychiatry is not currently used clinically, but it has the potential to inform new clinical interventions and treatments for mental illness to help guide the treatment of mental disorders. For example, clinicians can use computational models to assess an individual's brain activity and symptoms

to choose the most appropriate treatment for them. By using computational and mathematical models to better understand the underlying mechanisms of these diseases, researchers in the field can identify potential targets for intervention and assess the likely effects of different treatment options. However, more research is needed to fully understand the clinical potential of computational psychiatry and to develop the necessary tools and techniques to apply it in the clinical setting. Given the complexity of psychiatric disorders, future applications should be subject to enhanced regulatory oversight of clinical practice, as well as the evaluation and post hoc analysis of actual clinical benefits and model performance[41].

DATA SOURCES OF COMPUTING PSYCHIATRY

Based on the review of the existing studies, we conclude that data sources mainly include the following methods: scales, public data, language, physiological signals, blood, multimodal data, *etc.* (Table 1). This paper will discuss some of these categories.

Scales

Clinical scales[42-45] are one of the most widely used tools in clinical evaluation, and mature scales include the World Health Organization-Quality of Life-Brief (WHO-QoL-Bref), cognitive function test, Hamilton Depression Scale, Autism Diagnostic Observation Schedule, Hamilton Anxiety Scale, Fibromyalgia and Chronic Fatigue Rating Scale, *etc.* Large datasets accumulated through electronic medical records[46] facilitate the determination of goals by using computational methods. Self-reported digital scales[47,48] are used in the following manner. Researchers load the quantitative list of questions into the app, allow users to answer questions by using smart devices, and ultimately screen for symptoms based on the answers. This approach relies on mobile technology rather than traditional clinical scales.

Large-scale online data

Dubois *et al*[49] used a large online sample to demonstrate an association between human exploration strategies and impulse psychiatry, which not only demonstrated that impulsivity is associated with specific forms of exploration but also explored links between impulsivity and other psychiatric dimensions. Moreover, Nam *et al*[50] used machine learning and web analysis to identify factors associated with depression from national population surveys. Nielsen *et al*[51] discussed how large multisite public datasets contribute to the application of machine learning in psychiatry. Furthermore, Hu *et al*[52] collected users' text expressions on social platforms (such as Weibo) as data sources to predict their depression symptoms. Artificial intelligence (especially big data)[53] plays a vital role in health care, thus demonstrating its significant potential in applications[54].

Images and videos

Research indicates that psychiatric patients have different color vision and are less able to discriminate between colors than ordinary people. Therefore, the color recognition of images can be used to examine the difference between psychiatric patients and control groups or as a prognostic diagnosis. Shen *et al*[55] reviewed the paintings of 281 patients with chronic schizophrenia and 35 patients with healthy controls and used a series of computational analyses to scan and process the images. The results showed that color paint images have the potential to be used as a clinical diagnostic and prognostic tool for patients with chronic schizophrenia. The video data collected by the camera exhibit a large deviation, which is caused by noise in the natural environment. Moreover, existing studies provide optimized schemes through data collection pipelines, feature engineering, and data expansion strategies. The standard diagnosis for autism spectrum disorders takes several hours and assesses 20 to 100 behaviors (*e.g.*, eye contact, social smiling, *etc.*). Leblanc *et al*[56] introduced feature replacement methods to analyze family videos to establish the diagnosis of autism. They rated 140 videos of children on YouTube, filled in missing values by using feature replacement methods, and optimized the performance of the autism detection classifier. Dynamic feature replacement methods are superior to traditional methods in terms of performance and can reduce the impacts of missing values on video diagnosis[56]. Furthermore, Tariq *et al*[57] used mobile devices to classify videos by machine learning and labeled video features. This method ensures the accuracy of assessment and improves the speed of diagnosis.

Language

Automated speech analysis has been used in psychiatric diagnosis[58,59] and learns baseline interview data through machine learning algorithms to predict mental illness. Carrillo *et al*[60] conducted baseline autobiographical interviews with patients and transcribed them by using machine learning algorithms to predict the effectiveness of psilocybin for depression. The combination of machine learning with automated speech algorithms[61] contributes new ideas for the prediction and diagnosis of psychiatry. Moreover, the acquisition of language is relatively mild compared to acquiring intrusive data and

Table 1 Data sources for computational psychiatry

Module	Category
Single data	Clinical scales[42,45], electronic medical records[46], and digital scales[47,48]
	large online sample[49], national population surveys[50], and large multisite public datasets[51]
	Images[55] and videos[56,57]
	Language[62] and baseline interviews[60]
	Emotional faces[63,64], electrocardiogram[65], electroencephalogram[68-70], magnetoencephalogram[71], and magnetic resonance imaging[72,73,75]
	Human motion bone data[79]
	Blood[81,85]
Multimodal data	Multimodal data[45,86,89]

supports self-testing by users[62]. Computational linguistics combined with artificial intelligence provides a good aid to clinical diagnosis and risk monitoring.

Physiological signals

Physiological signals include emotional faces[63,64], electrocardiogram[65], electroencephalogram (EEG)[66-69], magnetoencephalogram[71], and functional magnetic resonance imaging (fMRI)[72-77]. There are two main methods to collect biological signals: invasive and noninvasive methods. Noninvasive data acquisition is commonly used, including electroencephalogram and functional magnetic resonance imaging. In recent years, physiological signals have been increasingly used to measure emotional responses. Compared with audiovisual data, physiological signals provide more detailed and real information. However, there are too many interference factors in the collection process of physiological signals, and the processing mechanism is more complex.

Human motion bone data

The clinical and scientific value of full body movement assessment has been increasingly recognized, and it is often used in the diagnosis of cerebral palsy. Previous studies were mostly based on computer vision[78]. However, during the process of sorting out the relevant studies, we noticed an interesting experimental study[79]. From the perspective of full body kinematics, the team built a machine-learning model to establish the purpose of automatic recognition and classification of depression. They used Kinect to capture human motion bone data, conducted experiments with four machine learning tools (including a support vector machine, logistic regression, random forest, and gradient lift), and finally utilized the evaluation and classification of patients with depression and without depression. This experimental study allows us to demonstrate the auxiliary role of kinematics in the identification of depression. However, when motion capture equipment is used to record the joint skeleton data of participants in motion, the captured data often contain noise due to the influence of the environment and sensor accuracy, which limits the accuracy of the data.

Blood

Biomarkers[80] are a group of proposed markers in recent years related to cell growth, proliferation, and disease occurrence, and they can be used to reflect drug reactions during pathological processes or after therapeutic interventions. Wagh *et al*[81] reviewed gene expression studies based on peripheral blood to identify gene expression biomarkers for schizophrenia. According to a genome-wide association study (GWAS), C-reactive protein (CRP) which is a biomarker of chronic inflammation, in the blood is likely associated with an increased risk of major depression; however, it is also correlated with a decreased risk of anorexia nervosa, obsessive-compulsive disorder, and schizophrenia[82]. By examining RNA, researchers can determine the patient's current state of anxiety, depression, and mania[83]. Moreover, despite the differences in population characteristics, analysis methods of gene expression, and nature of the research, the results still proved the validity of blood-based gene expression. Fernandes *et al*[84] used a machine learning algorithm composed of peripheral blood immunoinflammatory biomarkers and cognitive biomarkers in the diagnosis of bipolar disorder and schizophrenia with clinical effectiveness. The manner in which machine learning is combined with pharmacogenomic data provides a new way to predict patients with major depression. In a systematic review of recent advances in machine learning and pharmacogenomics studies, Bobo *et al*[85] demonstrated the effectiveness of pharmacogenomics in predicting short-term antidepressant responses and suggested that the prediction of treatment outcomes may depend on background factors that cannot be captured by machine learning algorithms.

Multimodal data

In addition to collection methods of single data, multimodal datasets are increasingly used in psychiatry, such as the use of clinical scale evaluation and resting-state functional magnetic resonance imaging (MRI) to establish a prediction model of mood disorders, anxiety, and anhedonia[45], as well as a machine learning framework based on multimodal neuropsychiatric data to predict the responses of patients with schizophrenia to treatment[86]. Chen *et al*[87] conducted a comprehensive review of the practice of machine learning combined with neuroimaging in psychiatry, which emphasized the importance of multimodal data and the extraction of multimedia information. Data were collected through a combination of electronic questionnaires, standard clinical care record reviews, and device output analysis[88]. Although this statistical method integrating multimodal data demonstrates advantages over the general methods of single data, it is usually prone to overfitting and poor generalization[89]. The method of how to avoid these problems should be further explored in the future.

CHALLENGES OF COMPUTATIONAL PSYCHIATRY

The building of an AI ecosystem for computational psychiatry currently faces multiple challenges, which can be broadly divided into three categories: technical factors, cost and context, and ethical challenges. In this section, each challenge is explained separately.

Technical factors

It is important to note that computational psychiatry is still in its early stages, and there are many challenges that must be overcome. The most fundamental challenge is technical difficulty. Examples include data availability and quality, data transparency[90], technology openness, and professional integration. The quality of the raw data and the details of the processing are directly related to the interpretation of the results. One primary way to address this challenge is to increase collaboration with experts in other fields, such as computer science and engineering. By combining their expertise, researchers can develop new algorithms and tools to better handle the complex datasets associated with mental health research. Automation, rigor, and standardization of treatment methods[16] is another manner to advance the field of computational psychiatry, which can help to ensure that the results of computational research are replicable and can be generalized to a wider population. Due to the fact that "data-driven" research is based on the analysis and application of data, the transparent presentation of data results without bias and selectivity is the norm that researchers must follow. In response, there is a need to develop an interpretable, transparent, and universally applicable scientific review framework [91] to ensure the feasibility of using AI in psychiatry. Although the rapid development of artificial intelligence approaches has made up for the shortcomings of traditional mental illness research methods, thus identifying increasingly more information related to brain function, it must be stated that mental illness researchers and clinicians know very little about computational technology methods[92, 93]. It is recommended that there should be improvements in the computational literacy of neuroscientists and mental health professionals[94] while also leveraging the talent development role of higher education to bring more people with cross-disciplinary professional backgrounds into the field. Another note about computational psychiatry is the importance of ensuring that the field remains accessible and inclusive. As computing becomes more widely used in mental health research, it is important that these technologies are not just reserved for the best-funded or best-known researchers. Instead, an open and inclusive approach should be taken to provide researchers from diverse backgrounds and institutions with the tools and resources that are needed to conduct computational psychiatry research. It is also important for researchers to engage with policy-makers and advocacy groups[95] to ensure that findings from computational psychiatry are translated into practical applications.

Costs and different theoretical backgrounds

The costs mentioned in this section include time costs[18] and labor costs, which are uncontrollable factors that should be considered in clinical modeling. Due to the wide range of projects contained in the ecosystem, the system operation needs to be repeatedly monitored, evaluated, adjusted, and optimized, thus requiring a large amount of time. Moreover, there are many participating roles in each link, and there are cost consumption problems in coordination and communication management. For example, a team of clinicians may accept social and institutional pressures, and there may be conflicts between experienced mature doctors and novice decision-makers. The intersection and unification of viewpoints under different theoretical backgrounds in interdisciplinary cooperation also require coordination and compromise. Second, the reasonable match between professional salary structure and working style will also affect the clinical practice effects. In addition to the abovementioned overt factors, some individuals have raised concerns about the use of computational techniques in studies of mental health conditions, wherein they have argued that these methods may oversimplify complex phenomena and ignore important environment-specific factors. We also need to consider whether the modeling state of computational psychiatry follows the natural trajectory of core neurobiology[3] and whether computational psychiatry is detached from the developmental background of the field of psychiatry. When we

discuss the development of psychiatry with sophisticated AI approaches, we must not lose sight of the core purpose of disease treatment.

Ethical challenge

In addition, there are ethical issues with the use of computing in mental health research[96,97]. The application of AI to psychiatry needs to consider AI ethical issues, including respecting patient autonomy by providing adequate consent[70,98], data ownership, the ignoring of conscious experience, privacy protection[99], and equity[100]. An ethically acceptable manner[101,102] is an obstacle to the transformation of computational psychiatry from theory to practice. Some researchers have argued that the use of these techniques can lead to biased or discriminatory results, especially if the algorithm is not properly trained or verified. In the practice of treating and predicting mental illness, we call upon researchers and health care professionals to approach patients with rigorous optimism concerning the principles of kindness[103], harmfulness, respect for autonomy and justice[42], and prevention of ethical issues from the aspects of communication, consent, and contrast[104]. According to four basic ethical principles (respect, no harm, benefit, and justice), researchers should fully respect the independent will of data providers when collecting and using data, as well as pay attention to the protection of their personal privacy and process data anonymously. In addition, the participants' rights and interests should be the first priority. Justice and fairness should be adhered to. Moreover, informed consent should be obtained, and the process should be open and fair. Although we are aware that computational AI approaches (such as machine learning) can have a profound impact in psychiatry, there are still no applications that constitute standard clinical practice. The early consideration of these ethical challenges and the establishment of standards and requirements to eventually allow for the early use of the benefits of AI for mental health care should be enacted. Despite these concerns, we remain convinced that the potential benefits of computational psychiatry far outweigh the risks[105]. By properly using AI to study mental health conditions, researchers can gain a more comprehensive and nuanced understanding of mental illness, which could ultimately lead to better treatments.

LIMITATIONS

There were several limitations to this study. First, all of the relevant literature that was analyzed in this paper is in English and does not cover studies in other languages (such as Chinese, Korean, Japanese, and German). Thus, the coverage of the research may still be insufficient. Second, this paper is only a summary of the research in related fields, which cannot be applied to clinical treatment. This review only collates extensive research on data sources, tools, and model frameworks in computational psychiatry and does not use explicit methods, such as systematic reviews, nor does it address substantive clinical outcomes.

CONCLUSION

This paper builds an artificial intelligence ecosystem for computational psychiatry by reviewing the literature, including the following four stages: data acquisition, preparation for modeling, model building, and application evaluation. In terms of data acquisition, we discussed different data acquisition methods and data forms and summarized single data source methods, such as scale, open data, language, and physiological signals, as well as multimodal data statistical methods combining different types of data. In terms of preparation for modeling, we explored constraints from both the clinician and algorithm engineer industry norms and emphasized the importance of data preprocessing and quality testing. For model building, we proposed two steps of normative modeling (initial model training and model modification) and discussed supervised learning and unsupervised virtual seats in machine learning. Finally, based on the relevant theory and experience, we prospectively assessed the aspect of application evaluation and clarified the complexity and necessity of model performance evaluation and post analysis.

In conclusion, computational psychiatry is a promising field that has the potential to revolutionize our understanding and treatment of mental health conditions. In recent years, research on computational psychiatry has produced many good results. For example, it has made profound theoretical breakthroughs in the integration of computer science, biology, psychiatry, statistics, and other disciplines. In addition, it has allowed for the performance of more in-depth research in the use of computing and mathematical techniques to explain mental diseases and has made many attempts and modifications in data collection, model construction, and other aspects. It is worth mentioning that this field has accumulated a rich amount of data, with data originating from traditional clinical scale evaluations to the application of big data, from language to EEG, and from a single dataset to multimodal data, which provides a solid foundation for future clinical practice.

However, it should not be ignored that computational psychiatry is still in its early stages and experiences of technical challenges, such as data quality and tool openness, cost issues (such as role conflict and development cycle), and ethical challenges (such as data privacy, respect, and equity). More work will need to be performed to realize its full potential to ensure that existing discoveries are eventually translated into clinical applications. Specifically, the need for an artificial intelligence ecosystem for computational psychiatry can help researchers clarify their work, build on it, further develop better algorithms and techniques to analyze complex datasets, establish more rigorous and standardized experimental methods, and collaborate with policy-makers and advocacy groups to ensure that the findings of computational psychiatry are translated into practical applications. When considering that the use of artificial intelligence needs to experience a series of ethical problems caused by computing technology, the establishment of relevant application standards and moral guidelines should be emphasized in the future. Moreover, future research should focus on the integration of computational psychiatry with other disciplines, such as psychology, neuroscience, and genetics. By combining multidisciplinary and multidisciplinary expertise, researchers can gain a more comprehensive understanding of the crux of mental illness and develop more effective treatments and interventions.

FOOTNOTES

Author contributions: Liu XQ designed the study; Liu XQ, Ji XY, Weng X and Zhang YF wrote the manuscript and conducted the literature analyses; All of the authors contributed equally to this work and have approved the final manuscript.

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

Country/Territory of origin: China

ORCID number: Xin-Qiao Liu 0000-0001-6620-4119; Xin-Yu Ji 0000-0003-1337-0185; Xing Weng 0000-0002-3574-9527; Yi-Fan Zhang 0000-0002-8870-9983.

S-Editor: Liu JH
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **COVID-19 Mental Disorders Collaborators**. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet* 2021; **398**: 1700-1712 [PMID: 34634250 DOI: 10.1016/S0140-6736(21)02143-7]
2 **Taquet M**, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry* 2021; **8**: 416-427 [PMID: 33836148 DOI: 10.1016/S2215-0366(21)00084-5]
3 **Montague PR**, Dolan RJ, Friston KJ, Dayan P. Computational psychiatry. *Trends Cogn Sci* 2012; **16**: 72-80 [PMID: 22177032 DOI: 10.1016/j.tics.2011.11.018]
4 **Friston K**. Computational psychiatry: from synapses to sentience. *Mol Psychiatry* 2023; **28**: 256-268 [PMID: 36056173 DOI: 10.1038/s41380-022-01743-z]
5 **Constant A**, Badcock P, Friston K, Kirmayer LJ. Integrating Evolutionary, Cultural, and Computational Psychiatry: A Multilevel Systemic Approach. *Front Psychiatry* 2022; **13**: 763380 [PMID: 35444580 DOI: 10.3389/fpsyt.2022.763380]
6 **Huys QJM**, Browning M, Paulus MP, Frank MJ. Advances in the computational understanding of mental illness. *Neuropsychopharmacology* 2021; **46**: 3-19 [PMID: 32620005 DOI: 10.1038/s41386-020-0746-4]
7 **Huys QJ**, Maia TV, Frank MJ. Computational psychiatry as a bridge from neuroscience to clinical applications. *Nat Neurosci* 2016; **19**: 404-413 [PMID: 26906507 DOI: 10.1038/nn.4238]
8 **Sarris J**. Disruptive innovation in psychiatry. *Ann N Y Acad Sci* 2022; **1512**: 5-9 [PMID: 35233789 DOI: 10.1111/nyas.14764]
9 **Macpherson T**, Churchland A, Sejnowski T, DiCarlo J, Kamitani Y, Takahashi H, Hikida T. Natural and Artificial Intelligence: A brief introduction to the interplay between AI and neuroscience research. *Neural Netw* 2021; **144**: 603-613 [PMID: 34649035 DOI: 10.1016/j.neunet.2021.09.018]
10 **Kucikova L**, Danso S, Jia L, Su L. Computational Psychiatry and Computational Neurology: Seeking for Mechanistic

Modeling in Cognitive Impairment and Dementia. *Front Comput Neurosci* 2022; **16**: 865805 [PMID: 35645752 DOI: 10.3389/fncom.2022.865805]

11 **Khaleghi A**, Zarafshan H, Vand SR, Mohammadi MR. Effects of Non-invasive Neurostimulation on Autism Spectrum Disorder: A Systematic Review. *Clin Psychopharmacol Neurosci* 2020; **18**: 527-552 [PMID: 33124586 DOI: 10.9758/cpn.2020.18.4.527]

12 **Mostafavi SA**, Khaleghi A, Mohammadi MR. Noninvasive brain stimulation in alcohol craving: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2020; **101**: 109938 [PMID: 32234509 DOI: 10.1016/j.pnpbp.2020.109938]

13 **Zarafshan H**, Khaleghi A, Mohammadi MR, Moeini M, Malmir N. Electroencephalogram complexity analysis in children with attention-deficit/hyperactivity disorder during a visual cognitive task. *J Clin Exp Neuropsychol* 2016; **38**: 361-369 [PMID: 26678277 DOI: 10.1080/13803395.2015.1119252]

14 **Bhugra D**, Tasman A, Pathare S, Priebe S, Smith S, Torous J, Arbuckle MR, Langford A, Alarcón RD, Chiu HFK, First MB, Kay J, Sunkel C, Thapar A, Udomratn P, Baingana FK, Kestel D, Ng RMK, Patel A, Picker L, McKenzie KJ, Moussaoui D, Muijen M, Bartlett P, Davison S, Exworthy T, Loza N, Rose D, Torales J, Brown M, Christensen H, Firth J, Keshavan M, Li A, Onnela JP, Wykes T, Elkholy H, Kalra G, Lovett KF, Travis MJ, Ventriglio A. The WPA-Lancet Psychiatry Commission on the Future of Psychiatry. *Lancet Psychiatry* 2017; **4**: 775-818 [PMID: 28946952 DOI: 10.1016/S2215-0366(17)30333-4]

15 **Rutherford S**, Kia SM, Wolfers T, Fraza C, Zabihi M, Dinga R, Berthet P, Worker A, Verdi S, Ruhe HG, Beckmann CF, Marquand AF. The normative modeling framework for computational psychiatry. *Nat Protoc* 2022; **17**: 1711-1734 [PMID: 35650452 DOI: 10.1038/s41596-022-00696-5]

16 **Wu C**, Ferreira F, Fox M, Harel N, Hattangadi-Gluth J, Horn A, Jbabdi S, Kahan J, Oswal A, Sheth SA, Tie Y, Vakharia V, Zrinzo L, Akram H. Clinical applications of magnetic resonance imaging based functional and structural connectivity. *Neuroimage* 2021; **244**: 118649 [PMID: 34648960 DOI: 10.1016/j.neuroimage.2021.118649]

17 **Janssen RJ**, Mourão-Miranda J, Schnack HG. Making Individual Prognoses in Psychiatry Using Neuroimaging and Machine Learning. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018; **3**: 798-808 [PMID: 29789268 DOI: 10.1016/j.bpsc.2018.04.004]

18 **Martin VP**, Rouas JL, Philip P, Fourneret P, Micoulaud-Franchi JA, Gauld C. How Does Comparison With Artificial Intelligence Shed Light on the Way Clinicians Reason? *Front Psychiatry* 2022; **13**: 926286 [PMID: 35757203 DOI: 10.3389/fpsyt.2022.926286]

19 **Cullen M**, Davey B, Friston KJ, Moran RJ. Active Inference in OpenAI Gym: A Paradigm for Computational Investigations Into Psychiatric Illness. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018; **3**: 809-818 [PMID: 30082215 DOI: 10.1016/j.bpsc.2018.06.010]

20 **Lanillos P**, Oliva D, Philippsen A, Yamashita Y, Nagai Y, Cheng G. A review on neural network models of schizophrenia and autism spectrum disorder. *Neural Netw* 2020; **122**: 338-363 [PMID: 31760370 DOI: 10.1016/j.neunet.2019.10.014]

21 **Loosen AM**, Hauser TU. Towards a computational psychiatry of juvenile obsessive-compulsive disorder. *Neurosci Biobehav Rev* 2020; **118**: 631-642 [PMID: 32942176 DOI: 10.1016/j.neubiorev.2020.07.021]

22 **Mujica-Parodi LR**, Strey HH. Making Sense of Computational Psychiatry. *Int J Neuropsychopharmacol* 2020; **23**: 339-347 [PMID: 32219396 DOI: 10.1093/ijnp/pyaa013]

23 **Durstewitz D**, Koppe G, Meyer-Lindenberg A. Deep neural networks in psychiatry. *Mol Psychiatry* 2019; **24**: 1583-1598 [PMID: 30770893 DOI: 10.1038/s41380-019-0365-9]

24 **Ruengchaijatuporn N**, Chatnuntawech I, Teerapittayanon S, Sriswasdi S, Itthipuripat S, Hemrungrojn S, Bunyabukkana P, Petchlorlian A, Chunamchai S, Chotibut T, Chunharas C. An explainable self-attention deep neural network for detecting mild cognitive impairment using multi-input digital drawing tasks. *Alzheimers Res Ther* 2022; **14**: 111 [PMID: 35945568 DOI: 10.1186/s13195-022-01043-2]

25 **Torabi Moghadam B**, Etemadikhah M, Rajkowska G, Stockmeier C, Grabherr M, Komorowski J, Feuk L, Carlström EL. Analyzing DNA methylation patterns in subjects diagnosed with schizophrenia using machine learning methods. *J Psychiatr Res* 2019; **114**: 41-47 [PMID: 31022588 DOI: 10.1016/j.jpsychires.2019.04.001]

26 **Trinhammer ML**, Merrild ACH, Lotz JF, Makransky G. Predicting crime during or after psychiatric care: Evaluating machine learning for risk assessment using the Danish patient registries. *J Psychiatr Res* 2022; **152**: 194-200 [PMID: 35752071 DOI: 10.1016/j.jpsychires.2022.06.009]

27 **Watts D**, Moulden H, Mamak M, Upfold C, Chaimowitz G, Kapczinski F. Predicting offenses among individuals with psychiatric disorders - A machine learning approach. *J Psychiatr Res* 2021; **138**: 146-154 [PMID: 33857785 DOI: 10.1016/j.jpsychires.2021.03.026]

28 **Wang X**, Nie D, Lu B. Emotional state classification from EEG data using machine learning approach. *Neurocomputing* 2014; **129**: 94-106 [DOI: 10.1016/j.neucom.2013.06.046]

29 **Eldar E**, Roth C, Dayan P, Dolan RJ. Decodability of Reward Learning Signals Predicts Mood Fluctuations. *Curr Biol* 2018; **28**: 1433-1439.e7 [PMID: 29706512 DOI: 10.1016/j.cub.2018.03.038]

30 **Honnorat N**, Dong A, Meisenzahl-Lechner E, Koutsouleris N, Davatzikos C. Neuroanatomical heterogeneity of schizophrenia revealed by semi-supervised machine learning methods. *Schizophr Res* 2019; **214**: 43-50 [PMID: 29274735 DOI: 10.1016/j.schres.2017.12.008]

31 **Washington PY**, Kalantarian H, Kent J, Husic A, Kline A, Leblanc É, Hou C, Mutlu C, Dunlap K, Penev Y, Varma M, Stockham NT, ChrismanBS, Paskov KM, Sun MW, Jung JY, Voss C, Haber N, Wall DP. Training an Emotion Detection Classifier using Frames from a Mobile Therapeutic Game for Children with Developmental Disorders. *ArXiv* 2020 [DOI: 10.48550/arXiv.2012.08678]

32 **Banerjee A**, Mutlu OC, Kline A, Washington P, Wall D. Training and Profiling a Pediatric Emotion Recognition Classifier on Mobile Devices for Autism Detection and Treatment (Preprint) [DOI: 10.2196/preprints.39917]

33 **Dimitri GM**, Spasov S, Duggento A, Passamonti L, Lio P, Toschi N. Unsupervised stratification in neuroimaging through deep latent embeddings. *Annu Int Conf IEEE Eng Med Biol Soc* 2020; **2020**: 1568-1571 [PMID: 33018292 DOI: 10.1109/EMBC44109.2020.9175810]

34 **Jacob S**, Wolff JJ, Steinbach MS, Doyle CB, Kumar V, Elison JT. Neurodevelopmental heterogeneity and computational approaches for understanding autism. *Transl Psychiatry* 2019; **9**: 63 [PMID: 30718453 DOI: 10.1038/s41398-019-0390-0]

35 **Langley C**, Cirstea BI, Cuzzolin F, Sahakian BJ. Theory of Mind and Preference Learning at the Interface of Cognitive Science, Neuroscience, and AI: A Review. *Front Artif Intell* 2022; **5**: 778852 [PMID: 35493614 DOI: 10.3389/frai.2022.778852]

36 **Adams RA**, Huys QJ, Roiser JP. Computational Psychiatry: towards a mathematically informed understanding of mental illness. *J Neurol Neurosurg Psychiatry* 2016; **87**: 53-63 [PMID: 26157034 DOI: 10.1136/jnnp-2015-310737]

37 **Maia TV**, Frank MJ. From reinforcement learning models to psychiatric and neurological disorders. *Nat Neurosci* 2011; **14**: 154-162 [PMID: 21270784 DOI: 10.1038/nn.2723]

38 **Barnard PJ**, Teasdale JD. Interacting cognitive subsystems: A systemic approach to cognitive-affective interaction and change. *Cogn Emot* 1991; **5**: 1-39 [DOI: 10.1080/02699939108411021]

39 **Donini M**, Monteiro JM, Pontil M, Hahn T, Fallgatter AJ, Shawe-Taylor J, Mourão-Miranda J; Alzheimer's Disease Neuroimaging Initiative. Combining heterogeneous data sources for neuroimaging based diagnosis: re-weighting and selecting what is important. *Neuroimage* 2019; **195**: 215-231 [PMID: 30894334 DOI: 10.1016/j.neuroimage.2019.01.053]

40 **Liu XQ**, Guo YX, Zhang WJ, Gao WJ. Influencing factors, prediction and prevention of depression in college students: A literature review. *World J Psychiatry* 2022; **12**: 860-873 [PMID: 36051603 DOI: 10.5498/wjp.v12.i7.860]

41 **Starke G**, De Clercq E, Borgwardt S, Elger BS. Computing schizophrenia: ethical challenges for machine learning in psychiatry. *Psychol Med* 2021; **51**: 2515-2521 [PMID: 32536358 DOI: 10.1017/S0033291720001683]

42 **Kanchanatawan B**, Sriswasdi S, Maes M. Supervised machine learning to decipher the complex associations between neuro-immune biomarkers and quality of life in schizophrenia. *Metab Brain Dis* 2019; **34**: 267-282 [PMID: 30467771 DOI: 10.1007/s11011-018-0339-7]

43 **Kosmicki JA**, Sochat V, Duda M, Wall DP. Searching for a minimal set of behaviors for autism detection through feature selection-based machine learning. *Transl Psychiatry* 2015; **5**: e514 [PMID: 25710120 DOI: 10.1038/tp.2015.7]

44 **Liu Q**, Woo M, Zou X, Champaneria A, Lau C, Mubbashar MI, Schwarz C, Gagliardi JP, Tenenbaum JD. Symptom-based patient stratification in mental illness using clinical notes. *J Biomed Inform* 2019; **98**: 103274 [PMID: 31499185 DOI: 10.1016/j.jbi.2019.103274]

45 **Mellem MS**, Liu Y, Gonzalez H, Kollada M, Martin WJ, Ahammad P. Machine Learning Models Identify Multimodal Measurements Highly Predictive of Transdiagnostic Symptom Severity for Mood, Anhedonia, and Anxiety. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2020; **5**: 56-67 [PMID: 31543457 DOI: 10.1016/j.bpsc.2019.07.007]

46 **Edgcomb JB**, Zima B. Machine Learning, Natural Language Processing, and the Electronic Health Record: Innovations in Mental Health Services Research. *Psychiatr Serv* 2019; **70**: 346-349 [PMID: 30784377 DOI: 10.1176/appi.ps.201800401]

47 **Bangerter A**, Manyakov NV, Lewin D, Boice M, Skalkin A, Jagannatha S, Chatterjee M, Dawson G, Goodwin MS, Hendren R, Leventhal B, Shic F, Ness S, Pandina G. Caregiver Daily Reporting of Symptoms in Autism Spectrum Disorder: Observational Study Using Web and Mobile Apps. *JMIR Ment Health* 2019; **6**: e11365 [PMID: 30912762 DOI: 10.2196/11365]

48 **Jones RM**, Tarpey T, Hamo A, Carberry C, Lord C. Smartphone measures of day-to-day behavior changes in children with autism. *NPJ Digit Med* 2018; **1**: 34 [PMID: 31304316 DOI: 10.1038/s41746-018-0043-3]

49 **Dubois M**, Hauser TU. Value-free random exploration is linked to impulsivity. *Nat Commun* 2022; **13**: 4542 [PMID: 35927257 DOI: 10.1038/s41467-022-31918-9]

50 **Nam SM**, Peterson TA, Seo KY, Han HW, Kang JI. Discovery of Depression-Associated Factors From a Nationwide Population-Based Survey: Epidemiological Study Using Machine Learning and Network Analysis. *J Med Internet Res* 2021; **23**: e27344 [PMID: 34184998 DOI: 10.2196/27344]

51 **Nielsen AN**, Barch DM, Petersen SE, Schlaggar BL, Greene DJ. Machine Learning With Neuroimaging: Evaluating Its Applications in Psychiatry. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2020; **5**: 791-798 [PMID: 31982357 DOI: 10.1016/j.bpsc.2019.11.007]

52 **Hu X**, Shu J, Jin Z. Depression tendency detection model for Weibo users based on Bi-LSTM. 2021 IEEE International Conference on Artificial Intelligence and Computer Applications (ICAICA) 2021 [DOI: 10.1109/icaica52286.2021.9497931]

53 **Rutledge RB**, Chekroud AM, Huys QJ. Machine learning and big data in psychiatry: toward clinical applications. *Curr Opin Neurobiol* 2019; **55**: 152-159 [PMID: 30999271 DOI: 10.1016/j.conb.2019.02.006]

54 **Graham SA**, Lee EE, Jeste DV, Van Patten R, Twamley EW, Nebeker C, Yamada Y, Kim HC, Depp CA. Artificial intelligence approaches to predicting and detecting cognitive decline in older adults: A conceptual review. *Psychiatry Res* 2020; **284**: 112732 [PMID: 31978628 DOI: 10.1016/j.psychres.2019.112732]

55 **Shen H**, Wang SH, Zhang Y, Wang H, Li F, Lucas MV, Zhang YD, Liu Y, Yuan TF. Color painting predicts clinical symptoms in chronic schizophrenia patients *via* deep learning. *BMC Psychiatry* 2021; **21**: 522 [PMID: 34686178 DOI: 10.1186/s12888-021-03452-3]

56 **Leblanc E**, Washington P, Varma M, Dunlap K, Penev Y, Kline A, Wall DP. Feature replacement methods enable reliable home video analysis for machine learning detection of autism. *Sci Rep* 2020; **10**: 21245 [PMID: 33277527 DOI: 10.1038/s41598-020-76874-w]

57 **Tariq Q**, Daniels J, Schwartz JN, Washington P, Kalantarian H, Wall DP. Mobile detection of autism through machine learning on home video: A development and prospective validation study. *PLoS Med* 2018; **15**: e1002705 [PMID: 30481180 DOI: 10.1371/journal.pmed.1002705]

58 **Corcoran CM**, Cecchi GA. Using Language Processing and Speech Analysis for the Identification of Psychosis and Other Disorders. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2020; **5**: 770-779 [PMID: 32771179 DOI: 10.1016/j.bpsc.2020.06.004]

59 **Corcoran CM**, Mittal VA, Bearden CE, E Gur R, Hitczenko K, Bilgrami Z, Savic A, Cecchi GA, Wolff P. Language as a biomarker for psychosis: A natural language processing approach. *Schizophr Res* 2020; **226**: 158-166 [PMID: 32499162 DOI: 10.1016/j.schres.2020.04.032]

60 **Carrillo F**, Sigman M, Fernández Slezak D, Ashton P, Fitzgerald L, Stroud J, Nutt DJ, Carhart-Harris RL. Natural speech

algorithm applied to baseline interview data can predict which patients will respond to psilocybin for treatment-resistant depression. *J Affect Disord* 2018; **230**: 84-86 [PMID: 29407543 DOI: 10.1016/j.jad.2018.01.006]

61 **Bedi G**, Cecchi GA, Slezak DF, Carrillo F, Sigman M, de Wit H. A window into the intoxicated mind? *Neuropsychopharmacology* 2014; **39**: 2340-2348 [PMID: 24694926 DOI: 10.1038/npp.2014.80]

62 **Sommer IE**, N de Boer J. How to reap the benefits of language for psychiatry. *Psychiatry Res* 2022; **318**: 114932 [PMID: 36332505 DOI: 10.1016/j.psychres.2022.114932]

63 **Portugal LCL**, Schrouff J, Stiffler R, Bertocci M, Bebko G, Chase H, Lockovitch J, Aslam H, Graur S, Greenberg T, Pereira M, Oliveira L, Phillips M, Mourão-Miranda J. Predicting anxiety from wholebrain activity patterns to emotional faces in young adults: a machine learning approach. *Neuroimage Clin* 2019; **23**: 101813 [PMID: 31082774 DOI: 10.1016/j.nicl.2019.101813]

64 **Liu XQ**, Guo YX, Xu Y. Risk factors and digital interventions for anxiety disorders in college students: Stakeholder perspectives. *World J Clin Cases* 2023; **11**: 1442-1457 [PMID: 36926387 DOI: 10.12998/wjcc.v11.i7.1442]

65 **Brosschot JF**, Thayer JF. Heart rate response is longer after negative emotions than after positive emotions. *Int J Psychophysiol* 2003; **50**: 181-187 [PMID: 14585487 DOI: 10.1016/s0167-8760(03)00146-6]

66 **Greenman DLB**, La MAN, Shah S, Chen Q, Berman KF, Weinberger DR, Tan HY. Parietal-Prefrontal Feedforward Connectivity in Association With Schizophrenia Genetic Risk and Delusions. *Am J Psychiatry* 2020; **177**: 1151-1158 [PMID: 32456505 DOI: 10.1176/appi.ajp.2020.19111176]

67 **Petrantonakis PC**, Hadjileontiadis LJ. A novel emotion elicitation index using frontal brain asymmetry for enhanced EEG-based emotion recognition. *IEEE Trans Inf Technol Biomed* 2011; **15**: 737-746 [PMID: 21622077 DOI: 10.1109/TITB.2011.2157933]

68 **Şen B**, Peker M, Çavuşoğlu A, Çelebi FV. A comparative study on classification of sleep stage based on EEG signals using feature selection and classification algorithms. *J Med Syst* 2014; **38**: 18 [PMID: 24609509 DOI: 10.1007/s10916-014-0018-0]

69 **Taylor JA**, Matthews N, Michie PT, Rosa MJ, Garrido MI. Auditory prediction errors as individual biomarkers of schizophrenia. *Neuroimage Clin* 2017; **15**: 264-273 [PMID: 28560151 DOI: 10.1016/j.nicl.2017.04.027]

70 **Howe Iii EG**, Elenberg F. Ethical Challenges Posed by Big Data. *Innov Clin Neurosci* 2020; **17**: 24-30 [PMID: 33898098]

71 **Medina R**, Bouhaben J, de Ramón I, Cuesta P, Antón-Toro L, Pacios J, Quintero J, Ramos-Quiroga JA, Maestú F. Electrophysiological Brain Changes Associated With Cognitive Improvement in a Pediatric Attention Deficit Hyperactivity Disorder Digital Artificial Intelligence-Driven Intervention: Randomized Controlled Trial. *J Med Internet Res* 2021; **23**: e25466 [PMID: 34842533 DOI: 10.2196/25466]

72 **Adams RA**, Pinotsis D, Tsirlis K, Unruh L, Mahajan A, Horas AM, Convertino L, Summerfelt A, Sampath H, Du XM, Kochunov P, Ji JL, Repovs G, Murray JD, Friston KJ, Hong LE, Anticevic A. Computational Modeling of Electroencephalography and Functional Magnetic Resonance Imaging Paradigms Indicates a Consistent Loss of Pyramidal Cell Synaptic Gain in Schizophrenia. *Biol Psychiatry* 2022; **91**: 202-215 [PMID: 34598786 DOI: 10.1016/j.biopsych.2021.07.024]

73 **Čukić M**, López V, Pavón J. Classification of Depression Through Resting-State Electroencephalogram as a Novel Practice in Psychiatry: Review. *J Med Internet Res* 2020; **22**: e19548 [PMID: 33141088 DOI: 10.2196/19548]

74 **Parkes L**, Satterthwaite TD, Bassett DS. Towards precise resting-state fMRI biomarkers in psychiatry: synthesizing developments in transdiagnostic research, dimensional models of psychopathology, and normative neurodevelopment. *Curr Opin Neurobiol* 2020; **65**: 120-128 [PMID: 33242721 DOI: 10.1016/j.conb.2020.10.016]

75 **Tolmeijer E**, Kumari V, Peters E, Williams SCR, Mason L. Using fMRI and machine learning to predict symptom improvement following cognitive behavioural therapy for psychosis. *Neuroimage Clin* 2018; **20**: 1053-1061 [PMID: 30343250 DOI: 10.1016/j.nicl.2018.10.011]

76 **Winterburn JL**, Voineskos AN, Devenyi GA, Plitman E, de la Fuente-Sandoval C, Bhagwat N, Graff-Guerrero A, Knight J, Chakravarty MM. Can we accurately classify schizophrenia patients from healthy controls using magnetic resonance imaging and machine learning? *Schizophr Res* 2019; **214**: 3-10 [PMID: 29274736 DOI: 10.1016/j.schres.2017.11.038]

77 **Rosa MJ**, Portugal L, Hahn T, Fallgatter AJ, Garrido MI, Shawe-Taylor J, Mourao-Miranda J. Sparse network-based models for patient classification using fMRI. *Neuroimage* 2015; **105**: 493-506 [PMID: 25463459 DOI: 10.1016/j.neuroimage.2014.11.021]

78 **Silva N**, Zhang D, Kulvicius T, Gail A, Barreiros C, Lindstaedt S, Kraft M, Bölte S, Poustka L, Nielsen-Saines K, Wörgötter F, Einspieler C, Marschik PB. The future of General Movement Assessment: The role of computer vision and machine learning - A scoping review. *Res Dev Disabil* 2021; **110**: 103854 [PMID: 33571849 DOI: 10.1016/j.ridd.2021.103854]

79 **Li W**, Wang Q, Liu X, Yu Y. Simple action for depression detection: using kinect-recorded human kinematic skeletal data. *BMC Psychiatry* 2021; **21**: 205 [PMID: 33888072 DOI: 10.1186/s12888-021-03184-4]

80 **Loth E**, Ahmad J, Chatham C, López B, Carter B, Crawley D, Oakley B, Hayward H, Cooke J, San José Cáceres A, Bzdok D, Jones E, Charman T, Beckmann C, Bourgeron T, Toro R, Buitelaar J, Murphy D, Dumas G. The meaning of significant mean group differences for biomarker discovery. *PLoS Comput Biol* 2021; **17**: e1009477 [PMID: 34793435 DOI: 10.1371/journal.pcbi.1009477]

81 **Wagh VV**, Vyas P, Agrawal S, Pachpor TA, Paralikar V, Khare SP. Peripheral Blood-Based Gene Expression Studies in Schizophrenia: A Systematic Review. *Front Genet* 2021; **12**: 736483 [PMID: 34721526 DOI: 10.3389/fgene.2021.736483]

82 **Reay WR**, Geaghan MP, Atkins JR, Carr VJ, Green MJ, Cairns MJ. Genetics-informed precision treatment formulation in schizophrenia and bipolar disorder. *Am J Hum Genet* 2022; **109**: 1620-1637 [PMID: 36055211 DOI: 10.1016/j.ajhg.2022.07.011]

83 **IU School of Medicine**. Researchers Develop Blood Test For Depression, Bipolar Disorder. EurekAlert 2021. Available from: https://www.eurekalert.org/pub_releases/2021-04/iuso-iso040721.php

84 **Fernandes BS**, Karmakar C, Tamouza R, Tran T, Yearwood J, Hamdani N, Laouamri H, Richard JR, Yolken R, Berk M, Venkatesh S, Leboyer M. Precision psychiatry with immunological and cognitive biomarkers: a multi-domain prediction

for the diagnosis of bipolar disorder or schizophrenia using machine learning. *Transl Psychiatry* 2020; **10**: 162 [PMID: 32448868 DOI: 10.1038/s41398-020-0836-4]

85 **Bobo WV**, Van Ommeren B, Athreya AP. Machine learning, pharmacogenomics, and clinical psychiatry: predicting antidepressant response in patients with major depressive disorder. *Expert Rev Clin Pharmacol* 2022; **15**: 927-944 [PMID: 35968639 DOI: 10.1080/17512433.2022.2112949]

86 **Ambrosen KS**, Skjerbæk MW, Foldager J, Axelsen MC, Bak N, Arvastson L, Christensen SR, Johansen LB, Raghava JM, Oranje B, Rostrup E, Nielsen MØ, Osler M, Fagerlund B, Pantelis C, Kinon BJ, Glenthøj BY, Hansen LK, Ebdrup BH. A machine-learning framework for robust and reliable prediction of short- and long-term treatment response in initially antipsychotic-naïve schizophrenia patients based on multimodal neuropsychiatric data. *Transl Psychiatry* 2020; **10**: 276 [PMID: 32778656 DOI: 10.1038/s41398-020-00962-8]

87 **Chen ZS**, Kulkarni PP, Galatzer-Levy IR, Bigio B, Nasca C, Zhang Y. Modern views of machine learning for precision psychiatry. *Patterns (N Y)* 2022; **3**: 100602 [PMID: 36419447 DOI: 10.1016/j.patter.2022.100602]

88 **Sohl K**, Kilian R, Brewer Curran A, Mahurin M, Nanclares-Nogués V, Liu-Mayo S, Salomon C, Shannon J, Taraman S. Feasibility and Impact of Integrating an Artificial Intelligence-Based Diagnosis Aid for Autism Into the Extension for Community Health Outcomes Autism Primary Care Model: Protocol for a Prospective Observational Study. *JMIR Res Protoc* 2022; **11**: e37576 [PMID: 35852831 DOI: 10.2196/37576]

89 **Mihalik A**, Ferreira FS, Moutoussis M, Ziegler G, Adams RA, Rosa MJ, Prabhu G, de Oliveira L, Pereira M, Bullmore ET, Fonagy P, Goodyer IM, Jones PB; NeuroScience in Psychiatry Network (NSPN) Consortium, Shawe-Taylor J, Dolan R, Mourão-Miranda J. Multiple Holdouts With Stability: Improving the Generalizability of Machine Learning Analyses of Brain-Behavior Relationships. *Biol Psychiatry* 2020; **87**: 368-376 [PMID: 32040421 DOI: 10.1016/j.biopsych.2019.12.001]

90 **Rüppel J**. ["Allowing the Data to 'Speak for Themselves'" - The Classification of Mental Disorders and the Imaginary of Computational Psychiatry]. *Psychiatr Prax* 2021; **48**: S16-S20 [PMID: 33652482 DOI: 10.1055/a-1364-5551]

91 **Chandler C**, Foltz PW, Elvevåg B. Using Machine Learning in Psychiatry: The Need to Establish a Framework That Nurtures Trustworthiness. *Schizophr Bull* 2020; **46**: 11-14 [PMID: 31901100 DOI: 10.1093/schbul/sbz105]

92 **Tandon N**, Tandon R. Using machine learning to explain the heterogeneity of schizophrenia. Realizing the promise and avoiding the hype. *Schizophr Res* 2019; **214**: 70-75 [PMID: 31500998 DOI: 10.1016/j.schres.2019.08.032]

93 **Cao XJ**, Liu XQ. Artificial intelligence-assisted psychosis risk screening in adolescents: Practices and challenges. *World J Psychiatry* 2022; **12**: 1287-1297 [PMID: 36389087 DOI: 10.5498/wjp.v12.i10.1287]

94 **Stringaris A**. Editorial: Are computers going to take over: implications of machine learning and computational psychiatry for trainees and practising clinicians. *J Child Psychol Psychiatry* 2019; **60**: 1251-1253 [PMID: 31724195 DOI: 10.1111/jcpp.13168]

95 **Saha K**, Torous J, Ernala SK, Rizuto C, Stafford A, De Choudhury M. A computational study of mental health awareness campaigns on social media. *Transl Behav Med* 2019; **9**: 1197-1207 [PMID: 30834942 DOI: 10.1093/tbm/ibz028]

96 **Brown C**, Story GW, Mourão-Miranda J, Baker JT. Will artificial intelligence eventually replace psychiatrists? *Br J Psychiatry* 2021; **218**: 131-134 [PMID: 31806072 DOI: 10.1192/bjp.2019.245]

97 **Gauld C**, Micoulaud-Franchi JA, Dumas G. Comment on Starke *et al*.: 'Computing schizophrenia: ethical challenges for machine learning in psychiatry': from machine learning to student learning: pedagogical challenges for psychiatry. *Psychol Med* 2021; **51**: 2509-2511 [PMID: 33087200 DOI: 10.1017/S0033291720003906]

98 **McKernan LC**, Clayton EW, Walsh CG. Protecting Life While Preserving Liberty: Ethical Recommendations for Suicide Prevention With Artificial Intelligence. *Front Psychiatry* 2018; **9**: 650 [PMID: 30559686 DOI: 10.3389/fpsyt.2018.00650]

99 **Wiese W**. [From the Ethics of AI to the Ethics of Consciousness: Ethical Aspects of Computational Psychiatry]. *Psychiatr Prax* 2021; **48**: S21-S25 [PMID: 33652483 DOI: 10.1055/a-1369-2824]

100 **Wiese W**, Friston KJ. AI ethics in computational psychiatry: From the neuroscience of consciousness to the ethics of consciousness. *Behav Brain Res* 2022; **420**: 113704 [PMID: 34871706 DOI: 10.1016/j.bbr.2021.113704]

101 **Dluhoš P**, Schwarz D, Cahn W, van Haren N, Kahn R, Španiel F, Horáček J, Kašpárek T, Schnack H. Multi-center machine learning in imaging psychiatry: A meta-model approach. *Neuroimage* 2017; **155**: 10-24 [PMID: 28428048 DOI: 10.1016/j.neuroimage.2017.03.027]

102 **Koutsouleris N**, Hauser TU, Skvortsova V, De Choudhury M. From promise to practice: towards the realisation of AI-informed mental health care. *Lancet Digit Health* 2022; **4**: e829-e840 [PMID: 36229346 DOI: 10.1016/S2589-7500(22)00153-4]

103 **Logan DE**, Breazeal C, Goodwin MS, Jeong S, O'Connell B, Smith-Freedman D, Heathers J, Weinstock P. Social Robots for Hospitalized Children. *Pediatrics* 2019; **144** [PMID: 31243158 DOI: 10.1542/peds.2018-1511]

104 **Walsh CG**, Ribeiro JD, Franklin JC. Predicting suicide attempts in adolescents with longitudinal clinical data and machine learning. *J Child Psychol Psychiatry* 2018; **59**: 1261-1270 [PMID: 29709069 DOI: 10.1111/jcpp.12916]

105 **Bzdok D**, Meyer-Lindenberg A. Machine Learning for Precision Psychiatry: Opportunities and Challenges. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018; **3**: 223-230 [PMID: 29486863 DOI: 10.1016/j.bpsc.2017.11.007]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2023 April 18; 11(4): 92-101

DOI: 10.13105/wjma.v11.i4.92

ISSN 2308-3840 (online)

MINIREVIEWS

Lipocalin-2 as a biomarker for diabetic nephropathy

Kiran Dahiya, Praveen Prashant, Rakesh Dhankhar, Kumud Dhankhar, Sushil Kumar, Sonia Vashist

Specialty type: Medicine, general and internal

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Miao MS, China; Singh Y, United States

Received: December 23, 2022
Peer-review started: December 23, 2022
First decision: February 21, 2023
Revised: March 11, 2023
Accepted: March 29, 2023
Article in press: March 29, 2023
Published online: April 18, 2023

Kiran Dahiya, Praveen Prashant, Department of Biochemistry, Pt BD Sharma Post Graduate Institute of Medical Sciences, Rohtak 124001, Haryana, India

Rakesh Dhankhar, Department of Radiation Oncology, Pt BD Sharma Post Graduate Institute of Medical Sciences, Rohtak 124001, India

Kumud Dhankhar, Phase III, JSS Medical College, Mysuru 570015, Karnataka, India

Sushil Kumar, Civil Hospital, Jhajjar 124103, Haryana, India

Sonia Vashist, Department of Dermatology, Dr Sonia's Dermatology Clinic, Rewari 123401, Haryana, India

Corresponding author: Kiran Dahiya, MBBS, MD, Doctor, Professor, Department of Biochemistry, Pt BD Sharma Post Graduate Institute of Medical Sciences, Pt BD Sharma University of Health Sciences, Rohtak 124001, Haryana, India. kirandahiya_2002@yahoo.com

Abstract

Diabetes is a major global public health issue. The prevalence of type 1 diabetes is comparatively static, as hereditary and genetic causes are involved, while type 2 diabetes (T2D) prevalence is increasing day by day. T2D is associated with chronic complications, including diabetic neuropathy (DN), nephropathy, retinopathy, and other complications like diabetic foot. DN is the main complication of both types of diabetes. DN can be diagnosed by routine laboratory tests, microalbuminuria > 300 mg/24 h, and a gradual decrease in glomerular filtration rate. As the appearance of microalbuminuria is a late manifestation, an early marker for renal damage is needed. Lipocalin-2, also known as neutrophil gelatinase-associated lipocalin (NGAL), is a small protein purified from neutrophil granules and a good marker for kidney disease. NGAL is a transporter protein responsible for many physiological processes, such as inflammation, generation of the immune response, and metabolic homeostasis. NGAL has been reported to depict the early changes in renal damage when urine microalbumin is still undetecable. Therefore, elucidating the role of NGAL in detecting DN and understanding its mechanism can help establish it as a potential early marker for DN.

Key Words: Type 1 diabetes; Type 2 diabetes; Diabetic nephropathy; Lipocalin-2; Early biomarkers for kidney disease; Acute kidney injury

Core Tip: Diabetic nephropathy (DN) is a chronic complication of diabetes. The mainstay markers for kidney injury are a gradual decrease in glomerular filtration rate and microalbuminuria. Microalbuminuria appears late in DN; thus, new biomarkers are required. Different researchers highlighted the role of lipocalin-2 (NGAL) in the early detection of nephropathy before the appearance of microalbumin in urine. In this review, we briefly describe the role of NGAL in various diseases and cancers and detail its role as an early biomarker in DN.

Citation: Dahiya K, Prashant P, Dhankhar R, Dhankhar K, Kumar S, Vashist S. Lipocalin-2 as a biomarker for diabetic nephropathy. *World J Meta-Anal* 2023; 11(4): 92-101
URL: https://www.wjgnet.com/2308-3840/full/v11/i4/92.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i4.92

INTRODUCTION

Diabetic nephropathy (DN) is a chronic complication of diabetes, and it affects more than 40% of both type 1 diabetes (T1D) and type 2 diabetes (T2D) cases and may lead to end-stage renal disease as reported worldwide. DN can be diagnosed clinically based on a gradual decrease in glomerular filtration rate (GFR) and an increase in urine albumin > 300 mg/24 h, which is shown to be associated with cardiovascular complications. An early diagnostic and prognostic marker is still needed to detect DN early for better treatment outcomes and predictive value[1,2].

The current diagnostic markers for DN, *i.e.*, microalbuminuria and serum creatinine levels, have questionable reliability even when specific indicators like creatinine clearance or ratio of creatinine and albumin in 24-hour urine samples are used. Microalbuminuria can be associated with other physiological and pathological conditions such as exercise, diet, infections, and dehydration[3]. Serum creatinine levels vary according to age, gender, hydration, muscle mass, and kidney conditions, and are often elevated later in advancing disease processes. Therefore, the reliability of these markers in early renal damage detection is questionable[4-10].

SELECTION OF A RENAL BIOMARKER

The characteristics of a biomarker shall be considered to determine its usefulness. Its measurement should be easy and accurate, and results should be reproducible. It should also indicate an early renal injury, and the response to the treatment, cost-effectiveness, and availability should be taken into account. It should be able to be applied to a large population and augment the disease's clinical diagnosis and prognosis[11].

The commonly used markers for acute kidney injury (AKI) and renal dysfunctions are plenty, which may be extrapolated to DN. The biomarkers for oxidative stress include 8-hydroxy-2'-deoxyguanine (8-OHdG) as a novel but controversial marker for DNA damage; pentosidine, 2,4-dinitrophenylhydrazine, and advanced oxidation protein products for protein injury; and F2-α prostaglandin and 4-hydroxy-2-nonenal for lipid injury. The glutathione-s-transferase, an enzyme-like protein, is a marker for the glutathione antioxidant system. Some other biomarkers of inflammation, like cytokines and a variety of chemokines, are essential biomarkers for AKI and kidney dysfunction and include interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and interferon-inducible protein-10 (IP-10). The renin-angiotensin-aldosterone system biomarkers are also used as kidney injury markers[12-14].

Biomarkers for damage to glomerular filtration membranes include urinary mRNA levels of podocin, synaptopodin, and nephrin. The levels of basement membrane injury markers like type IV collagen are substantially higher before microalbuminuria and and serum creatinine abnormality appear[15,16]. The biomarkers for endothelial cell injury, like vascular endothelial growth factor, von Willebrand factor (vWF), and intercellular adhesion molecule-1(ICAM-1), are found raised in patients with DN[17-20]. The biomarkers for mesangial expansion and fibrosis are also crucial, as DN is seen with extracellular matrix alterations and mesangial expansion, *e.g.*, transforming growth factor-β1 (TGF-β1) and pigment epithelial-derived factor[21,22]. The alteration of renal function is associated with glomerular and renal tubular dysfunction[23]. Transferrin, ceruloplasmin, and immunoglobulin G are early biomarkers for glomerular dysfunction. The renal tubular dysfunction markers include α-1 microglobulin, retinol-binding protein 4, lipocalin-2, N-acetyl-β-D-glucosidase, kidney injury molecule-1, and heart-type fatty acid binding protein[24-27].

Lipocalin-2

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, is a small protein purified from neutrophil granules and is considered a good marker for AKI and kidney disease. It belongs to the lipocalin family and is encoded by the lipocalin-2 (LCN2) gene on chromosome 9[28-30]. NGAL is a transporter protein responsible for many physiological processes, such as inflammation, the generation of an immune response, and metabolic homeostasis. Several studies have reported the role of lipocalin-2 in renal diseases, suggesting its role as a novel biomarker for acute renal injury and chronic kidney disorders. A few studies have also demonstrated its inverse relation with serum creatinine in T1D and T2D, although albuminuria was undetectable in these patients. In patients with DN, NGAL levels were significantly higher in serum and urine, which correlated with the estimated glomerular filtration rate (eGFR) inversely (Figure 1). However, these patients did not have albuminuria, implicating the potential role of NGAL as a diagnostic biomarker for DN[29-33].

EXPRESSION OF NGAL IN BODY TISSUES

NGAL is expressed in several body tissues, including the kidney, liver, lungs, trachea, small intestine, bone marrow, prostate, non-neoplastic breast tissue, macrophages, and fat tissues. Expression of NGAL is seen in fetal skin in the epidermis as early as the 20th week of intrauterine life and later concentrated around hair follicles only[32,34].

The normal concentration of NGAL in serum averages 20 ng/mL, while in urine also, it is 20 ng/mL. Its low molecular weight and positive charge make it undergo filtration, so renal clearance is seen as the primary regulator of the concentration of NGAL[35,36].

FUNCTIONS OF NGAL

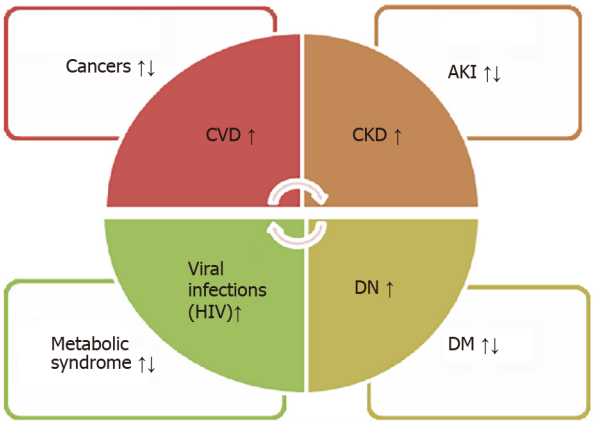
As part of transport proteins, lipocalin-2 is also seen in many physiological conditions of the body involved in the innate immune response. It is generated through neutrophil degranulation and thus, released at the site of bacterial infection for bacterial sequestration. Iron transport is another role of NGAL as it is accumulated in the cytoplasm, and iron-responsive genes are stimulated in response to this increased concentration. Apo-NGAL is responsible for transporting chelated iron from the inside to the extracellular matrix. Apo-NGAL binds to the 24p3 receptor and internalizes to bind with the cellular siderophore, thus transporting it out of the cell. It signalizes the apoptotic cascade to start due to the expression of the pro-apoptotic protein Bim. The initiation of programmed cell death, whether under normal or abnormal circumstances, depends on the Bim protein. Its activation is precisely regulated at various levels to ensure its proper functioning. Bim is essential in preventing autoimmunity during normal immune responses; however, excessive activation can lead to chronic inflammation and tumor development. In nerve cells, the overexpression of Bim can result in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. On the other hand, cancer cells typically inhibit Bim expression from facilitating their proliferation and metastasis[29,37-44].

NGAL AND RENAL DAMAGE

The low molecular weight of NGAL makes it easily filterable through the glomerulus and later reabsorbed in the proximal tubules. If renal tubular damage starts, the reabsorption changes, and thus, excretion of NGAL starts early; epithelial damage thus results in increased NGAL concentration in serum and urine[45].

OVEREXPRESSION OF NGAL IN OTHER DISEASES

Several inflammatory and metabolic disorders are seen with altered concentrations of NGAL. Inflammatory conditions like pancreatitis, meningitis, psoriasis, and myocarditis are seen with increased NGAL expression. In certain autoimmune diseases like psoriasis, NGAL mRNA levels were found raised ten times or more. NGAL levels have been reported to be considerably higher in viral infective diseases but markedly lower in human immunodeficiency virus-infected patients who were not receiving therapy than in healthy controls[46,47]. Higher levels of NGAL were found to be associated with anemia independent of eGFR and other parameters like myeloperoxidase and high-sensitivity C-reactive protein[36].



DOI: 10.13105/wjma.v11.i4.92

Figure 1 Alteration of lipocalin-2 levels in different diseases. Lipocalin-2 levels increase in all except a few cancers where its levels are found to decrease. AKI: Acute kidney injury; CKD: Chronic kidney disease; CVD: Cardiovascular disease; DM: Diabetes mellitus.

NGAL IN CANCERS

The possible role of NGAL in various cancer models has been studied and is suggested to be both beneficial and detrimental. The nuclear factor kappa B (NF-κB) signaling pathway regulates the transcription of NGAL, and the mitogen-activated protein kinase (MAPK) pathway may cooperate with NF-κB to upregulate the expression of NGAL. Moreover, epigenetic modifications might significantly initiate NGAL expression in tumor cells[28,48-56]. It may explain the increased levels of NGAL in most cancers. It remains to identify the specific molecular forms of NGAL (in serums and cells) associated with a particular cancer type (solid or liquid)[48]. Functionally, NGAL appears to exhibit all the significant events of tumorigenesis, including tumor proliferation, tumor cell survival, distant migration, local invasion, tumor angiogenesis, and resistance to anti-cancer drugs[57]. NGAL protein and mRNA levels are quantitatively measured in body fluids like blood, urine, and tissues and found overexpressed in various cancers like ovarian, endometrial, bladder, liver, breast, brain, lung, pancreatic, colorectal, and several other solid tumors[48-50,54]. The NGAL complex may help assess tumor stage in endometrial cancers before surgical treatment. The NGAL complex is found in blood tumor cells in patients with different types of leukemia[55,58-60].

METABOLIC DISORDERS AND NGAL

In metabolic diseases, including obesity, kidney disorders, and pre-eclamptic subjects, NGAL levels were significantly higher in animal models and obese human subjects[61-63]. T2D is characterized by inflammatory processes in the whole body, resulting in endothelial dysfunction. Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, as well as chemokines and adhesion molecules, have been shown to contribute to vascular complications in T2D. In T1D, an early predictive role of NGAL as a biomarker for nephropathy and incipient cardiovascular morbidity before and independent of microalbuminuria has been observed[6].

NGAL IN DN

The plasma NGAL (pNGAL) is filtered by the glomerulus and can be almost reabsorbed in the proximal tubules. The chance of detection of urinary NGAL (uNGAL) and pNGAL in animal and human subjects with renal injury has led to evaluating NGAL as an early noninvasive biomarker in human acute and chronic kidney injury in numerous research studies. Lipocalin-2 is, therefore, one of the most promising early, next-generation biomarkers for AKI. Glomerular basement thickening and mesangial expansion have been reported in several studies. The pathogenesis of DN is associated with glomerular and renal tubular interstitial injury. The primary mechanism of NGAL clearance from the blood is *via* megalin-dependent endocytosis in the proximal tubules of the kidney. Therefore, urinary excretion of NGAL is only expected when there is proximal renal tubular injury which prevents NGAL reabsorption or increased *de novo* NGAL synthesis. The NGAL protein secreted into the urine from the distal nephron segments is predominantly monomeric and differs from the dimeric NGAL originating from neutrophils. The overexpression of NGAL in the distal tubules and its rapid secretion into the urinary tract align with its role as an antimicrobial strategy. Furthermore, recent evidence suggests that NGAL

may also promote cell survival and proliferation, given the documented apoptotic cell death in distal nephron segments in various animal and human models of AKI[6,28,62]

Various proteomic and transcriptomic studies have identified NGAL as one of the most upregulated genes (LCN2 gene) and one of the most highly induced proteins in the kidney very early in the course of acute kidney disease in animal as well as human models[63,64]. NGAL is a novel marker for the diagnosis of DN. It is a marker for kidney injury or any other condition affecting the functions of the kidneys. Early diagnosis of AKI is often challenging and complicated, as suitable early markers for renal damage and kidney function are scarce. NGAL, being an early marker of AKI, overcomes such limitations and seems to demonstrate its role in the diagnosis at an early stage[65,66].

Various studies have reported increased urinary and serum levels of NGAL in AKI. NGAL as an early biomarker to diagnose DN, even earlier to incipient nephropathy, can be seen as a tubular injury marker. Both pNGAL and uNGAL can predict early tubular damage and can be used as a noninvasive tool for diagnosing, staging, and monitoring progressing DN[67]. Subclinical and early kidney injury can be seen in children with T1D with normal renal function. The pNGAL and uNGAL derangement, low-range albuminuria, and normal eGFR can indicate early kidney injury even in optimal glycaemic control. pNGAL and uNGAL in these changes result from tubular injury[68].

In non-terminal chronic kidney disease, NGAL can be used as a novel, independent renal predictor of CKD progression along with the severity of the renal disease. The urinary NGAL can be used as a marker for the early detection of DN, and its mean value has been observed to correlate with the degree of renal impairment. The parallel elevation in uNGAL with disease severity or with increasing stages of CKD supports the hypothesis of active tubular production, excluding a passive consequence of reduced renal clearance capacity. Urinary NGAL has been reported to correlate positively with urine albumin/creatinine ratio, duration of diabetes, hemoglobin A1C, and dyslipidemia. As the positive urine NGAL results were found even in normoalbuminuric patients, uNGAL can be used as an early biomarker for DN in normoalbuminuric patients, especially those with long-standing and uncontrolled diabetes[28,69-72]. Urinary NGAL levels may help monitor the status and treatment of diverse renal diseases reflecting defects in the glomerular filtration barrier, proximal tubule reabsorption, and distal nephrons[34].

It was appreciated that uNGAL is produced in response to ischemia, toxins, or inflammation in the tubular epithelial cells. For each 300 ng/mL increase in uNGAL, an increased risk for the resultant outcome of CKD (due to T1D and T2D) progression, end-stage kidney disease, or death in CKD patients is seen. Urinary NGAL of the microalbuminuric group increased way higher than the normoalbuminuric group[73-75].

The plasma levels of NGAL and IGFBP4 have been appreciated to be higher in patients with DN. Regular follow-up and monitoring before the symptomatic presentation of DN can be carried out with serial monitoring of uNGAL levels, but defining the baseline concentration of NGAL in patients is required[76-78].

The uNGAL may be a more specific marker of active renal tubular epithelial damage and tubulointerstitial inflammation, whereas pNGAL may be more indicative of the renal (and possibly extra-renal) vasculature state, including glomerular filtration ability. Increased level of NGAL as an endogenous filtration biomarker in type 2 diabetic patients is considered a predictive biomarker for early detection of DN. The uNGAL was found to be higher in patients with microalbuminuria than normoalbuminuria, especially in those with long-standing, uncontrolled diabetes and dyslipidemia[79-82]. The serum NGAL (sNGAL) showed an excellent diagnostic value comparable to uNGAL[83].

Urinary NGAL has a positive association with microalbuminuria and can be a noninvasive tool for diagnosing and monitoring the progression of DN. Urinary NGAL measurement is more sensitive than microalbumin, detecting early renal involvement in patients with diabetes mellitus. The uNGAL and creatinine ratio (uNCR) might prove promising in identifying cases with a high clinical suspicion of diabetic kidney disease and in patients with confirmatory biopsy. T2D patients with increased uNCR may have worse outcomes and higher chances of DN complications. However, pNGAL rises markedly with the reduction in GFR, resulting in many false positive inclusions of AKI in chronic patients. So along with eGFR, the uNGAL and plasma brain natriuretic peptide should be used in chronic kidney disease patients to assess AKI[69,84,85].

The increase in uNGAL and cystatin-C levels was directly proportional to microalbuminuria in diabetic patients. T2D patients with early DN had high uNGAL and cystatin-C levels. NGAL reflects tubular damage, and nitric oxide may be used as an angiogenic and oxidative stress marker. Using specific biomarkers along with NGAL can increase its diagnostic efficacy in differentiating renal causes from other clinical conditions[85-88]. uNGAL may be a more specific marker for active renal tubular epithelial damage and tubulointerstitial inflammation, whereas pNGAL may be more indicative of the renal (and possibly extra-renal) vasculature state, including glomerular filtration ability[89].

However, some studies have shown that exosomal-NGAL (NGAL-E) is a better marker than free-NGAL in T1D. NGAL was present in subjects' urinary enriched extracellular vesicle fraction (NGAL-E); however, NGAL-E did not correlate with glycated hemoglobin and albumin/creatinine ratio in the early stages[90].

NGAL was readily detected in the urine after anti-neoplastic drug administration in a dose- and duration-dependent manner. By comparison, uNGAL excretion following cisplatin administration was quantified within 96 h of drug administration so that it can be used as an early marker of kidney injury

in cancer subjects very early, showing its efficacy as an early marker in other pathologies leading to renal dysfunction[91,92].

A metanalytical study also concluded that NGAL is a potential diagnostic marker for patients with DN and that its diagnostic value for microalbuminuria and macroalbuminuria is superior to that for microalbuminuria alone[93]. Several studies collectively and strongly support using NGAL as a biomarker for predicting AKI. However, the lack of published studies that adhere to diagnostic study guidelines, heterogeneity in AKI definition, the lack of uniformly applicable cut-off values, and variability in the performance of commercially available NGAL assays are big challenges to establish its role concretely[94]. The specificity and sensitivity of NGAL were found to be moderate to excellent in various studies in various conditions, including indoor and outdoor patients, as a good predictor of AKI [10,63,95-98]. Although some limitations are reported, NGAL (sNGAL and uNGAL) can be prognostic of renal damage even in the case of subclinical or modest renal damage that can only be diagnosed by creatinine studies late in the course of the disease[99].

CONCLUSION

The studies reported in the present review describe the role of NGAL in nephropathy, particularly DN. Early detection of renal changes is vital for diagnostic and prognostic purposes. NGAL is an important renal dysfunction marker. Although its role in other conditions like infections, metabolic disorders, and cancers is already established, its function in nephropathy is also promising, as it increases significantly before other usual markers appear in the urine and blood.

FOOTNOTES

Author contributions: Dahiya K contributed to concept designing, content writing, and manuscript formatting; Prashant P explored the resources, prepared the manuscript, formatted and compiled the content, and coordinated the report; Dhankhar R contributed to manuscript preparation and manuscript proofreading and formatting; Dhankhar K contributed to manuscript writing, designing, and proofreading; Kumar S contributed to manuscript preparation and content compilation; Vashist S contributed to manuscript writing, content compilation, and proofreading.

Conflict-of-interest statement: All the authors report have no conflicts of interest to disclose for this article.

Country/Territory of origin: India

ORCID number: Kiran Dahiya 0000-0002-7734-5387; Praveen Prashant 0000 -0002-2202-5503; Rakesh Dhankhar 0000-0002-5835-9812; Sonia Vashist 0000-0002-1465-334X.

S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Yu HG

REFERENCES

1 **De Fronzo RA**. Diabetic Nephropathy: Etiologic and Therapeutic Considerations. *Diabetes Rev* 1995; **3**: 510-564
2 **Haneda M**, Utsunomiya K, Koya D, Babazono T, Moriya T, Makino H, Kimura K, Suzuki Y, Wada T, Ogawa S, Inaba M, Kanno Y, Shigematsu T, Masakane I, Tsuchiya K, Honda K, Ichikawa K, Shide K; Joint Committee on Diabetic Nephropathy. A new Classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. *J Diabetes Investig* 2015; **6**: 242-246 [PMID: 25802733 DOI: 10.1111/jdi.12319]
3 **Tapp RJ**, Shaw JE, Zimmet PZ, Balkau B, Chadban SJ, Tonkin AM, Welborn TA, Atkins RC. Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Am J Kidney Dis* 2004; **44**: 792-798 [PMID: 15492944 DOI: 10.1016/S0272-6386(04)01079-0]
4 **Satirapoj B**. Tubulointerstitial Biomarkers for Diabetic Nephropathy. *J Diabetes Res* 2018; **2018**: 2852398 [PMID: 29577044 DOI: 10.1155/2018/2852398]
5 **Tuttle KR**, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ, Patel UD, Ratner RE, Whaley-Connell AT, Molitch ME. Diabetic kidney disease: a report

from an ADA Consensus Conference. *Diabetes Care* 2014; **37**: 2864-2883 [PMID: 25249672 DOI: 10.2337/dc14-1296]

6 **Papadopoulou-Marketou N**, Chrousos GP, Kanaka-Gantenbein C. Diabetic nephropathy in type 1 diabetes: a review of early natural history, pathogenesis, and diagnosis. *Diabetes Metab Res Rev* 2017; **33** [PMID: 27457509 DOI: 10.1002/dmrr.2841]

7 **Qiu X**, Liu C, Ye Y, Li H, Chen Y, Fu Y, Liu Z, Huang X, Zhang Y, Liao X, Liu H, Zhao W, Liu X. The diagnostic value of serum creatinine and cystatin c in evaluating glomerular filtration rate in patients with chronic kidney disease: a systematic literature review and meta-analysis. *Oncotarget* 2017; **8**: 72985-72999 [PMID: 29069842 DOI: 10.18632/oncotarget.20271]

8 **Alaini A**, Malhotra D, Rondon-Berrios H, Argyropoulos CP, Khitan ZJ, Raj DSC, Rohrscheib M, Shapiro JI, Tzamaloukas AH. Establishing the presence or absence of chronic kidney disease: Uses and limitations of formulas estimating the glomerular filtration rate. *World J Methodol* 2017; **7**: 73-92 [PMID: 29026688 DOI: 10.5662/wjm.v7.i3.73]

9 **Delanaye P**, Cavalier E, Pottel H. Serum Creatinine: Not So Simple! *Nephron* 2017; **136**: 302-308 [PMID: 28441651 DOI: 10.1159/000469669]

10 **Devarajan P**. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. *Scand J Clin Lab Invest Suppl* 2008; **241**: 89-94 [PMID: 18569973 DOI: 10.1080/00365510802150158]

11 **Tesch GH**. Review: Serum and urine biomarkers of kidney disease: A pathophysiological perspective. *Nephrology (Carlton)* 2010; **15**: 609-616 [PMID: 20883281 DOI: 10.1111/j.1440-1797.2010.01361.x]

12 **Brownlee M**. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**: 813-820 [PMID: 11742414 DOI: 10.1038/414813a]

13 **Cooper ME**. Pathogenesis, prevention, and treatment of diabetic nephropathy. *Lancet* 1998; **352**: 213-219 [PMID: 9683226 DOI: 10.1016/S0140-6736(98)01346-4]

14 **Forbes JM**, Coughlan MT, Cooper ME. Oxidative stress as a major culprit in kidney disease in diabetes. *Diabetes* 2008; **57**: 1446-1454 [PMID: 18511445 DOI: 10.2337/db08-0057]

15 **Reddy GR**, Kotlyarevska K, Ransom RF, Menon RK. The podocyte and diabetes mellitus: is the podocyte the key to the origins of diabetic nephropathy? *CurrOpinNephrolHypertens* 2008; **17**: 32-36 [PMID: 18090667 DOI: 10.1097/MNH.0b013e3282f2904d]

16 **Wang G**, Lai FM, Lai KB, Chow KM, Li KT, Szeto CC. Messenger RNA expression of podocyte-associated molecules in the urinary sediment of patients with diabetic nephropathy. *Nephron ClinPract* 2007; **106**: c169-c179 [PMID: 17596726 DOI: 10.1159/000104428]

17 **Jensen T**. Increased plasma concentration of von Willebrand factor in insulin dependent diabetics with incipient nephropathy. *BMJ* 1989; **298**: 27-28 [PMID: 2492846 DOI: 10.1136/bmj.298.6665.27-a]

18 **Yu Y**, Suo L, Yu H, Wang C, Tang H. Insulin resistance and endothelial dysfunction in type 2 diabetes patients with or without microalbuminuria. *Diabetes Res ClinPract* 2004; **65**: 95-104 [PMID: 15223221 DOI: 10.1016/j.diabres.2004.01.006]

19 **Hirano T**, Ookubo K, Kashiwazaki K, Tajima H, Yoshino G, Adachi M. Vascular endothelial markers, von Willebrand factor and thrombomodulin index, are specifically elevated in type 2 diabetic patients with nephropathy: comparison of primary renal disease. *ClinChimActa* 2000; **299**: 65-75 [PMID: 10900293 DOI: 10.1016/s0009-8981(00)00274-6]

20 **Fang YH**, Zhang JP, Zhou SX, Zheng JF, Yu YW, Yan SG, Fan WK, Cheng YS. [Relationship between serum vWF and PAF in type 2 diabetic patients and diabetic nephropathy]. *Di Yi Jun Yi Da XueXueBao* 2005; **25**: 729-731 [PMID: 15958323]

21 **Tamaki K**, Okuda S. Role of TGF-beta in the progression of renal fibrosis. *ContribNephrol* 2003; **139**: 44-65 [PMID: 12854318 DOI: 10.1159/000071736]

22 **Xie F**. Significance of serum and urinary TGF-β1 to the early diagnosis of diabetic nephropathy. *Strait Pharmaceutical J* 2009; **21**: 145-146

23 **Narita T**, Sasaki H, Hosoba M, Miura T, Yoshioka N, Morii T, Shimotomai T, Koshimura J, Fujita H, Kakei M, Ito S. Parallel increase in urinary excretion rates of immunoglobulin G, ceruloplasmin, transferrin, and orosomucoid in normoalbuminuric type 2 diabetic patients. *Diabetes Care* 2004; **27**: 1176-1181 [PMID: 15111541 DOI: 10.2337/diacare.27.5.1176]

24 **Hong CY**, Hughes K, Chia KS, Ng V, Ling SL. Urinary alpha1-microglobulin as a marker of nephropathy in type 2 diabetic Asian subjects in Singapore. *Diabetes Care* 2003; **26**: 338-342 [PMID: 12547859 DOI: 10.2337/diacare.26.2.338]

25 **Salem MA**, el-Habashy SA, Saeid OM, el-Tawil MM, Tawfik PH. Urinary excretion of n-acetyl-beta-D-glucosaminidase and retinol binding protein as alternative indicators of nephropathy in patients with type 1 diabetes mellitus. *Pediatr Diabetes* 2002; **3**: 37-41 [PMID: 15016173 DOI: 10.1034/j.1399-5448.2002.30107.x]

26 **Bagshaw SM**, Bellomo R. Early diagnosis of acute kidney injury. *CurrOpinCrit Care* 2007; **13**: 638-644 [PMID: 17975383 DOI: 10.1097/MCC.0b013e3282f07570]

27 **Han WK**, Wagener G, Zhu Y, Wang S, Lee HT. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery. *Clin J Am SocNephrol* 2009; **4**: 873-882 [PMID: 19406962 DOI: 10.2215/CJN.04810908]

28 **Bolignano D**, Donato V, Coppolino G, Campo S, Buemi A, Lacquaniti A, Buemi M. Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage. *Am J Kidney Dis* 2008; **52**: 595-605 [PMID: 18725016 DOI: 10.1053/j.ajkd.2008.01.020]

29 **Kjeldsen L**, Johnsen AH, Sengeløv H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. *J BiolChem* 1993; **268**: 10425-10432 [PMID: 7683678 DOI: 10.1016/S0021-9258(18)82217-7]

30 **Gharishvandi F**, Kazerouni F, Ghanei E, Rahimipour A, Nasiri M. Comparative assessment of neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C as early biomarkers for early detection of renal failure in patients with hypertension. *Iran Biomed J* 2015; **19**: 76-81 [PMID: 25864811 DOI: 10.6091/ibj.1380.2015]

31 **Chan P**, Simon-Chazottes D, Mattei MG, Guenet JL, Salier JP. Comparative mapping of lipocalin genes in human and mouse: the four genes for complement C8 gamma chain, prostaglandin-D-synthase, oncogene-24p3, and progestagen-associated endometrial protein map to HSA9 and MMU2. *Genomics* 1994; **23**: 145-150 [PMID: 7829063 DOI:

10.1006/geno.1994.1470]
32 **Cowland JB**, Borregaard N. Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. *Genomics* 1997; **45**: 17-23 [PMID: 9339356 DOI: 10.1006/geno.1997.4896]
33 **Flower DR**. The lipocalin protein family: structure and function. *Biochem J* 1996; **318** (Pt 1): 1-14 [PMID: 8761444 DOI: 10.1042/bj3180001]
34 **Kuwabara T**, Mori K, Mukoyama M, Kasahara M, Yokoi H, Saito Y, Yoshioka T, Ogawa Y, Imamaki H, Kusakabe T, Ebihara K, Omata M, Satoh N, Sugawara A, Barasch J, Nakao K. Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. *Kidney Int* 2009; **75**: 285-294 [PMID: 19148153 DOI: 10.1038/ki.2008.499]
35 **Paragas N**, Qiu A, Hollmen M, Nickolas TL, Devarajan P, Barasch J. NGAL-Siderocalin in kidney disease. *BiochimBiophysActa* 2012; **1823**: 1451-1458 [PMID: 22728330 DOI: 10.1016/j.bbamcr.2012.06.014]
36 **Shrestha K**, Borowski AG, Troughton RW, Klein AL, Tang WH. Association between systemic neutrophil gelatinase-associated lipocalin and anemia, relative hypochromia, and inflammation in chronic systolic heart failure. *Congest Heart Fail* 2012; **18**: 239-244 [PMID: 22994438 DOI: 10.1111/j.1751-7133.2012.00287.x]
37 **Akerstrom B**, Flower DR, Salier JP. Lipocalins: unity in diversity. *BiochimBiophysActa* 2000; **1482**: 1-8 [PMID: 11058742 DOI: 10.1016/s0167-4838(00)00137-0]
38 **Yan L**, Borregaard N, Kjeldsen L, Moses MA. The high molecular weight urinary matrix metalloproteinase (MMP) activity is a complex of gelatinase B/MMP-9 and neutrophil gelatinase-associated lipocalin (NGAL). Modulation of MMP-9 activity by NGAL. *J BiolChem* 2001; **276**: 37258-37265 [PMID: 11486009 DOI: 10.1074/jbc.M106089200]
39 **Goetz DH**, Holmes MA, Borregaard N, Bluhm ME, Raymond KN, Strong RK. The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Mol Cell* 2002; **10**: 1033-1043 [PMID: 12453412 DOI: 10.1016/s1097-2765(02)00708-6]
40 **Miethke M**, Skerra A. Neutrophil gelatinase-associated lipocalin expresses antimicrobial activity by interfering with L-norepinephrine-mediated bacterial iron acquisition. *Antimicrob Agents Chemother* 2010; **54**: 1580-1589 [PMID: 20086155 DOI: 10.1128/AAC.01158-09]
41 **Devireddy LR**, Gazin C, Zhu X, Green MR. A cell-surface receptor for lipocalin 24p3 selectively mediates apoptosis and iron uptake. *Cell* 2005; **123**: 1293-1305 [PMID: 16377569 DOI: 10.1016/j.cell.2005.10.027]
42 **Liu Z**, Petersen R, Devireddy L. Impaired neutrophil function in 24p3 null mice contributes to enhanced susceptibility to bacterial infections. *J Immunol* 2013; **190**: 4692-4706 [PMID: 23543755 DOI: 10.4049/jimmunol.1202411]
43 **Schroll A**, Eller K, Feistritzer C, Nairz M, Sonnweber T, Moser PA, Rosenkranz AR, Theurl I, Weiss G. Lipocalin-2 ameliorates granulocyte functionality. *Eur J Immunol* 2012; **42**: 3346-3357 [PMID: 22965758 DOI: 10.1002/eji.201142351]
44 **La Manna G**, Ghinatti G, Tazzari PL, Alviano F, Ricci F, Capelli I, Cuna V, Todeschini P, Brunocilla E, Pagliaro P, Bonsi L, Stefoni S. Neutrophil gelatinase-associated lipocalin increases HLA-G(+)/FoxP3(+) T-regulatory cell population in an in vitro model of PBMC. *PLoS One* 2014; **9**: e89497 [PMID: 24586826 DOI: 10.1371/journal.pone.0089497]
45 **Schmidt-Ott KM**, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, Barasch J. Dual action of neutrophil gelatinase-associated lipocalin. *J Am SocNephrol* 2007; **18**: 407-413 [PMID: 17229907 DOI: 10.1681/ASN.2006080882]
46 **Nomura I**, Gao B, Boguniewicz M, Darst MA, Travers JB, Leung DY. Distinct patterns of gene expression in the skin lesions of atopic dermatitis and psoriasis: a gene microarray analysis. *J Allergy ClinImmunol* 2003; **112**: 1195-1202 [PMID: 14657882 DOI: 10.1016/j.jaci.2003.08.049]
47 **Wang Y**, Lam KS, Kraegen EW, Sweeney G, Zhang J, Tso AW, Chow WS, Wat NM, Xu JY, Hoo RL, Xu A. Lipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance, and hyperglycemia in humans. *ClinChem* 2007; **53**: 34-41 [PMID: 17040956 DOI: 10.1373/clinchem.2006.075614]
48 **Chakraborty S**, Kaur S, Guha S, Batra SK. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. *BiochimBiophysActa* 2012; **1826**: 129-169 [PMID: 22513004 DOI: 10.1016/j.bbcan.2012.03.008]
49 **Lippi G**, Meschi T, Nouvenne A, Mattiuzzi C, Borghi L. Neutrophil gelatinase-associated lipocalin in cancer. *AdvClinChem* 2014; **64**: 179-219 [PMID: 24938019 DOI: 10.1016/b978-0-12-800263-6.00004-5]
50 **Yang J**, Moses MA. Lipocalin 2: a multifaceted modulator of human cancer. *Cell Cycle* 2009; **8**: 2347-2352 [PMID: 19571677 DOI: 10.4161/cc.8.15.9224]
51 **Candido S**, Maestro R, Polesel J, Catania A, Maira F, Signorelli SS, McCubrey JA, Libra M. Roles of neutrophil gelatinase-associated lipocalin (NGAL) in human cancer. *Oncotarget* 2014; **5**: 1576-1594 [PMID: 24742531 DOI: 10.18632/oncotarget.1738]
52 **Liao CJ**, Huang YH, Au HK, Wang LM, Chu ST. The cancer marker neutrophil gelatinase-associated lipocalin is highly expressed in human endometrial hyperplasia. *MolBiol Rep* 2012; **39**: 1029-1036 [PMID: 21573795 DOI: 10.1007/s11033-011-0828-9]
53 **Ricci S**, Bruzzese D, DI Carlo A. Evaluation of MMP-2, MMP-9, TIMP-1, TIMP-2, NGAL and MMP-9/NGAL complex in urine and sera from patients with bladder cancer. *Oncol Lett* 2015; **10**: 2527-2532 [PMID: 26622883 DOI: 10.3892/ol.2015.3558]
54 **Kaur S**, Chakraborty S, Baine MJ, Mallya K, Smith LM, Sasson A, Brand R, Guha S, Jain M, Wittel U, Singh SK, Batra SK. Potentials of plasma NGAL and MIC-1 as biomarker(s) in the diagnosis of lethal pancreatic cancer. *PLoS One* 2013; **8**: e55171 [PMID: 23383312 DOI: 10.1371/journal.pone.0055171]
55 **Monisha J**, Roy NK, Padmavathi G, Banik K, Bordoloi D, Khwairakpam AD, Arfuso F, Chinnathambi A, Alahmadi TA, Alharbi SA, Sethi G, Kumar AP, Kunnumakkara AB. NGAL is Downregulated in Oral Squamous Cell Carcinoma and Leads to Increased Survival, Proliferation, Migration and Chemoresistance. *Cancers (Basel)* 2018; **10** [PMID: 29996471 DOI: 10.3390/cancers10070228]
56 **Devarajan P**. Neutrophil gelatinase-associated lipocalin: new paths for an old shuttle. *Cancer Ther* 2007; **5**: 463-470 [PMID: 18449360]
57 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI:

10.1016/j.cell.2011.02.013]
58 **Bouchet S**, Bauvois B. Neutrophil Gelatinase-Associated Lipocalin (NGAL), Pro-Matrix Metalloproteinase-9 (pro-MMP-9) and Their Complex Pro-MMP-9/NGAL in Leukaemias. *Cancers (Basel)* 2014; **6**: 796-812 [PMID: 24713998 DOI: 10.3390/cancers6020796]
59 **Kamiguti AS**, Lee ES, Till KJ, Harris RJ, Glenn MA, Lin K, Chen HJ, Zuzel M, Cawley JC. The role of matrix metalloproteinase 9 in the pathogenesis of chronic lymphocytic leukaemia. *Br J Haematol* 2004; **125**: 128-140 [PMID: 15059134 DOI: 10.1111/j.1365-2141.2004.04877.x]
60 **Villalva C**, Sorel N, Bonnet ML, Guilhot J, Mayeur-Rousse C, Guilhot F, Chomel JC, Turhan AG. Neutrophil gelatinase-associated lipocalin expression in chronic myeloid leukemia. *Leuk Lymphoma* 2008; **49**: 984-988 [PMID: 18464118 DOI: 10.1080/10428190801942360]
61 **Zhao P**, Elks CM, Stephens JM. The induction of lipocalin-2 protein expression in vivo and in vitro. *J BiolChem* 2014; **289**: 5960-5969 [PMID: 24391115 DOI: 10.1074/jbc.M113.532234]
62 **Filiopoulos V**, Biblaki D, Vlassopoulos D. Neutrophil gelatinase-associated lipocalin (NGAL): a promising biomarker of contrast-induced nephropathy after computed tomography. *Ren Fail* 2014; **36**: 979-986 [PMID: 24673459 DOI: 10.3109/0886022X.2014.900429]
63 **Mishra J**, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J Am SocNephrol* 2003; **14**: 2534-2543 [PMID: 14514731 DOI: 10.1097/01.asn.0000088027.54400.c6]
64 **Yuen PS**, Jo SK, Holly MK, Hu X, Star RA. Ischemic and nephrotoxic acute renal failure are distinguished by their broad transcriptomic responses. *Physiol Genomics* 2006; **25**: 375-386 [PMID: 16507785 DOI: 10.1152/physiolgenomics.00223.2005]
65 **Gazareena SS**, Korani MAER, Tawfeek AR, Omar TA, Dwidar GIEA. Role of urinary neutrophil gelatinase-associated lipocalin in diabetic and nondiabetic patients with nephropathy. *Menoufia Med J* 2021; **34**: 135-140 [DOI: 10.4103/mmj.mmj_72_20]
66 **Ronco C**. N-GAL: diagnosing AKI as soon as possible. *Crit Care* 2007; **11**: 173 [PMID: 18001501 DOI: 10.1186/cc6162]
67 **Kaul A**, Behera MR, Rai MK, Mishra P, Bhaduaria DS, Yadav S, Agarwal V, Karoli R, Prasad N, Gupta A, Sharma RK. Neutrophil Gelatinase-associated Lipocalin: As a Predictor of Early Diabetic Nephropathy in Type 2 Diabetes Mellitus. *Indian J Nephrol* 2018; **28**: 53-60 [PMID: 29515302 DOI: 10.4103/ijn.IJN_96_17]
68 **Sołtysiak J**, Skowrońska B, Fichna P, Stankiewicz W, Lewandowska-Stachowiak M, Ostalska-Nowicka D, Zachwieja J. Neutrophil gelatinase-associated lipocalin and Cathepsin L as early predictors of kidney dysfunction in children with type 1 diabetes. *Endokrynol Pol* 2014; **65**: 479-484 [PMID: 25554617 DOI: 10.5603/EP.2014.0067]
69 **Padmini PJ**, Ashok V. Urine neutrophil gelatinase-associated lipocalin as an early biochemical marker of microalbuminuria in predicting early kidney damage in patients with type 2 diabetes mellitus. *UkrBiochem J* 2021; **93**: 6 [DOI: DOI:10.15407/ubj93.06.055]
70 **Patel ML**, Sachan R, Verma A, Kamal R, Gupta KK. Neutrophil gelatinase-associated lipocalin as a biomarker of disease progression in patients with chronic kidney disease. *Indian J Nephrol* 2016; **26**: 125-130 [PMID: 27051137 DOI: 10.4103/0971-4065.157799]
71 **Forghani MS**, Khezrian F, Khezrian S, Ghafoori S, Saed L, Rahmani K. Urinary neutrophil gelatinaseassociatedlipocalin in early detection of diabetic nephropathy; a pilot study. *J Renal InjPrev* 2020; **9**: 23 [DOI: 10.34172/jrip.2020.23]
72 **Hafez MH**, El-Mougy FA, Makar SH, Abd El Shaheed S. Detection of an earlier tubulopathy in diabetic nephropathy among children with normoalbuminuria. *Iran J Kidney Dis* 2015; **9**: 126-131 [PMID: 25851291]
73 **Quang TH**, Nguyet MP, Thao DP, Thi MH, Phuong Thi Dam L, Thi HH, Van AP, Luong TC, Tuyet MNT, Duy QD, Nhu BD, Duc TN. Evaluation of Urinary Neutrophil Gelatinase Associated Lipocalin and Kidney Injury Molecule-1 as Diagnostic Markers for Early Nephropathy in Patients with Type 2 Diabetes Mellitus. *Diabetes MetabSyndrObes* 2020; **13**: 2199-2207 [PMID: 32612375 DOI: 10.2147/DMSO.S258678]
74 **Lobato GR**, Lobato MR, Thomé FS, Veronese FV. Performance of urinary kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, and N-acetyl-β-D-glucosaminidase to predict chronic kidney disease progression and adverse outcomes. *Braz J Med Biol Res* 2017; **50**: e6106 [PMID: 28380198 DOI: 10.1590/1414-431X20176106]
75 **Nielsen SE**, Schjoedt KJ, Astrup AS, Tarnow L, Lajer M, Hansen PR, Parving HH, Rossing P. Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Kidney Injury Molecule 1 (KIM1) in patients with diabetic nephropathy: a cross-sectional study and the effects of lisinopril. *Diabet Med* 2010; **27**: 1144-1150 [PMID: 20854382 DOI: 10.1111/j.1464-5491.2010.03083.x]
76 **Veiga G**, Alves B, Perez M, Alcantara LV, Raimundo J, Zambrano L, Encina J, Pereira EC, Bacci M, Murad N, Fonseca F. NGAL and SMAD1 gene expression in the early detection of diabetic nephropathy by liquid biopsy. *J ClinPathol* 2020; **73**: 713-721 [PMID: 32184218 DOI: 10.1136/jclinpath-2020-206494]
77 **Ali H**, Abu-Farha M, Alshawaf E, Devarajan S, Bahbahani Y, Al-Khairi I, Cherian P, Alsairafi Z, Vijayan V, Al-Mulla F, Al Attar A, Abubaker J. Association of significantly elevated plasma levels of NGAL and IGFBP4 in patients with diabetic nephropathy. *BMC Nephrol* 2022; **23**: 64 [PMID: 35148702 DOI: 10.1186/s12882-022-02692-z]
78 **Smertka M**, Chudek J. Using NGAL as an early diagnostic test of acute kidney injury. *Ren Fail* 2012; **34**: 130-133 [PMID: 22011215 DOI: 10.3109/0886022X.2011.623500]
79 **Şen S**, ÖzalpKızılay D, Taneli F, Özen Ç, Ertan P, Özunan İ, Yıldız R, Ersoy B. Urinary NGAL is a Potential Biomarker for Early Renal Injury in Insulin Resistant Obese Non-diabetic Children. *J Clin Res PediatrEndocrinol* 2021; **13**: 400-407 [PMID: 34013756 DOI: 10.4274/jcrpe.galenos.2021.2021.0020]
80 **Lima C**, Fatima VM, Macedo E. Neutrophil Gelatinase-Associated Lipocalin as a Promising Biomarker in Acute Kidney Injury. In: Kumar, V, Salgado, AA, Athari, SS. editors. Inflammation in the 21st Century. London: IntechOpen; 2020 [DOI: 10.5772/intechopen.93650]
81 **Shael SK**, Rasheed MK, Saeedi SM. Role of Serum β Trace Protein and Neutrophil Gelatinase Associated Lipocalin in Early Diabetic Nephropathy in Type 2 Diabetes of Iraqi Patients. *J Res Med Dent Sci* 2020; **8** 526-533.Available from: www.jrmds.in

82 **Elbana KA**, Bakr HG, Fekry A, Elkot MS. Urinary Neutrophil Gelatinase-Associated Lipocalin as an early marker for diagnosis of diabetic nephropathy in T2DM patients and its correlation to albumin creatinine ratio. *Annals of RSCB* 2021; **25**: 13517 Available from: www.annalsofrscb.ro/index.php/journal/article/view/8158

83 **Lacquaniti A**, Donato V, Pintaudi B, Di Vieste G, Chirico V, Buemi A, Di Benedetto A, Arena A, Buemi M. "Normoalbuminuric" diabetic nephropathy: tubular damage and NGAL. *ActaDiabetol* 2013; **50**: 935-942 [PMID: 23754672 DOI: 10.1007/s00592-013-0485-7]

84 **Duan S**, Lu F, Song D, Zhang C, Zhang B, Xing C, Yuan Y. Current Challenges and Future Perspectives of Renal Tubular Dysfunction in Diabetic Kidney Disease. *Front Endocrinol (Lausanne)* 2021; **12**: 661185 [PMID: 34177803 DOI: 10.3389/fendo.2021.661185]

85 **Sueud T**, Hadi NR, Abdulameer R, Jamil DA, Al-Aubaidy HA. Assessing urinary levels of IL-18, NGAL and albumin creatinine ratio in patients with diabetic nephropathy. *Diabetes MetabSyndr* 2019; **13**: 564-568 [PMID: 30641767 DOI: 10.1016/j.dsx.2018.11.022]

86 **Toson el-SA**, Waly S, Omran MM. Neutrophil gelatinase-associated lipocalin and oxidative stress markers based –scores to improve the diagnostic accuracy of chronic kidney diseases. *JBAAR* 2021; **5**: 44-55 [DOI: 10.21608/jbaar.2019.105942]

87 **Donadio C**. Effect of glomerular filtration rate impairment on diagnostic performance of neutrophil gelatinase-associated lipocalin and B-type natriuretic peptide as markers of acute cardiac and renal failure in chronic kidney disease patients. *Crit Care* 2014; **18**: R39 [PMID: 24581340 DOI: 10.1186/cc13752]

88 **Vijay S**, Hamide A, Senthilkumar GP, Mehalingam V. Utility of urinary biomarkers as a diagnostic tool for early diabetic nephropathy in patients with type 2 diabetes mellitus. *Diabetes MetabSyndr* 2018; **12**: 649-652 [PMID: 29673928 DOI: 10.1016/j.dsx.2018.04.017]

89 **Greco M**, Chiefari E, Mirabelli M, Salatino A, Tocci V, Cianfrone P et al Plasma or Urine Neutrophil Gelatinase-Associated Lipocalin (NGAL): Which Is Better at Detecting Chronic Kidney Damage in Type 2 Diabetes? Endocrines 2022; 3:175-186 [DOI:10. Greco M,Chiefari E, Mirabelli M, Salatino A, Tocci V, Cianfrone P et al Plasma or Urine Neutrophil Gelatinase-Associated Lipocalin (NGAL): Which Is Better at Detecting Chronic Kidney Damage in Type 2 Diabetes? Endocrines 2022;3:175-186 [DOI: 10.3390/endocrines3020016]

90 **Ugarte F**, Santapau D, Gallardo V, Garfias C, Yizmeyián A, Villanueva S, Sepúlveda C, Rocco J, Pasten C, Urquidi C, Cavada G, San Martin P, Cano F, Irarrázabal CE. Urinary Extracellular Vesicles as a Source of NGAL for Diabetic Kidney Disease Evaluation in Children and Adolescents With Type 1 Diabetes Mellitus. *Front Endocrinol (Lausanne)* 2021; **12**: 654269 [PMID: 35046888 DOI: 10.3389/fendo.2021.654269]

91 **Seibert FS**, Heringhaus A, Pagonas N, Rudolf H, Rohn B, Bauer F, Timmesfeld N, Trappe HJ, Babel N, Westhoff TH. Biomarkers in the prediction of contrast media induced nephropathy - the BITCOIN study. *PLoS One* 2020; **15**: e0234921 [PMID: 32673348 DOI: 10.1371/journal.pone.0234921]

92 **Mishra J**, Mori K, Ma Q, Kelly C, Barasch J, Devarajan P. Neutrophil gelatinase-associated lipocalin: a novel early urinary biomarker for cisplatin nephrotoxicity. *Am J Nephrol* 2004; **24**: 307-315 [PMID: 15148457 DOI: 10.1159/000078452]

93 **Chen B**, Li Y, Liu Y, Zang C, Wu M, Xu Z. Diagnostic value of neutrophil gelatinase-associated lipocalin in diabetic nephropathy: a meta-analysis. *Ren Fail* 2019; **41**: 489-496 [PMID: 31215304 DOI: 10.1080/0886022X.2019.1619581]

94 **Haase-Fielitz A**, Haase M, Devarajan P. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: a critical evaluation of current status. *Ann ClinBiochem* 2014; **51**: 335-351 [PMID: 24518531 DOI: 10.1177/0004563214521795]

95 **Prabhu A**, Sujatha DI, Ninan B, Vijayalakshmi MA. Neutrophil gelatinase associated lipocalin as a biomarker for acute kidney injury in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. *Ann VascSurg* 2010; **24**: 525-531 [PMID: 20363104 DOI: 10.1016/j.avsg.2010.01.001]

96 **Parikh CR**, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX; TRIBE-AKI Consortium. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. *J Am SocNephrol* 2011; **22**: 1748-1757 [PMID: 21836143 DOI: 10.1681/ASN.2010121302]

97 **Nickolas TL**, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, Buchen C, Khan F, Mori K, Giglio J, Devarajan P, Barasch J. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med* 2008; **148**: 810-819 [PMID: 18519927 DOI: 10.7326/0003-4819-148-11-200806030-00003]

98 **Shapiro NI**, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM, Moretti E, Nguyen HB, Gunnerson K, Milzman D, Gaieski DF, Goyal M, Cairns CB, Kupfer K, Lee SW, Rivers EP. The diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin in the prediction of acute kidney injury in emergency department patients with suspected sepsis. *Ann Emerg Med* 2010; **56**: 52-59.e1 [PMID: 20363526 DOI: 10.1016/j.annemergmed.2010.02.010]

99 **Sachan R**, Patel M, Gaurav A, Gangwar R, Sachan P. Correlation of serum neutrophil gelatinase associated lipocalin with disease severity in hypertensive disorders of pregnancy. *Adv Biomed Res* 2014; **3**: 223 [PMID: 25538909 DOI: 10.4103/2277-9175.145690]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2023 April 18; 11(4): 102-111

DOI: 10.13105/wjma.v11.i4.102

ISSN 2308-3840 (online)

MINIREVIEWS

Dehydroepiandrosterone sulfate supplementation in health and diseases

Parth Jethwani, Ashu Rastogi, Ravindra Shukla

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Covantsev S, Russia; Lafranceschina S, Italy

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: January 30, 2023
Revised: February 9, 2023
Accepted: April 10, 2023
Article in press: April 10, 2023
Published online: April 18, 2023

Parth Jethwani, Ravindra Shukla, Department of Endocrinology & Metabolism, All India Institute of Medical Sciences Jodhpur, Jodhpur 342001, Rajasthan, India

Ashu Rastogi, Department of Endocrinology, Postgraduate Institution of Medical education and Research Chandigarh, Chandigarh 160017, Chandigarh, India

Corresponding author: Ravindra Shukla, MD, Additional Professor, Department of Endocrinology & Metabolism, All India Institute of Medical Sciences Jodhpur, Room No. 3001, Jodhpur 342001, Rajasthan, India. ravindrashukla2@rediffmail.com

Abstract

Dehydroepiandrosterone sulfate (DHEAS) is a hormone produced by the zona reticularis of the adrenal gland and the ovaries. Initially considered as an inert compound merely serving as an intermediate in the conversion of cholesterol to androgens, interest in DHEA began to grow in the 1960s when it was found that DHEAS is the most abundant steroid hormone in human plasma and that its levels decline with age. In many countries, DHEA is considered a nutritional supplement. It has been used for a multitude of conditions which include sexual dysfunction, infertility, genitourinary syndrome of menopause, musculoskeletal disorders, cardiovascular diseases, ageing, neurological diseases, autoimmune conditions, adrenal insufficiency, and anorexia nervosa. We describe an overview of the historical evolution of DHEA, its physiology, and the disease states where it has been evaluated as a supplement.

Key Words: Dehydroepiandrosterone; Adrenal; Health supplements; Hypothyroidism; Autoimmunity; Depression; Cardiovascular disease

Core Tip: In this review we discuss the current evidence for the nutraceutical utility of dehydroepiandrosterone sulfate (DHEAS). Initially regarded as a panacea for a multitude of human diseases, studies conducted with DHEA supplementation have yielded largely inconclusive results, with the possible exception as an alternative agent in adrenal insufficiency patients with low energy and low libido (in affected females), and genitourinary syndrome of menopause (vaginal preparation). However, with its easy availability as a relatively inexpensive over-the-counter supplement in many countries, DHEA, like vitamin D, has continued to evoke curiosity in the scientific community. Hence, the subject of DHEA supplementation requires a pragmatic approach, backed by robust evidence, with careful weighing of potential benefits (or lack thereof) and possible adverse effects.

Citation: Jethwani P, Rastogi A, Shukla R. Dehydroepiandrosterone sulfate supplementation in health and diseases. *World J Meta-Anal* 2023; 11(4): 102-111
URL: https://www.wjgnet.com/2308-3840/full/v11/i4/102.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i4.102

INTRODUCTION

Dehydroepiandrosterone (DHEA) was first isolated and characterized by Adolf Butenandt in 1934, and he was subsequently awarded the Nobel Prize in 1939 for his "work on sex hormones". The sulfated form of DHEA, dehydroepiandrosterone sulfate (DHEAS), was then isolated in 1944 by Munson, Gallagher, and Koch in 1944[1]. The hormone was named dehydroepiandrostenedione by Lieberman in 1949[1].

In the 1980s, despite a lack of human studies and information on its function, efficacy, and safety, DHEA began to be marketed as a non-prescription drug in the United States (US) for multiple indications such as anti-ageing, anti-cancer, and anti-obesity. It gained limelight as a "super hormone" and an "anti-ageing" wonder drug which led to multiple studies around its use in various conditions.

Soon thereafter in 1985, the US FDA predictably banned over-the-counter sales of DHEA considering the lack of health benefits and long-term safety data. However, in 1994, DHEA was re-introduced in the market with the dietary supplement health and education act, which allowed certain substances to be marketed as dietary supplements not requiring FDA approval. Marketing as a cure-all elixir and the lack of regulation led to skyrocketing production of DHEA and it became easily available as an over-the-counter supplement. However, research around the hormone has made rapid strides ever since with implications for the diagnosis and treatment of a host of human diseases (Table 1).

SEARCH STRATEGY

The following databases were used to identify the relevant studies: PubMed/Medline, Scopus, and Cochrane. We also applied Reference Citation Analysis (RCA) to further enhance our search results. All the databases were searched from their inception till December 10, 2022. We did a search again and the search was extended up till February 7, 2023 to look for any additional articles. Keywords used were mainly related to the topics of interest, including "DHEA," "adrenal insufficiency"," menopause"," autoimmunity", "immunity", "cognition", "infertility", "sexual function", "genitourinary", "anorexia", "bone", "muscle", "musculoskeletal" "systemic lupus erythematosus" or "SLE", "schizophrenia", "depression", "cardiovascular disease", "rheumatoid arthritis", and "hypothyroidism".

There was no restriction for study design and language (where English language translation was available). All articles related to DHEA supplementation were reviewed and relevant articles were considered for inclusion in this scoping review.

NORMAL PHYSIOLOGY

About 75%-90% of DHEA is produced by the zona reticularis of the adrenal gland while the rest is produced in the ovaries and the brain. Its sulfated form, DHEAS, is exclusively synthesized by the adrenals. DHEA has a shorter half-life and is secreted in a pulsatile manner, mirroring the circadian rhythm of corticotrophin. In contrast, DHEAS has a longer half-life and relatively more stable levels across the day, providing a continuous reservoir of DHEA.

DHEA and DHEAS start increasing in boys and girls around the age of six to eight years, and this increase in adrenal androgens is known as adrenarche and the concomitant clinical appearance of pubic hair is known as pubarche. The levels rise steadily and peak in the second to third decade of life.

Table 1 Proposed therapeutic indications of dehydroepiandrosterone

Indication	Current evidence
Sexual dysfunction	Equivocal[6]
Infertility	Equivocal[13]
Genitourinary symptoms (alternative agent)	Positive[7,9]
Peri-menopausal and menopausal women	Equivocal[5]
Adrenal insufficiency (alternative agent)	Positive[17]
Anorexia nervosa	Equivocal[19]
Autoimmune diseases	Equivocal[24,27]
Musculoskeletal	Equivocal[43]
Neuropsychiatric diseases	Equivocal[48]
Anti-ageing agent	Negative[35,36]
Cardiovascular disorders	Equivocal[54,55]

Thereafter there is a progressive decline by around 2%-5% each year with advancing age, such that levels decrease by 80%-90% in the eighth to ninth decade of life[2].

The exact mechanism of action of DHEA remains uncertain with some evidence suggesting that it has pleiotropic effects. As DHEA has minor steroidogenic activity, it acts predominantly by conversion to androgens and estrogens in peripheral target tissues (Figure 1). It also functions as a neurosteroid and acts *via* receptors for N methyl-D aspartate receptors (NMDA) and gamma amino butyric acid alpha (GABAα), peroxisome proliferator-activated receptor α (PPARα), or receptors for pregnane X, androstanol, and estrogen receptor β[3].

DHEA IN DISEASE STATES

DHEA and sexual dysfunction

Serum levels of DHEA and DHEAS start declining from the third decade, leading to decreased androgen levels. In a randomized, double-blind, placebo-controlled trial by Panjari *et al*[4], 93 post-menopausal women with low libido were included and the effect of DHEA on sexual function was assessed. They observed that there was no significant improvement in sexual function with regard to the primary outcome measures which included the change in total satisfying sexual events and the Sabbatsberg Sexual Self-Rating Scale total score. There was no significant change in secondary outcome measures as well, which included measures of well-being and quality of life.

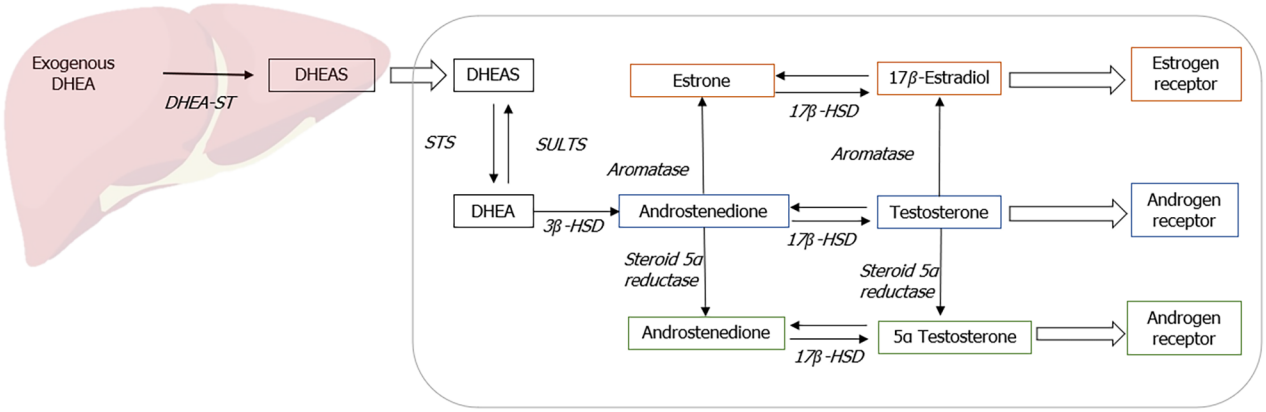
In a systematic review and meta-analysis of 28 studies of DHEA therapy in 1273 post-menopausal women, DHEA therapy did not improve sexual function, quality of life, or menopausal symptoms and was associated with androgenic side effects[5]. It is to be noted that these studies had a duration less than 3 mo. Also, oral DHEA was used in all of these, and there are no studies on local DHEA (*see below*). Currently, the endocrine society guidelines recommend against the use of DHEA for sexual dysfunction and other related indications because of a lack of long-term safety efficacy data[6].

Genitourinary syndrome of menopause

Genitourinary syndrome of menopause (GSM), a term first introduced in 2014, is a relatively common entity with a prevalence ranging from 27% to 82%. It encompasses symptoms ranging from vulvovaginal dryness and dyspareunia to urinary urgency and dysuria, and leads to significant impairment in quality of life and sexual function. In a randomized prospective double-blind placebo-controlled trial by Labrie *et al*[7], the efficacy of 0.5% intravaginal DHEA in women with GSM was assessed. They observed that vaginal DHEA (Prasterone) significantly relieved dyspareunia with improvement in vaginal secretions and epithelial integrity. Prasterone was first approved by the FDA in 2016 for the treatment of dyspareunia due to GSM[8]. Recent guidelines suggest vaginal DHEA as an alternative agent in individuals with GSM symptoms after the initial use of non-hormonal agents[9].

DHEA and infertility

DHEA has been found to improve ovarian steroidogenesis and also leads to an increase in IGF-1 which is speculated to have a favorable effect on oocyte quality and follicular development[10,11]. In a randomized prospective study by Wiser *et al*[12], they enrolled 33 women with poor ovarian reserve (17 in the DHEA group and 16 in the control group) and observed the effects of DHEA supplementation on



DOI: 10.13105/wjma.v11.i4.102

Figure 1 Metabolism of exogenously administered dehydroepiandrosterone. DHEA: Dehydroepiandrosterone; DHEAS: Dehydroepiandrosterone sulfate; DHEA-ST: Dehydroepiandrosterone-sulphotransferase; HSD: Hydroxysteroid dehydrogenase; STS: Steryl-suplhatase; SULTS: Sulphotransferases.

in vitro fertilization. Patients in the DHEA group had a significantly higher live birth rate as compared to controls. In a meta-analysis by Qin *et al*[13], they included nine studies and observed that clinical pregnancy rates were significantly increased in women with diminished ovarian reserve supplemented with DHEA. However, when the analysis was restricted to randomized control trials, there was no significant difference in pregnancy rates. In a recent meta-analysis by Schwarze *et al*[14], they included five studies with a total of 910 individuals with diminished ovarian reserve, of which 413 received DHEA. They observed that DHEA supplementation was associated with significantly improved pregnancy rates and decreased abortion frequency. There was no effect on the number of oocytes retrieved. Hence, the results have been largely conflicting and it is difficult to draw any conclusions as the definitions for diminished ovarian reserve, stimulation protocols used, and dosing and duration of DHEA varied notably between studies. Taken together, it implies that DHEA may have a role in the peri-implantation period but have less impact on ovulation induction/ooscytes retrieval. Future randomised controlled trials planned with primary endpoints of implantation success in such group of subjects, may yield a favorable role for DHEA supplementation.

DHEA in adrenal insufficiency

Adrenal insufficiency is associated with reduced androgen levels which have been suggested to have multiple effects including loss of libido, reduced energy, and consequently decreased quality of life despite optimal glucocorticoid replacement. DHEA therapy has been suggested as a potential therapy to mitigate these effects. In a randomized double-blind placebo-controlled study by Binder *et al*[15], they included 23 young women with secondary hypoadrenalism and observed significant improvements in pubic hair growth and psychological well-being. In a subsequent meta-analysis by Alkatib *et al*[16] which included 10 studies in women with either primary or secondary adrenal insufficiency, DHEA supplementation lead to minor improvements in quality of life. However, there was no effect on sexual function or anxiety. Currently, the guidelines suggest that DHEA replacement (25–50 mg as a single oral dose in the morning) may be considered in individuals with low energy and in women with reduced libido despite optimized glucocorticoid and mineralocorticoid replacement[17]. Monitoring is done by clinical and biochemical markers such as measurement of DHEAS, testosterone, androstenedione, and sex hormone-binding globulin (SHBG) 24 h after the last DHEA dose. If the patient fails to report a sustained, beneficial effect of replacement after 6 mo, the treatment should be discontinued.

DHEA in anorexia nervosa

DHEA levels have also been implicated to play a role in low bone mass in anorexia nervosa. In a randomized control trial by Gordon *et al*[18] which compared the effects of DHEA *vs* conventional hormone replacement therapy in young women with anorexia nervosa, they observed that while hip bone mineral density (BMD) increased significantly with both therapies, DHEA therapy was associated with increased bone formation markers. DHEA therapy in addition was associated with significant improvement in psychological parameters. However, in a recent systematic review and meta-analysis, DHEA treatment was not found to be associated with improvement in BMD compared with placebo after adjustment for weight gain[19]. Therefore, while DHEA does play a role in the bone pathology in anorexia nervosa, evidence with treatment remains sparse and further randomized trials are needed.

DHEAS in autoimmune diseases

DHEA has been found to modulate inflammatory responses by blunting the production of pro-inflammatory cytokines, downregulating complement activation *via* the generation of C1 inhibitor, and

enhancing T-cell and NK cell cytotoxicity[20]. In accordance, DHEAS levels have also been found to be decreased in multiple autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, autoimmune hypothyroidism, fibromyalgia, and polymyalgia rheumatica[21-23].

In a randomized double-blind placebo-controlled study by Nordmark *et al*[24], they included 41 women with SLE on steroids and assessed the efficacy of DHEA supplementation. They observed significant improvement in some domains of health-related quality of outcome measures which included an improvement in mental health. There was also an improvement in sexual well-being while there was no improvement in other domains such as physical function, general health, or vitality.

Similarly, DHEA levels have also been found to be low in Sjogren's syndrome, which has been hypothesized as a potential cause of fatigue in these individuals. In a multicenter randomized controlled trial by Virkki *et al*[25], they included 107 individuals with primary Sjogren's syndrome and assessed the efficacy of DHEA administration on several measures of fatigue. They observed that DHEA supplementation at a dose of 50 mg significantly improved measures of fatigue but a similar improvement was observed with placebo as well. Their results were similar to an earlier study by Hartkamp *et al*[26], and hence the authors suggested cognitive behavioral interventions in these individuals. In autoimmune hypothyroidism, Shukla *et al*[27] investigated the relationship between DHEAS levels and arthralgias in individuals with primary hypothyroidism. They assessed 73 individuals with subclinical hypothyroidism and observed that DHEAS levels < 43.6 mcg/dL significantly predicted early rheumatoid changes in individuals with primary hypothyroidism. They postulated the inhibition of 11-β HSD1, a possible bystander effect due to hypothalamic-pituitary-axis suppression and its immunosuppressive effects as some of the mechanisms to explain the effects. Thus, there is some evidence to suggest a potential role of DHEA in multiple immunological diseases, and clinical interventions targeting this area merit further investigation.

Cognition

Ageing is associated with declining DHEA levels and deterioration in cognition. Several studies have explored the relationship of DHEA supplementation with cognitive outcomes. DHEA is synthesized in the brain and is the most abundant neurosteroid in humans. DHEA and DHEAS have multiple actions including neuroprotection, acting *via* AMPA and NMDA receptors, neuronal differentiation and apoptosis *via* tyrosine kinase receptors, inhibition of 11-β HSD1 activity, and anti-oxidant and anti-inflammatory actions[28,29]. In a study by Wolf *et al*[30], the authors studied the effect of DHEA supplementation on cognition in healthy elderly men and women. This was a double-blind placebo-controlled study and they observed that DHEA supplementation at a dose of 50 mg had no effect on cognitive abilities in these individuals. In a double-blind placebo-controlled study by Alhaj *et al*[31], they studied the effects of DHEA administration on episodic memory in 24 healthy young men and observed that DHEA was associated with both subjective and objective improvements in memory when given at a dose of 150 mg over a period of 7 d. In a Cochrane review by Grimley Evans *et al*[32] that included five trials, they observed that DHEA supplementation was not associated with any beneficial effects on cognitive outcomes in healthy individuals over 50 years of age. Subsequently, in a double-blind placebo-controlled cross-over study by Merritt *et al*[33], 50 mg of oral DHEA supplementation did not improve short-term memory in post-menopausal women. Hence, although DHEA does seem to play a role in cognitive function, there is little evidence to support its role as therapy for the same. Therefore, large-scale clinical studies are needed to assess whether DHEA could be used as a diagnostic and therapeutic tool for clinical implications.

Anti-ageing agent

Concomitant to its potential multiple actions on well-being, sexual function, and cognition, early interest in DHEA came about with it being promoted as the "fountain of youth hormone." In the DHEAge study by Baulieu and colleagues, they observed the effects of DHEA supplementation at 50 mg daily for a year in 280 older men and women (age 60-79, 140 each). While there was some improvement in some parameters such as sexual function in women over 70 years of age, BMD at the femoral neck, and skin indices, there was no difference in libido, BMD, or sexual function in men[34]. Moreover, there was no difference in body composition or muscle strength in women. Thereafter, in a double-blind randomized placebo-controlled study by Nair *et al*[35], they investigated the effects of DHEA administration in 87 elderly men with low levels of DHEAS and bioavailable testosterone and 57 elderly women with low DHEAS levels. There was no improvement in body composition, quality of life, physical performance, or insulin supplementation with DHEA supplementation. Similarly, there have been studies that have found no effects of DHEA supplementation on sexual function or well-being parameters[36,37]. Taken together, studies have argued against the use of DHEA as a cure-all elixir and the lack of long-term safety data does not justify the use of DHEA in healthy elderly individuals.

DHEA and the musculoskeletal system

As age-related decline in androgens and estrogens is said to contribute to the loss of muscle mass and bone mineral density in older adults, DHEA has been suggested as a potential agent for minimizing these losses. Moreover, the peak and nadir of BMD mirror the rise and fall in levels of DHEA,

respectively, and this has led to multiple studies of DHEA supplementation for bone health.

In bone, DHEA has been postulated to have a dual, pro-anabolic, and anti-catabolic effect. The anabolic effect of DHEA comes from its ability to increase the activity of osteoblasts secondary to raised IGF-1 levels *via* the GH/IGF-1 pathway. The anti-catabolic action involves its ability to inhibit the overall function of osteoclasts *via* direct and indirect actions on the estrogen receptor. DHEA also results in increased osteoprotegerin levels, which contributed to reduced resorption by osteoclasts.

In a recent pooled analysis of four double-blind randomized control trials by Jankowski *et al*[38], they examined the efficacy of DHEA in 295 women and 290 men aged 55 years or elder given DHEA or placebo daily for 12 mo. They observed that men had a significant increase in DHEAS, estradiol, and IGF-1 while women in addition had a significant increase in testosterone levels as well. There was no effect of DHEA on BMD in men, while there was a small increase in lumbar spine (1.0% ± 3.4%) and trochanter (0.5% ± 3.8%) with maintained hip BMD in women. This modest increase in BMD is less than that found with other anti-osteoporotic agents including bisphosphonates, denosumab, and teriparatide. However, these trials did not primarily involve women with osteoporosis which may explain these findings.

DHEA is also said to contribute to muscle growth and strength through an anabolic effect augmenting protein synthesis. The mechanisms suggested involve the ability of the skeletal muscle to metabolize DHEA to active androgens and increased bioavailability of insulin-like growth factor-1 (IGF-1). IGF-1 is said to be involved in the proliferation of myogenic cells leading to muscle growth and repair[39,40].

Scattered studies have found some positive effects of DHEA on muscle strength, muscle mass, and mobility, as well as physical function[41,42]. However, in a systematic review by Baker *et al*[43], they included eight randomized control trials and observed that the effects of DHEA on muscle strength and physical performance were inconclusive.

DHEA supplementation in schizophrenia

DHEA has also been found to play a role in the pathophysiology of schizophrenia. It has been suggested to modulate neuronal differentiation and synaptogenesis. Additionally, it also interacts with multiple hormone receptor systems including gamma-aminobutyric acid, glutamate, and dopamine[44]. In a systematic review and meta-analysis by Misiak *et al*[45] which included 19 studies, DHEAS levels were found to be significantly elevated in individuals with schizophrenia.

DHEA supplementation in depression

DHEA being a neurosteroid has also been evaluated in depression on account of its multiple actions. Its direct actions involve its ability to regulate neuronal excitability by interactions with neurotransmitter receptors known to modulate mood. Other indirect actions involve its ability to regulate cortisol levels and its potential to increase IGF-1 levels.

In one of the initial studies by Wolkowitz *et al*[46], they included 22 individuals with major depression and observed that DHEA was associated with a significant improvement in depressive score compared to placebo. Thereafter in 2005, Schmidt *et al*[47] evaluated the efficacy of DHEA in 46 individuals (23 men and 23 women) aged 45 to 65 years with depression in a randomized double-blind placebo-controlled study. They observed that 6 wk of DHEA supplementation was associated with a significant improvement in measures of depression. In a recent meta-analysis by Peixoto *et al*[48] which included 14 studies, DHEA was associated with a beneficial effect on depressive symptoms compared to placebo. However, the quality of evidence was low due to high clinical heterogeneity in clinical studies. Hence, although DHEA has been found to have some beneficial effect on depressive symptoms, the results should be interpreted with caution and further well-designed larger clinical trials will help in assessing these findings.

DHEA and cardiovascular disease

DHEAS levels have also been found to be decreased in cardiovascular disease in a few studies, suggesting a possible therapeutic role in atherosclerosis and coronary artery disease[49,50]. The mechanisms suggested to explain these effects include inhibition of platelet aggregation, smooth muscle cell proliferation and plasminogen activator inhibitor-1 generation, increased nitric oxide generation, and vasodilation[51,52]. In the Women's Ischemia Syndrome Evaluation study, lower DHEAS levels were associated with higher cardiovascular mortality and all-cause mortality and this was independent of other major cardiovascular risk factors. However, when adjusted for the presence or severity of obstructive coronary artery disease, the risk became non-significant[49]. DHEAS levels have also been found to be associated with arrhythmias. In the Rotterdam study which involved 1180 individuals without atrial fibrillation at baseline, after a mean follow-up of 12.3 years, DHEAS levels were found to be inversely associated with the risk of atrial fibrillation[53]. However, several studies have also failed to show an association between DHEA levels and cardiovascular disease[54,55]. In a case-control study by Golden *et al*[54], they assessed the correlation between DHEAS levels and atherosclerosis in 364 postmenopausal women and observed that DHEAS levels were not associated with the risk of atherosclerosis which was assessed by carotid artery intimal medial thickness. In a recent study by Zhao *et al*

[56], they observed that while increased testosterone levels were associated with an increased risk of cardiovascular diseases, DHEAS levels were not associated with these outcomes. In fact, some studies have found DHEA supplementation to be associated with increased cardiovascular risk. DHEA supplementation has been found to be associated with a pro-atherogenic state *via* upregulation of lipoprotein processing genes leading to macrophage foam cell formation[57]. Similarly, DHEA supplementation has also been found to be associated with deranged lipid profiles[58,59]. In a double-blind randomized cross-over study by Srinivasan *et al*[58], they assessed the effect of 50 mg DHEA supplementation for 3 mo on lipid parameters, they observed significantly decreased levels of high-density lipoprotein (HDL) in women supplemented with DHEA. Hence, the association of lower DHEAS levels with increased cardiovascular risk remains uncertain. On the contrary, evidence suggests a cautionary approach in using DHEA supplementation in view of a possible association with adverse cardiovascular profile.

ADVERSE EFFECTS

The major concerns with DHEA revolve around its ability to convert to androgen and estrogen metabolites. Reported androgenic side effects involve mild acne, facial hair growth, and seborrhea[60]. DHEA has also been associated with a pro-atherogenic state with decreased HDL levels[57,58]. It has also been seen that DHEA leads to proliferation of breast cancer cells *via* stimulation of estrogen receptors[61]. Hence, there have been concerns with the use of DHEA in hormone dependent cancers including breast cancer, endometrial cancer, and prostate cancer[62,63]. Currently, there is limited evidence with a paucity of long-term safety data and caution needs to exercised.

CONCLUSION

Initially marketed as a magic bullet for a myriad of human diseases, its clinical utility remains limited with conflicting results across multiple studies. Nevertheless, it remains an important physiological precursor in the synthesis of androgens and estrogens. While there is considerable evidence to suggest the role of DHEA in adrenal insufficiency and GSM, its role in menopausal females, elderly individuals, and other conditions such as sexual dysfunction, infertility, autoimmunity, and neurological and cardiovascular diseases remains to be fully elucidated. The studies done till date are limited by variations in diagnostic thresholds, DHEA dosing and timing of treatment, relatively small sample size, and shorter duration. Further large-scale, multicentric, robust randomized control trials to assess the effects of DHEA supplementation going forward will help gain a foothold in this untapped research area.

FOOTNOTES

Author contributions: Shukla R conceptualized the topic and formulated the search strategy; Jethwani P performed the search, curated the data, and wrote the preliminary draft; Rastogi A critically reviewed the manuscript and added figures and tables; all three authors approved the manuscript.

Conflict-of-interest statement: All the authors declare no conflict of interest pertaining to the manuscript.

Country/Territory of origin: India

ORCID number: Ravindra Shukla 0000-0002-5742-4096.

S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Yu HG

REFERENCES

1 **Lieberman S**. An abbreviated account of some aspects of the biochemistry of DHEA, 1934-1995. *Ann N Y Acad Sci* 1995;

774: 1-15 [PMID: 8597450 DOI: 10.1111/j.1749-6632.1995.tb17368.x]

2 **Mazat L**, Lafont S, Berr C, Debuire B, Tessier JF, Dartigues JF, Baulieu EE. Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. *Proc Natl Acad Sci U S A* 2001; **98**: 8145-8150 [PMID: 11427700 DOI: 10.1073/pnas.121177998]

3 **Prough RA**, Clark BJ, Klinge CM. Novel mechanisms for DHEA action. *J Mol Endocrinol* 2016; **56**: R139-R155 [PMID: 26908835 DOI: 10.1530/JME-16-0013]

4 **Panjari M**, Bell RJ, Jane F, Wolfe R, Adams J, Morrow C, Davis SR. A randomized trial of oral DHEA treatment for sexual function, well-being, and menopausal symptoms in postmenopausal women with low libido. *J Sex Med* 2009; **6**: 2579-2590 [PMID: 19619146 DOI: 10.1111/j.1743-6109.2009.01381.x]

5 **Scheffers CS**, Armstrong S, Cantineau AE, Farquhar C, Jordan V. Dehydroepiandrosterone for women in the peri- or postmenopausal phase. *Cochrane Database Syst Rev* 2015; **1**: CD011066 [PMID: 25879093 DOI: 10.1002/14651858.CD011066.pub2]

6 **Wierman ME**, Arlt W, Basson R, Davis SR, Miller KK, Murad MH, Rosner W, Santoro N. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014; **99**: 3489-3510 [PMID: 25279570 DOI: 10.1210/jc.2014-2260]

7 **Labrie F**, Archer DF, Koltun W, Vachon A, Young D, Frenette L, Portman D, Montesino M, Côté I, Parent J, Lavoie L, Beauregard A, Martel C, Vaillancourt M, Balser J, Moyneur É; VVA Prasterone Research Group. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause* 2016; **23**: 243-256 [PMID: 26731686 DOI: 10.1097/GME.0000000000000571]

8 **The US Food and Drug Administration**. FDA approves Intrarosa for postmenopausal women experiencing pain during sex. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-intrarosa-postmenopausal-women-experiencing-pain-during-sex

9 **The NAMS 2020 GSM Position Statement Editorial Panel**. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause* 2020; **27**: 976-992 [PMID: 32852449 DOI: 10.1097/GME.0000000000001609]

10 **Hillier SG**, Whitelaw PF, Smyth CD. Follicular oestrogen synthesis: the 'two-cell, two-gonadotrophin' model revisited. *Mol Cell Endocrinol* 1994; **100**: 51-54 [PMID: 8056158 DOI: 10.1016/0303-7207(94)90278-x]

11 **Casson PR**, Lindsay MS, Pisarska MD, Carson SA, Buster JE. Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series. *Hum Reprod* 2000; **15**: 2129-2132 [PMID: 11006185 DOI: 10.1093/humrep/15.10.2129]

12 **Wiser A**, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. *Hum Reprod* 2010; **25**: 2496-2500 [PMID: 20729538 DOI: 10.1093/humrep/deq220]

13 **Qin JC**, Fan L, Qin AP. The effect of dehydroepiandrosterone (DHEA) supplementation on women with diminished ovarian reserve (DOR) in IVF cycle: Evidence from a meta-analysis. *J Gynecol Obstet Hum Reprod* 2017; **46**: 1-7 [PMID: 28403950 DOI: 10.1016/j.jgyn.2016.01.002]

14 **Schwarze JE**, Canales J, Crosby J, Ortega-Hrepich C, Villa S, Pommer R. DHEA use to improve likelihood of IVF/ICSI success in patients with diminished ovarian reserve: A systematic review and meta-analysis. *JBRA Assist Reprod* 2018; **22**: 369-374 [PMID: 30125071 DOI: 10.5935/1518-0557.20180046]

15 **Binder G**, Weber S, Ehrismann M, Zaiser N, Meisner C, Ranke MB, Maier L, Wudy SA, Hartmann MF, Heinrich U, Bettendorf M, Doerr HG, Pfaeffle RW, Keller E; South German Working Group for Pediatric Endocrinology. Effects of dehydroepiandrosterone therapy on pubic hair growth and psychological well-being in adolescent girls and young women with central adrenal insufficiency: a double-blind, randomized, placebo-controlled phase III trial. *J Clin Endocrinol Metab* 2009; **94**: 1182-1190 [PMID: 19126625 DOI: 10.1210/jc.2008-1982]

16 **Alkatib AA**, Cosma M, Elamin MB, Erickson D, Swiglo BA, Erwin PJ, Montori VM. A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. *J Clin Endocrinol Metab* 2009; **94**: 3676-3681 [PMID: 19773400 DOI: 10.1210/jc.2009-0672]

17 **Bornstein SR**, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016; **101**: 364-389 [PMID: 26760044 DOI: 10.1210/jc.2015-1710]

18 **Gordon CM**, Grace E, Emans SJ, Feldman HA, Goodman E, Becker KA, Rosen CJ, Gundberg CM, LeBoff MS. Effects of oral dehydroepiandrosterone on bone density in young women with anorexia nervosa: a randomized trial. *J Clin Endocrinol Metab* 2002; **87**: 4935-4941 [PMID: 12414853 DOI: 10.1210/jc.2002-020545]

19 **Lin J**, Kao TW, Cheng YC, Fan KC, Huang YC, Liu CW. Dehydroepiandrosterone status and efficacy of dehydroepiandrosterone supplementation for bone health in anorexia nervosa: A systematic review and meta-analysis. *Int J Eat Disord* 2022; **55**: 733-746 [PMID: 35460091 DOI: 10.1002/eat.23714]

20 **Prall SP**, Muehlenbein MP. DHEA Modulates Immune Function: A Review of Evidence. *Vitam Horm* 2018; **108**: 125-144 [PMID: 30029724 DOI: 10.1016/bs.vh.2018.01.023]

21 **Nilsson E**, de la Torre B, Hedman M, Goobar J, Thörner A. Blood dehydroepiandrosterone sulphate (DHEAS) levels in polymyalgia rheumatica/giant cell arteritis and primary fibromyalgia. *Clin Exp Rheumatol* 1994; **12**: 415-417 [PMID: 7955606]

22 **Durcan L**, Petri M. Immunomodulators in SLE: Clinical evidence and immunologic actions. *J Autoimmun* 2016; **74**: 73-84 [PMID: 27371107 DOI: 10.1016/j.jaut.2016.06.010]

23 **Vernerova L**, Mravcova M, Paulikova L, Vlcek M, Marko A, Meskova M, Penesova A, Rovensky J, Wendl J, Raslova K, Vohnout B, Jochmanova I, Lazurova I, Killinger Z, Steiner G, Smolen J, Imrich R. Contribution of Genetic Factors to Lower DHEAS in Patients with Rheumatoid Arthritis. *Cell Mol Neurobiol* 2018; **38**: 379-383 [PMID: 28712091 DOI: 10.1007/s10571-017-0522-0]

24 **Nordmark G**, Bengtsson C, Larsson A, Karlsson FA, Sturfelt G, Rönnblom L. Effects of dehydroepiandrosterone

supplement on health-related quality of life in glucocorticoid treated female patients with systemic lupus erythematosus. *Autoimmunity* 2005; **38**: 531-540 [PMID: 16373258 DOI: 10.1080/08916930500285550]

25 **Virkki LM**, Porola P, Forsblad-d'Elia H, Valtysdottir S, Solovieva SA, Konttinen YT. Dehydroepiandrosterone (DHEA) substitution treatment for severe fatigue in DHEA-deficient patients with primary Sjögren's syndrome. *Arthritis Care Res (Hoboken)* 2010; **62**: 118-124 [PMID: 20191499 DOI: 10.1002/acr.20022]

26 **Hartkamp A**, Geenen R, Godaert GL, Bootsma H, Kruize AA, Bijlsma JW, Derksen RH. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren syndrome: a randomised controlled trial. *Ann Rheum Dis* 2008; **67**: 91-97 [PMID: 17545193 DOI: 10.1136/ard.2007.071563]

27 **Shukla R**, Ganeshani M, Agarwal M, Jangir R, Kandel G, Sankanagoudar S, Srivastava S. Dehydroepiandrostenedione sulphate (DHEAS) levels predict high risk of rheumatoid arthritis (RA) in subclinical hypothyroidism. *PLoS One* 2021; **16**: e0246195 [PMID: 33592022 DOI: 10.1371/journal.pone.0246195]

28 **Maggio M**, De Vita F, Fisichella A, Colizzi E, Provenzano S, Lauretani F, Luci M, Ceresini G, Dall'Aglio E, Caffarra P, Valenti G, Ceda GP. DHEA and cognitive function in the elderly. *J Steroid Biochem Mol Biol* 2015; **145**: 281-292 [PMID: 24794824 DOI: 10.1016/j.jsbmb.2014.03.014]

29 **Ratner MH**, Kumaresan V, Farb DH. Neurosteroid Actions in Memory and Neurologic/Neuropsychiatric Disorders. *Front Endocrinol (Lausanne)* 2019; **10**: 169 [PMID: 31024441 DOI: 10.3389/fendo.2019.00169]

30 **Wolf OT**, Kudielka BM, Hellhammer DH, Hellhammer J, Kirschbaum C. Opposing effects of DHEA replacement in elderly subjects on declarative memory and attention after exposure to a laboratory stressor. *Psychoneuroendocrinology* 1998; **23**: 617-629 [PMID: 9802132 DOI: 10.1016/s0306-4530(98)00032-8]

31 **Alhaj HA**, Massey AE, McAllister-Williams RH. Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: a double-blind, placebo-controlled study. *Psychopharmacology (Berl)* 2006; **188**: 541-551 [PMID: 16231168 DOI: 10.1007/s00213-005-0136-y]

32 **Grimley Evans J**, Malouf R, Huppert F, van Niekerk JK. Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. *Cochrane Database Syst Rev* 2006; **2006**: CD006221 [PMID: 17054283 DOI: 10.1002/14651858.CD006221]

33 **Merritt P**, Stangl B, Hirshman E, Verbalis J. Administration of dehydroepiandrosterone (DHEA) increases serum levels of androgens and estrogens but does not enhance short-term memory in post-menopausal women. *Brain Res* 2012; **1483**: 54-62 [PMID: 22985672 DOI: 10.1016/j.brainres.2012.09.015]

34 **Baulieu EE**, Thomas G, Legrain S, Lahlou N, Roger M, Debuire B, Faucounau V, Girard L, Hervy MP, Latour F, Leaud MC, Mokrane A, Pitti-Ferrandi H, Trivalle C, de Lacharrière O, Nouveau S, Rakoto-Arison B, Souberbielle JC, Raison J, Le Bouc Y, Raynaud A, Girerd X, Forette F. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. *Proc Natl Acad Sci U S A* 2000; **97**: 4279-4284 [PMID: 10760294 DOI: 10.1073/pnas.97.8.4279]

35 **Nair KS**, Rizza RA, O'Brien P, Dhatariya K, Short KR, Nehra A, Vittone JL, Klee GG, Basu A, Basu R, Cobelli C, Toffolo G, Dalla Man C, Tindall DJ, Melton LJ 3rd, Smith GE, Khosla S, Jensen MD. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 2006; **355**: 1647-1659 [PMID: 17050889 DOI: 10.1056/NEJMoa054629]

36 **Arlt W**, Callies F, Koehler I, van Vlijmen JC, Fassnacht M, Strasburger CJ, Seibel MJ, Huebler D, Ernst M, Oettel M, Reincke M, Schulte HM, Allolio B. Dehydroepiandrosterone supplementation in healthy men with an age-related decline of dehydroepiandrosterone secretion. *J Clin Endocrinol Metab* 2001; **86**: 4686-4692 [PMID: 11600526 DOI: 10.1210/jcem.86.10.7974]

37 **Flynn MA**, Weaver-Osterholtz D, Sharpe-Timms KL, Allen S, Krause G. Dehydroepiandrosterone replacement in aging humans. *J Clin Endocrinol Metab* 1999; **84**: 1527-1533 [PMID: 10323374 DOI: 10.1210/jcem.84.5.5672]

38 **Jankowski CM**, Wolfe P, Schmiege SJ, Nair KS, Khosla S, Jensen M, von Muhlen D, Laughlin GA, Kritz-Silverstein D, Bergstrom J, Bettencourt R, Weiss EP, Villareal DT, Kohrt WM. Sex-specific effects of dehydroepiandrosterone (DHEA) on bone mineral density and body composition: A pooled analysis of four clinical trials. *Clin Endocrinol (Oxf)* 2019; **90**: 293-300 [PMID: 30421439 DOI: 10.1111/cen.13901]

39 **Morales AJ**, Nolan JJ, Nelson JC, Yen SS. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* 1994; **78**: 1360-1367 [PMID: 7515387 DOI: 10.1210/jcem.78.6.7515387]

40 **Stewart CE**, Pell JM. Point:Counterpoint: IGF is/is not the major physiological regulator of muscle mass. Point: IGF is the major physiological regulator of muscle mass. *J Appl Physiol (1985)* 2010; **108**: 1820-1; discussion 1823 [PMID: 19892924 DOI: 10.1152/japplphysiol.01246.2009]

41 **Valenti G**, Denti L, Maggio M, Ceda G, Volpato S, Bandinelli S, Ceresini G, Cappola A, Guralnik JM, Ferrucci L. Effect of DHEAS on skeletal muscle over the life span: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2004; **59**: 466-472 [PMID: 15123757 DOI: 10.1093/gerona/59.5.m466]

42 **Kenny AM**, Boxer RS, Kleppinger A, Brindisi J, Feinn R, Burleson JA. Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. *J Am Geriatr Soc* 2010; **58**: 1707-1714 [PMID: 20863330 DOI: 10.1111/j.1532-5415.2010.03019.x]

43 **Baker WL**, Karan S, Kenny AM. Effect of dehydroepiandrosterone on muscle strength and physical function in older adults: a systematic review. *J Am Geriatr Soc* 2011; **59**: 997-1002 [PMID: 21649617 DOI: 10.1111/j.1532-5415.2011.03410.x]

44 **Vuksan-Ćusa B**, Šagud M, Radoš I. The role of dehydroepiandrosterone (DHEA) in schizophrenia. *Psychiatr Danub* 2016; **28**: 30-33 [PMID: 26938818]

45 **Misiak B**, Piotrowski P, Chęć M, Samochowiec J. Cortisol and dehydroepiandrosterone sulfate in patients with schizophrenia spectrum disorders with respect to cognitive performance. *Compr Psychoneuroendocrinol* 2021; **6**: 100041 [PMID: 35757369 DOI: 10.1016/j.cpnec.2021.100041]

46 **Wolkowitz OM**, Reus VI, Keebler A, Nelson N, Friedland M, Brizendine L, Roberts E. Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry* 1999; **156**: 646-649 [PMID: 10200751 DOI: 10.1176/ajp.156.4.646]

47 **Schmidt PJ**, Daly RC, Bloch M, Smith MJ, Danaceau MA, St Clair LS, Murphy JH, Haq N, Rubinow DR. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Arch Gen Psychiatry* 2005; **62**: 154-162 [PMID: 15699292 DOI: 10.1001/archpsyc.62.2.154]

48 **Peixoto C**, José Grande A, Gomes Carrilho C, Nardi AE, Cardoso A, Barciela Veras A. Dehydroepiandrosterone for depressive symptoms: A systematic review and meta-analysis of randomized controlled trials. *J Neurosci Res* 2020; **98**: 2510-2528 [PMID: 32930419 DOI: 10.1002/jnr.24721]

49 **Shufelt C**, Bretsky P, Almeida CM, Johnson BD, Shaw LJ, Azziz R, Braunstein GD, Pepine CJ, Bittner V, Vido DA, Stanczyk FZ, Bairey Merz CN. DHEA-S levels and cardiovascular disease mortality in postmenopausal women: results from the National Institutes of Health--National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Clin Endocrinol Metab* 2010; **95**: 4985-4992 [PMID: 20739385 DOI: 10.1210/jc.2010-0143]

50 **Teixeira CJ**, Veras K, de Oliveira Carvalho CR. Dehydroepiandrosterone on metabolism and the cardiovascular system in the postmenopausal period. *J Mol Med (Berl)* 2020; **98**: 39-57 [PMID: 31713639 DOI: 10.1007/s00109-019-01842-5]

51 **Jesse RL**, Loesser K, Eich DM, Qian YZ, Hess ML, Nestler JE. Dehydroepiandrosterone inhibits human platelet aggregation in vitro and in vivo. *Ann N Y Acad Sci* 1995; **774**: 281-290 [PMID: 8597466 DOI: 10.1111/j.1749-6632.1995.tb17388.x-i1]

52 **Martina V**, Benso A, Gigliardi VR, Masha A, Origlia C, Granata R, Ghigo E. Short-term dehydroepiandrosterone treatment increases platelet cGMP production in elderly male subjects. *Clin Endocrinol (Oxf)* 2006; **64**: 260-264 [PMID: 16487434 DOI: 10.1111/j.1365-2265.2006.02454.x]

53 **Krijthe BP**, de Jong FH, Hofman A, Franco OH, Witteman JC, Stricker BH, Heeringa J. Dehydroepiandrosterone sulfate levels and risk of atrial fibrillation: the Rotterdam Study. *Eur J Prev Cardiol* 2014; **21**: 291-298 [PMID: 23152363 DOI: 10.1177/2047487312467903]

54 **Golden SH**, Maguire A, Ding J, Crouse JR, Cauley JA, Zacur H, Szklo M. Endogenous postmenopausal hormones and carotid atherosclerosis: a case-control study of the atherosclerosis risk in communities cohort. *Am J Epidemiol* 2002; **155**: 437-445 [PMID: 11867355 DOI: 10.1093/aje/155.5.437]

55 **Wu FC**, von Eckardstein A. Androgens and coronary artery disease. *Endocr Rev* 2003; **24**: 183-217 [PMID: 12700179 DOI: 10.1210/er.2001-0025]

56 **Zhao D**, Guallar E, Ouyang P, Subramanya V, Vaidya D, Ndumele CE, Lima JA, Allison MA, Shah SJ, Bertoni AG, Budoff MJ, Post WS, Michos ED. Endogenous Sex Hormones and Incident Cardiovascular Disease in Post-Menopausal Women. *J Am Coll Cardiol* 2018; **71**: 2555-2566 [PMID: 29852978 DOI: 10.1016/j.jacc.2018.01.083]

57 **Ng MK**, Nakhla S, Baoutina A, Jessup W, Handelsman DJ, Celermajer DS. Dehydroepiandrosterone, an adrenal androgen, increases human foam cell formation: a potentially pro-atherogenic effect. *J Am Coll Cardiol* 2003; **42**: 1967-1974 [PMID: 14662261 DOI: 10.1016/j.jacc.2003.07.024]

58 **Srinivasan M**, Irving BA, Dhatariya K, Klaus KA, Hartman SJ, McConnell JP, Nair KS. Effect of dehydroepiandrosterone replacement on lipoprotein profile in hypoadrenal women. *J Clin Endocrinol Metab* 2009; **94**: 761-764 [PMID: 19066301 DOI: 10.1210/jc.2008-1774]

59 **Qin Y**, O Santos H, Khani V, Tan SC, Zhi Y. Effects of dehydroepiandrosterone (DHEA) supplementation on the lipid profile: A systematic review and dose-response meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis* 2020; **30**: 1465-1475 [PMID: 32675010 DOI: 10.1016/j.numecd.2020.05.015]

60 **Wierman ME**, Kiseljak-Vassiliades K. Should Dehydroepiandrosterone Be Administered to Women? *J Clin Endocrinol Metab* 2022; **107**: 1679-1685 [PMID: 35254428 DOI: 10.1210/clinem/dgac130]

61 **Maggiolini M**, Donzé O, Jeannin E, Andò S, Picard D. Adrenal androgens stimulate the proliferation of breast cancer cells as direct activators of estrogen receptor alpha. *Cancer Res* 1999; **59**: 4864-4869 [PMID: 10519397]

62 **Stoll BA**. Dietary supplements of dehydroepiandrosterone in relation to breast cancer risk. *Eur J Clin Nutr* 1999; **53**: 771-775 [PMID: 10556982 DOI: 10.1038/sj.ejcn.1600889]

63 **Arnold JT**. DHEA metabolism in prostate: For better or worse? *Mol Cell Endocrinol* 2009; **301**: 83-88 [PMID: 19013497 DOI: 10.1016/j.mce.2008.10.019]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2023 April 18; 11(4): 112-124

DOI: 10.13105/wjma.v11.i4.112

ISSN 2308-3840 (online)

SYSTEMATIC REVIEWS

Current approach for Boerhaaves syndrome: A systematic review of case reports

Ippei Yamana, Takahisa Fujikawa, Yuichiro Kawamura, Suguru Hasegawa

Specialty type: Surgery

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Fakhradiyev I, Kazakhstan; Giordano A, Italy

Received: December 16, 2022
Peer-review started: December 16, 2022
First decision: January 31, 2023
Revised: February 7, 2024
Accepted: April 6, 2023
Article in press: April 6, 2023
Published online: April 18, 2023

Ippei Yamana, Takahisa Fujikawa, Yuichiro Kawamura, Department of Surgery, Kokura Memorial Hospital, Kitakyushu, Fukuoka 802-8555, Japan

Suguru Hasegawa, Department of Gastroenterological Surgery, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan

Corresponding author: Takahisa Fujikawa, FACS, MD, PhD, Chief Doctor, Department of Surgery, Kokura Memorial Hospital, 3-2-1 Asano, Kokurakita-ku, Kitakyushu, Fukuoka 802-8555, Japan. fujikawa-t@kokurakinen.or.jp

Abstract

BACKGROUND

There is no consensus on the appropriate therapeutic strategy for Boerhaave syndrome due to its rarity and changing therapeutic approaches. We conducted a systematic review of case reports documenting Boerhaave syndrome.

AIM

To assess the therapeutic methods and clinical outcomes and discuss the current trends in the management of Boerhaave syndrome.

METHODS

We searched PubMed, Google scholar, MEDLINE, and The Cochrane Library for studies concerning Boerhaave syndrome published between 2017 and 2022.

RESULTS

Of the included studies, 49 were case reports, including a total of 56 cases. The mean age was 55.8 ± 16 years old. Initial conservative treatment was performed in 25 cases, while operation was performed in 31 cases. The rate of conservative treatment was significantly higher than that of operation in cases of shock vital on admission (9.7% *vs* 44.0%; P = 0.005). Seventeen out of 25 conservative cases (68.0%) were initially treated endoscopic esophageal stenting; 2 of those 17 cases subsequently underwent operation due to poor infection control. Twelve cases developed postoperative leakage (38.7%), and 4 of those 12 cases underwent endoscopic esophageal stenting to stop the leakage. The length of the hospital stay was not significantly different between the conservative treatment and operation cases (operation *vs* conservation: 33.52 ± 22.69 *vs* 38.81 ± 35.28 days; P = 0.553).

CONCLUSION

In the treatment of Boerhaave syndrome, it is most important to diagnose the

issue immediately. Primary repair with reinforcement is the gold-standard procedure. The indication of endoscopic esophageal stenting or endoluminal vacuum-assisted therapy should always be considered for patients in a poor general condition and who continue to have leakage after repair.

Key Words: Boerhaave syndrome; Esophageal perforation; Self expandable metalic stent; Minimally invasive surgical procedures; Anastomotic leakage; Shock

Core Tip: Totally 49 published case reports concerning the Boerhaave syndrome were systematically reviewed. In the treatment of Boerhaave syndrome, it is most important to diagnose the issue immediately. Primary repair with reinforcement is the gold-standard procedure. The indication of endoscopic esophageal stenting or endoluminal vacuum-assisted therapy should always be considered for patients in a poor general condition and who continue to have leakage after repair.

Citation: Yamana I, Fujikawa T, Kawamura Y, Hasegawa S. Current approach for Boerhaaves syndrome: A systematic review of case reports. *World J Meta-Anal* 2023; 11(4): 112-124
URL: https://www.wjgnet.com/2308-3840/full/v11/i4/112.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i4.112

INTRODUCTION

Since Herman Boerhaave first recognized the disease in 1724, spontaneous esophageal perforation has been described as a medical emergency in the relevant literature[1]. The annual incidence of spontaneous esophageal perforation, also called Boerhaave syndrome, is 3.1 per 1000000; although rare, this condition is associated with high rates of misdiagnosis and mortality[2].

Boerhaave syndrome can be caused by vomiting and is frequently associated with alcohol intoxication[3]. A long period of time between perforation and treatment often results in mediastinitis, followed by septic shock and multiorgan failure[4-10]. Surgery and conservative management are the major treatment options for Boerhaave syndrome. However, few reports have examined whether operation or conservation is the preferred treatment method. Indeed, in the past five years, only one systematic review of Australasian literature on Boerhaave syndrome has been reported[11]. At present, there is no consensus on the optimal therapeutic strategy due to the rarity of Boerhaave syndrome and changing therapeutic approaches.

We therefore reviewed and evaluated 56 cases published in 49 case report articles in PubMed, Google scholar, MEDLINE, and The Cochrane Library in the past 5 years to assess the therapeutic methods and clinical outcomes and discuss the current trends in the management of Boerhaave syndrome.

MATERIALS AND METHODS

Study selection

A case report literature review was conducted using Pubmed, Google scholar, Cochrane Library, and MEDLINE for articles published between October 2017 and October 2022. The search was limited to articles in English. “Boerhaave syndrome” or “spontaneous esophageal perforation” were key words in the search. All titles and abstracts of publications were screened to select articles describing Boerhaave syndrome or spontaneous esophageal perforation. The searches were further broadened by extensively checking all references in the articles retrieved that met the inclusion criteria.

Inclusion and exclusion criteria

The inclusion criterion was patients who underwent operation or conservative therapy for Boerhaave syndrome. The exclusion criteria were meta-analyses, reviews, articles without outcomes reported, articles without the operation method reported, articles involving cases of treatment refusal, articles involving recurrent cases of esophageal perforation, articles involving best supportive care, articles involving pediatric cases, articles focusing on other diseases, and articles in non-English languages.

Data extraction

The study design, and data on the patients' demographics, interventions, and outcomes were extracted from the included studies. An independent researcher collected the study data using a standard Excel™ data collection sheet (Microsoft Corporation, Japan). This spreadsheet was used to calculate the descriptive statistics of all parameters that were evaluated in the present study. Continuous and categorical variables were shown as the mean and standard deviation (SD) and range.

Quality appraisal

The overall quality of the cases was classified as good to moderate. The majority of patients adequately described the chief complaint (100%), the patient's medical history (82.1%), the sex (98.2%), the length from symptom onset (98.2%), the length of the hospital stay (76.8%), imaging findings (100%), treatments (100%), and outcomes (100%).

Statistical analyses

All values were presented as the mean ± SD. Intergroup differences were evaluated by an analysis of variance, while a nonparametric analysis was conducted for data with a skewed distribution. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University)[12]. EZR for R (The R Foundation for Statistical Computing, version 2.13.0) is a modified version of the R commander (version 1.6–3) that includes statistical functions that are frequently used in biostatistics. P values of < 0.05 were considered statistically significant.

RESULTS

The results of the literature search are shown in Figure 1. Through our search, we identified 1310 studies. Of these, 990 studies were excluded by title and abstract. Of the remaining 115 potentially relevant articles, we excluded 48 concerning other diseases, 11 with insufficient data, 3 concerning recurrence cases, 2 involving best supportive care, and 2 pediatric cases. This resulted in the inclusion of 49 case report articles involving 56 cases for this study.

Patients' characteristics

Table 1 shows the details of the included studies. Of the 55 patients whose sex was mentioned, 51 were male, and 4 were female (1 case with no information). The mean age was 55.8 ± 16 years old. Thirty-six of the 55 cases (65.5%) were referred to the hospital within 24 h after symptom onset (1 case with no information). The most common method of the diagnosis was computed tomography (n = 31), followed by esophagography (n = 15), endoscopy (n = 9), and exploratory laparotomy (n = 1). A total of 42 cases (75%) were accurately diagnosed on admission. Fourteen patients (25%) showed shock vitals when they arrived at the hospital. Twelve (21.4%) were intra-mediastinum type, and 44 (78.6%) were extra-mediastinum type. The mean (range) size of the laceration in the 30 cases for which such details were described was 3.8 (1-12) cm (Table 2).

Initial treatment for Boerhaave syndrome

Conservative treatment was performed in 25 cases, while operation was performed in 31 cases. Conservative treatment included endoscopic esophageal stents in 17 cases, endoscopic clipping in 5, thoracic drainage in 21, and endoluminal vacuum-assisted (EVAC) therapy in 1. The operation approach was trans-thoracic and trans-abdominal approaches in 18 and 10 cases, respectively; a combined trans-abdominal and trans-thoracic approach was performed in 3 cases. In the trans-thoracic approach, minimally invasive surgery was performed in 5 cases (23.8%). In the trans-abdominal approach, minimally invasive surgery was performed in 8 cases (61.5%). The operation methods were primary repair only in eight cases, primary repair with omentoplasty in six cases, primary repair with fundus pouch in six cases, primary repair with intercostal muscle pouch in five cases, primary repair with pericardial fat pouch in five cases, T tube in two cases, esophagectomy in one case, and esophagostomy in one case. Twelve out of 31 cases (38.7%) developed postoperative leakage. Two of those cases underwent EVAC therapy, and four of the cases underwent endoscopic esophageal stenting. Seven out of the 56 total cases (12.5%) died following treatment for Boerhaave syndrome; notably, 4 of those 7 cases (57.1%) had already had shock vitals on arrival at the hospital (Table 3).

Endoscopic esophageal stenting

Seventeen cases underwent endoscopic esophageal stenting initially, and 14 of them (82.4%) had severe comorbidities. Ten of the 17 cases (58.8%) who underwent endoscopic esophageal stenting had had shock vitals on arrival at the hospital. One case (14.3%) was the intra-mediastinum type, while the other 16 (85.7%) were the extra-mediastinum type. Two of the 17 cases who underwent endoscopic esophageal stenting had initially undergone operation due to poor infection control.

Table 1 Descriptive comparative characteristics of all included 49 studies

Ref.	Age	Sex	Accurate diagnosis	Rupture type	Shock vital	Laceration size (cm)	Treatment	Prognosis
Jahangir *et al*[4], 2021	64	M	Yes	Intrapleural type	Yes	1	Stent, thoracic drainage	Death
Issa *et al*[23], 2019	32	M	Yes	Intrapleural type	No	2	Stent, thoracic drainage	Alive
Tan *et al*[5], 2022	84	M	No	Intrapleural type	No	Unknown	Thoracotomy, primary repair only	Death
Chang *et al*[13], 2021	67	M	Yes	Intrapleural type	No	3	Thoracopy, primary repair only, feeding jejunostomy	Alive
Chang *et al*[13], 2021	62	M	Yes	Intrapleural type	No	2	Thoracopy, primary repair only, feeding jejunostomy	Alive
Sheshala *et al* [24], 2021	39	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Alive
Matsumoto *et al* [25], 2019	60	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Alive
Ayazi *et al*[6], 2021	22	M	Yes	Intrapleural type	Yes	Unknown	Thoracotomy, esophagectomy, gastrostomy	Death
Maki *et al*[44], 2022	76	M	Yes	Intramediastinal type	No	7	Transhiatal approach, primary repair plus omentoplasty, feeding jejunostomy	Alive
Ioannidis *et al* [39], 2021	83	F	Yes	Intrapleural type	No	Unknown	Thoracic drainage	Alive
Y K *et al*[26], 2018	86	M	Yes	Intrapleural type	Yes	5	Stent, thoracic drainage, feeding jejunostomy	Alive
Czopnik *et al* [3], 2017	47	M	Yes	Intrapleural type	No	5	Transhiatal approach, primary repair, gastrostomy	Alive
Awadelkarim *et al*[27], 2021	36	M	Yes	Intrapleural type	Yes	2	Stent, thoracic drainage	Alive
Chalikonda *et al* [28], 2019	74	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Alive
Śnieżyński *et al* [29], 2021	53	M	Yes	Intrapleural type	No	3	Stent, thoracic drainage	Alive
Matsuura *et al* [21], 2022	69	M	Yes	Intramediastinal type	No	Unknown	Endoscopic clipping	Alive
Chen *et al*[19], 2021	57	M	No	Intramediastinal type	No	Unknown	Transhiatal approach, primary repair only, feeding jejunostomy	Alive
Truyens *et al* [30], 2020	66	M	Yes	Intramediastinal type	Yes	Unknown	Antibiotic administration	Alive
Truyens *et al* [30], 2020	77	M	Yes	Intramediastinal type	No	Unknown	Stent	Alive
Swol *et al*[7], 2019	70	M	Yes	Intramediastinal type	No	2	Transhiatal approach, primary repair plus fundus pauch	Death
Park *et al*[45], 2021	Unknown	Unknown	Yes	Intramediastinal type	No	5	Laparoscopic transhiatal approch, primary repair plus omentoplasty → endoscopic clipping, stent	Alive
Rahman *et al* [49], 2021	53	M	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair plus intercostal muscle pauch, gastro-jujuno tube → stent	Alive
Nachiappan *et al*[46], 2022	59	M	No	Intrapleural type	No	1,5	Endscopic clipping, stent → laparo-scopic transhiatal approach, primary repair plus omentoplasty	Alive
Pasternak *et al* [14], 2019	37	M	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair only, gastrostomy	Alive
Kita *et al*[55], 2022	46	M	Yes	Intramediastinal type	No	4	Laparoscopic transhiatal approch, primary repair plus fundus pauch	Alive

Kita *et al*[55], 2022	48	M	Yes	Intramediastinal type	No	3	Laparoscopic transhiatal approch, primary repair plus fundus pauch	Alive
Kita *et al*[55], 2022	65	M	Yes	Intramediastinal type	No	5	Laparoscopic transhiatal approch, primary repair plus fundus pauch	Alive
Saffo *et al*[8], 2021	76	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Death
Kochar *et al*[50], 2019	40	M	Yes	Intrapleural type	Yes	Unknown	Thoracotomy, primary repair plus intercostal muscle pauch, intraoperative stent, thoracic drainage	Alive
Bury *et al*[51], 2022	50	M	No	Intrapleural type	No	4	Thoracotomy, primary repair plus intercostal muscle pauch, thoracic drainage	Alive
Aref *et al*[47], 2019	32	M	Yes	Intramediastinal type	No	2	Laparoscopic transhiatal approach, primary repair plus omentoplasty	Alive
Bani Fawwaz *et al*[15], 2022	63	M	Yes	Intrapleural type	Yes	3	Stent, thoracic drainage	Alive
Bani Fawwaz *et al*[15], 2022	56	F	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair plus T tube, Belsey fundoplication, intraoperative stent, thoracic drainage, gastrostpomy	Alive
Xu *et al*[22], 2021	63	M	Yes	Intrapleural type	No	Unknown	Endoscopic clipping	Alive
Tuñon *et al*[57], 2021	24	M	Yes	Intrapleural type	No	4	Endoluminal vacuum therapy → endoscopic clipping	Alive
Lee *et al*[58], 2018	52	M	Yes	Intrapleural type	No	Unknown	Thoracoscopic approach, primary repair only → endoluminal vacuum therapy, thoracic drainage	Alive
He *et al*[54], 2018	57	M	Yes	Intramediastinal type	No	6	Endoscopic clipping	Death
Kim *et al*[59], 2019	56	M	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair only → endoluminal vacuum therapy, thoracic drainage	Alive
Shennib *et al* [52], 2021	47	M	No	Intrapleural type	Yes	5	Thoracotomy, primary repair plus pericardial pauch, gastrostomy, feeding jejunostomy	Alive
Agrawal *et al* [40], 2019	26	M	No	Intrapleural type	No	Unknown	thoracic drainage	Alive
Sato *et al*[31], 2018	52	M	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair only → stent, thoracic drainage	Alive
Sato *et al*[31], 2018	53	M	No	Intrapleural type	Yes	Unknown	Stent, thoracic drainage	Alive
Ali *et al*[16], 2020	30	F	No	Intrapleural type	No	4	Thoracotomy, primary repair only	Alive
Anand *et al*[48], 2022	64	M	Yes	Intrapleural type	No	2	Thoracotomy, primary repair plus intercostal muscle pauch, thoracic drainage	Alive
Barakat *et al* [32], 2017	62	M	Yes	Intrapleural type	No	1	Stent, endoscopic clipping	Alive
Alakkari *et al* [17], 2019	69	F	Yes	Intrapleural type	No	Unknown	Thoracotomy, primary repair plus T tube	Alive
Zhu *et al*[18], 2021	33	M	No	Intrapleural type	No	Unknown	Stent, PEG →thoracotomy, drainage	Alive
Sekiya *et al*[56], 2019	61	M	Yes	Intrapleural type	No	3	Thoracoscopic and laparoscopic approach, primary repair plus pericardial pauch, gastrostomy	Alive
Sekiya *et al*[56], 2019	64	M	Yes	Intrapleural type	No	4	Thoracoscopic and laparoscopic approach, primary repair plus pericardial pauch, feeding jejunostomy	Alive
Olivero *et al*	67	M	No	Intrapleural type	No	2	Thoracotomy, primary repair plus	Alive

[53], 2019							pericardial pauch, thoracic drainage	
Felipe *et al*[38], 2021	47	M	Yes	Intrapleural type	No	12	Thoracotomy and laparotomy approach, esophagostomy, gastrostomy → stent	Alive
Ahmad *et al* [33], 2018	63	M	Yes	Intrapleural type	No	2.5	Stent, thoracic drainage	Alive
Hashmi *et al* [10], 2021	83	M	Yes	Intrapleural type	Yes	Unknown	Antibiotic administration	Death
Teblick *et al*[34], 2018	74	M	Yes	Intrapleural type	No	Unknown	Stent, thoracic drainage	Alive
He *et al*[9], 2018	27	M	Yes	Intrapleural type	No	6	Thoracotomy, primary repair plus pleural flap, feeding jejunostomy	Alive

PEG: Percutaneous endoscopic gastrostomy; M: Male; F: Female.

Table 2 Characteristics of the patients with Boerhaave syndrome included in the review, *n* (%)

Sex		[a]Male 51, female 4
Age		55.8 ± 16
The length from symptom within 24 h		[b]36 (65.5)
The method of diagnosis	CT	31
	Esophagography	15
	Endoscopy	9
	Exploratory laparotomy	1
Accurate diagnosis on admission		42 (75)
Shock vital on admission		14 (25)
Rupture type	Intramediastinal	12 (21.4)
	Extramediatinal	44 (78.6)
Lacelation size (cm) (range)		[c]3.8 (1-12)

[a]One case with no information.
[b]One case with no information.
[c]26 cases with no information.
CT: Computed tomography.

Four of the cases who initially underwent operation consequently underwent endoscopic esophageal stenting to stop leakage.

Minimally invasive surgery

Eleven out of 31 cases (35.5%) underwent minimally invasive surgery. Seven of the 13 cases (53.8%) who underwent the trans-abdominal approach received the trans-hiatal approach specifically with laparoscopic surgery. Five of the 21 cases (23.8%) who underwent the trans-thoracic approach received thoracoscopic surgery. The length of the hospital stay after surgery tended to be shorter with minimally invasive surgery than with non-minimally invasive surgery [minimally invasive surgery (n = 10) *vs* non-minimally invasive surgery (n = 15): 25.5 ± 17.1 *vs* 38.86 ± 24.85 d; P = 0.153] (Figure 2A).

Conservative treatment vs surgery

Table 4 shows the differences in details between patients who underwent an operation and those who received conservative treatment. The sex, age, rate of patients admitting within 24h after symptom onset, rupture type, and rate of survival did not significantly differ between patients who underwent an operation and those who received conservative treatment. The rate of patients with shock vitals on admission did differ significantly between patients who underwent an operation and those who received conservative treatment (9.7% *vs* 44.0%; P = 0.005). The length of hospital stay was not significantly different among the 43 cases (operation *vs* conservative treatment: 33.52 ± 22.09 *vs* 38.81 ± 35.28 d; P = 0.55) (Figure 2B).

Table 3 Initial treatment for Boerhaave syndrome

			The number do not add up because of duplication case
Conservation (n = 25)[a]	Esophageal stent		17
	Clipping		5
	Thoracic drainage		21
	EVAC[b]		1
Operation (n = 31)	Approach	Trans-thoracic approach	18
		Trans-abdominal approach	10
		Trans-thoracic and abdominal approach	3
	Method	Primary repair only	8
		Primary repair with omentoplasty	6
		Primary repair with fundus pauch	6
		Primary repair with intercostal muscle pauch	5
		Primary repair with pericardial fat pauch	5
		T tube	2
		Esophagectomy	1
		Esophagostomy and gastrostomy	1

[a]Duplication exist.
[b]Endoluminal vacuum-assisted therapy.
EVAC: Endoluminal vacuum-assisted.

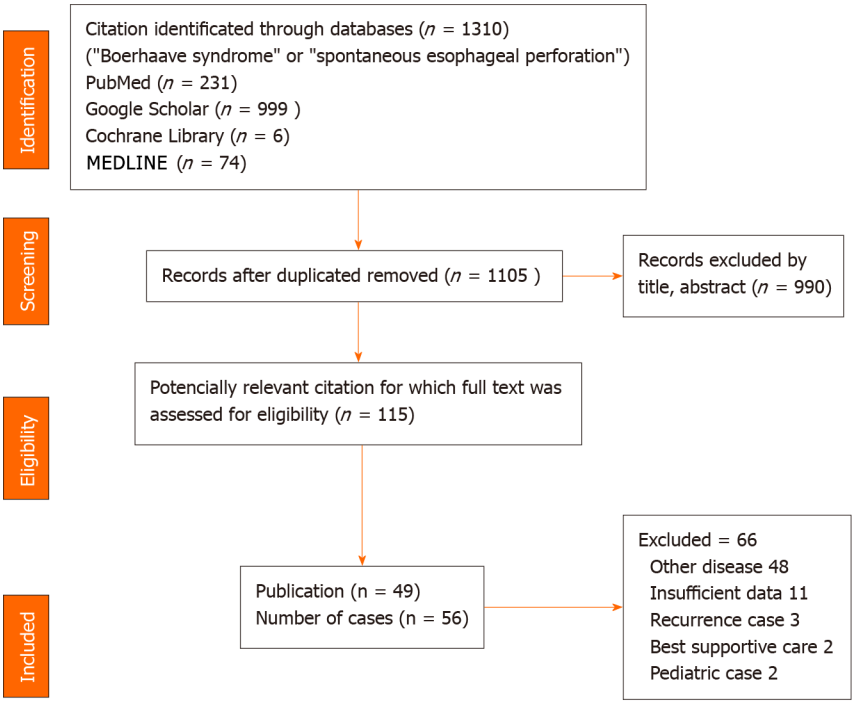
Table 4 The length of hospital stay was not significantly different among the 43 cases

Factor	Group	Operation (n = 31)	Conservation (n = 25)	P value
Sex (%)	M	27 (90.0)	24 (96.0)	0.617
	F	3 (10.0)	1 (4.0)	
mean ± SD		53.17 (14.68)	59.00 (18.14)	0.193
The length from symptom within 24 h (%)	Yes	10 (32.3)	9 (36.0)	1
	No	20 (64.5)	16 (64.0)	
Shock vital on admission (%)	Yes	3 (9.7)	11 (44.0)	0.005
	No	28 (90.3)	14 (56.0)	
rupture type	Intramediastinal (%)	8 (25.8)	4 (16.0)	0.516
	Extramediastinal (%)	23 (74.2)	21 (84.0)	
Alive (%)	Yes	28 (90.3)	21 (84.0)	0.688
	No	3 (9.7)	4 (16.0)	

F: Female; M: Male.

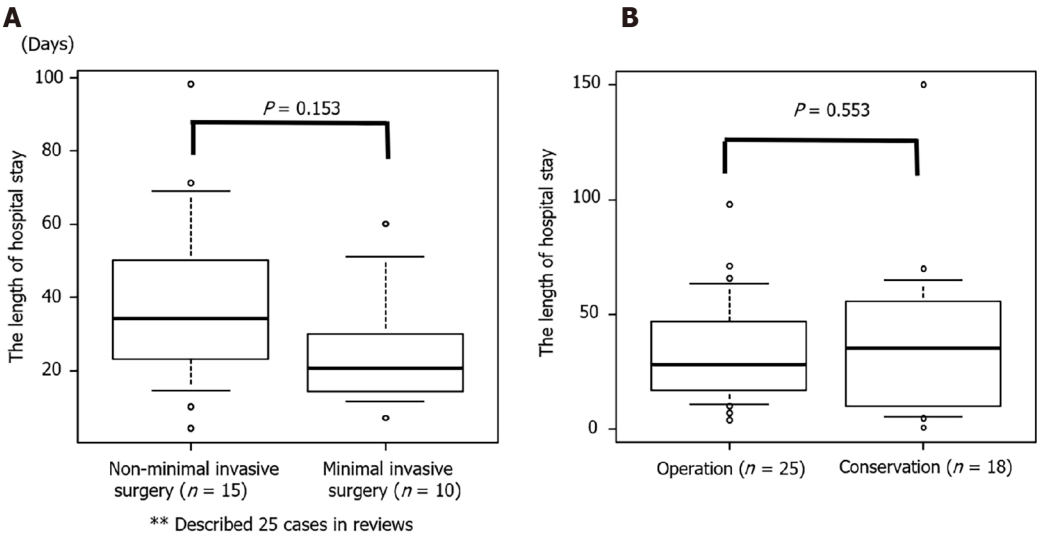
DISCUSSION

Primary surgical repair has been the gold-standard treatment for esophageal perforation for a long time [13-19]. Primary repair of the esophagus conducted with mediastinal and thoracic drainage is reported to have a 90% success rate. Cases in which esophageal rupture is diagnosed at an early stage (within 24 h) without associated esophageal disease are reported to show a particularly high success rate[20].



DOI: 10.13105/wjma.v11.i4.112

Figure 1 PRISMA flow diagram demonstrating articles selection process.



DOI: 10.13105/wjma.v11.i4.112

Figure 2 Comparison of length of hospital stay. A: The length of hospital stay in the non-minimally and minimally invasive surgery groups; B: The length of hospital stay in the operation and conservative treatment groups.

There has been a recent trend toward more non-operative management[21,22], such as esophageal stent replacement *via* an endoscopic approach[23-32]. The indications for esophageal stenting include multiple comorbidities, advanced mediastinal sepsis, hemodynamic compromise, and clinical intolerance of extensive surgical repair[33]. In our review, the rate of conservation was significantly higher than that of operation in instances of shock vital on admission (44.0% *vs* 9.7%; $P = 0.005$).

Esophageal stenting was able to be attempted for patients who were in a bad general condition or intolerant to surgery[34]. Endoscopic esophageal stenting was also performed for cases of postoperative leakage. Kauer *et al*[35] in 2008 first described the usefulness of stent placement in the management of thoracic anastomotic leakage after esophagectomy. An interval approach utilizing covered metallic stent was then introduced for the management of anastomotic leakage after esophagectomy[36]. However, no prospective clinical study comparing the outcomes of esophageal stenting to that of conservative/surgical treatment has yet been performed. Bi *et al*[37] reported that the efficacy of the three-tube method, (tube drainage of the abscess, placement of a jejunal feeding tube, and placement of a

gastrointestinal decompression tube, with implantation of a covered metallic stent) for the management of anastomotic leakage following esophagectomy. This means that it is important not only to place esophageal stents but also to provide adequate drainage, a concept that can also be applied for treating Boerhaave syndrome.

Surgical approaches differed among facilities in our review. The operation approach in our evaluated studies was the trans-thoracic approach in 18 cases, trans-abdominal approach in 10 cases, and combined trans-thoracic and trans-abdominal approach in 3 cases. The approach seemed to differ depending on laceration site, the patient's general condition, and whether the operator was a thoracic surgeon or a gastrointestinal surgeon. The reported operative methods for Boerhaave syndrome include primary repair (with/without reinforcement), an exclusion diversion operation[38], esophageal resection, and simple thoracic drainage[39-40]. Previous reports mentioned that reinforcement with vascularized tissue was associated with reduced fistula formation and mortality rates in comparison to repair without reinforcement[41-43]. In the case of friability of the tissue, primary repair with reinforcement, such as omental flaps[44-47], intercostal muscle flaps[48-51], and pericardial flaps[52-54], should be performed. A comprehensive evaluation of the degree of laceration, extent of laceration, and general condition required for deciding the repair method should be conducted.

There have been a few recent reports concerning minimally invasive surgery for Boerhaave syndrome. Kita *et al*[55] suggested that a good clinical course can be obtained by laparoscopic trans-hiatal esophageal repair for Boerhaave's syndrome with localized mediastinal collections to avoid surgical invasion due to thoracotomy. Sekiya *et al*[56] reported the convenience and usefulness of minimally invasive surgery *via* an abdominal and left thoracic approach, which provides excellent visualization of the abdominal and thoracic cavities and facilitates quick switching between views. The authors further suggested that, in cases with an interval to the diagnosis < 24 h, no severe comorbidities, and a perforation site in the left lower esophagus, a trans-hiatal approach for minimally invasive surgery is feasible to repair the laceration and ameliorate the infection[56]. In our systematic review, the length of hospital stay after minimally invasive surgery tended to be shorter than after non-minimally invasive surgery (25.5 ± 17.1 *vs* 38.86 ± 24.85 d; $P = 0.153$). Minimally invasive surgery is useful for its cosmetic aspect, camera magnification effect, and ease of suturing, especially a laparoscopic trans-hiatal approach.

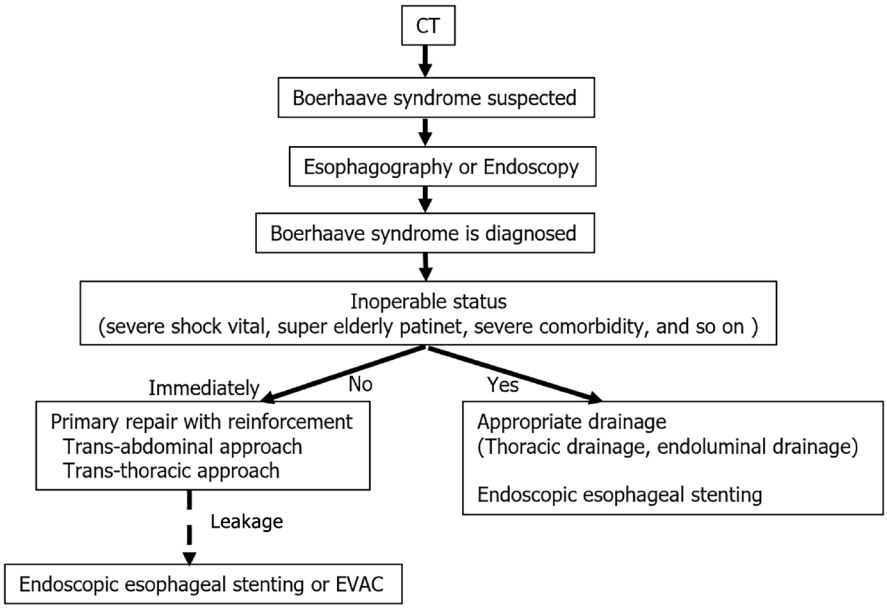
In our systematic review, 12 out of 31 cases (38.7%) developed postoperative leakage. Two of those 13 Leakage cases underwent EVAC therapy. Recently, the efficacy of EVAC therapy for esophago-pleural fistula after an operation for Boerhaave syndrome was reported[57-59]. EVAC therapy can be applied in postoperative management according to the principle applied for external wounds that provide wound drainage and tissue granulation. EVAC therapy can be applied to conservatively treat cases where primary surgical repair of esophageal perforation is unsuccessful. Moreover, with the use of an S-B tube, the patient can simultaneously receive intraluminal EVAC therapy with enteral nutrition in a non-invasive manner[58]. This may accelerate the healing of the injured esophagus and reduce the duration of hospitalization.

We suggest an algorithm that might be useful in the treatment of Boerhaave syndrome in Figure 3, with reference to our systematic review. If Boerhaave syndrome is suspected on computed tomography, esophagography or upper gastrointestinal endoscopy should be performed immediately. The treatment of Boerhaave syndrome is basically primary repair with reinforcement. If postoperative leakage occurs, endoscopic esophageal stenting or EVAC therapy should be considered. If the patient is inoperable (severe shock vitals, super-elderly patients, severe comorbidities, *etc.*), endoscopic esophageal stenting and thoracic drainage should be considered.

Several limitations associated with the present study warrant mention. Importantly, due to its rarity, there are few large case series on Boerhaave syndrome. Furthermore, the therapeutic strategies for Boerhaave syndrome have changed over time, with new approaches being developed recently. We reviewed and analyzed 49 articles; however, the review process may have included various publication biases.

CONCLUSION

In the treatment of Boerhaave syndrome, it is most important to diagnose the issue immediately. Primary repair with reinforcement is the gold-standard procedure. The optimal treatment should be determined according to the etiology, general physical condition of the patient, and site of perforation, as well as the extent of contamination, as determined by radiology. The indication of endoscopic esophageal stenting or endoluminal vacuum-assisted therapy should always be considered for patients in a poor general condition and who continue to have leakage after repair.



DOI: 10.13105/wjma.v11.i4.112

Figure 3 Algorithm for the treatment of Boerhaave syndrome with reference to the systematic review findings. CT: Computed tomography; EVAC: Endoluminal vacuum-assisted.

ARTICLE HIGHLIGHTS

Research perspectives

As far, it has long been reported that Boerhaave syndrome has a poor prognosis when diagnosed late. However, no consensus has been reached concerning the appropriate therapeutic strategy for Boerhaave syndrome because of the rarity of the disease and the changing therapeutic trends.

Research conclusions

We assess the therapeutic methods [operation *vs* drainage *vs* stent *vs* endoluminal vacuum-assisted (EVAC), *etc.*] and clinical outcomes and discuss the current trends in the management of Boerhaave syndrome.

Research results

We believe that this systematic review will be useful in future treatment of Boerhaave syndrome when there is doubt as to whether conservative treatment or surgery should be done, as well as the method of surgery.

Research methods

We searched PubMed, Google scholar, MEDLINE, and The Cochrane Library for studies concerning Boerhaave syndrome published between 2017 and 2022.

Research objectives

In results, the key to treatment of Boerhaave syndrome was early diagnosis. In addition, although surgery was the basic treatment, esophageal stents and drainage may be useful for patients with intolerance. Furthermore, for postoperative leakage, esophageal stents, drainage, and EVAC were useful.

Research motivation

In the treatment of Boerhaave syndrome, it is most important to diagnose the issue immediately. Primary repair with reinforcement is the gold-standard procedure. The indication of endoscopic esophageal stenting or endoluminal vacuum-assisted therapy should always be considered for patients in a poor general condition and who continue to have leakage after repair.

Research background

Because Boerhaave syndrome is a rare disease, observational studies should be conducted in collaboration with other centers. We hope that this will result in a high-quality strategy.

ACKNOWLEDGEMENTS

We gratefully acknowledge the work of past and present members.

FOOTNOTES

Author contributions: Yamana I and Fujikawa T contributed equally to this work; Yamana I and Fujikawa T designed the research study; Yamana I and Fujikawa T performed the research; Kawamura Y contributed new reagents and analytic tools; Yamana I analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Japan

ORCID number: Takahisa Fujikawa 0000-0002-4543-9282; Suguru Hasegawa 0000-0002-8641-8197.

S-Editor: Liu JH
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Adams BD**, Sebastian BM, Carter J. Honoring the Admiral: Boerhaave-van Wassenaer's syndrome. *Dis Esophagus* 2006; **19**: 146-151 [PMID: 16722990 DOI: 10.1111/j.1442-2050.2006.00556.x]
2 **Vidarsdottir H**, Blondal S, Alfredsson H, Geirsson A, Gudbjartsson T. Oesophageal perforations in Iceland: a whole population study on incidence, aetiology and surgical outcome. *Thorac Cardiovasc Surg* 2010; **58**: 476-480 [PMID: 21110271 DOI: 10.1055/s-0030-1250347]
3 **Czopnik P**, Aporowicz M, Niepokój-Czopnik A, Szajerka T, Domosławski P. Barogenic rupture of esophagus (Boerhaave syndrome) as diagnostic and therapeutic challenge requiring rapid and effective interdisciplinary cooperation - case report. *Pol Przegl Chir* 2017; **89**: 37-39 [PMID: 29335396 DOI: 10.5604/01.3001.0010.6750]
4 **Jahangir A**, Sahra S, Anwar S, Mobarakai N, Jahangir A. Catastrophic right-sided Candida empyema from spontaneous esophageal perforation. *Respir Med Case Rep* 2021; **33**: 101460 [PMID: 34401296 DOI: 10.1016/j.rmcr.2021.101460]
5 **Tan N**, Luo YH, Li GC, Chen YL, Tan W, Xiang YH, Ge L, Yao D, Zhang MH. Presentation of Boerhaave's syndrome as an upper-esophageal perforation associated with a right-sided pleural effusion: A case report. *World J Clin Cases* 2022; **10**: 6192-6197 [PMID: 35949820 DOI: 10.12998/wjcc.v10.i18.6192]
6 **Ayazi K**, Samsami M, Qaderi S, Farsad SM, Tofigh AM, Nematihonar B, Tahmasbi H, Bagherour JZ. Spontaneous perforation as a fatal presentation of esophageal tuberculosis: A case report. *Int J Surg Case Rep* 2021; **78**: 197-200 [PMID: 33360335 DOI: 10.1016/j.ijscr.2020.12.042]
7 **Swol J**, Ficker JH, Mannke B. Cervical Emphysema in Boerhaave Syndrome. *Dtsch Arztebl Int* 2019; **116**: 211 [PMID: 31056087 DOI: 10.3238/arztebl.2019.0211]
8 **Saffo S**, Farrell J, Nagar A. Circumferential esophageal perforation resulting in tension hydropneumothorax in a patient with septic shock. *Acute Crit Care* 2021; **36**: 264-268 [PMID: 33691378 DOI: 10.4266/acc.2020.01067]
9 **He F**, Dai M, Zhou J, He J, Ye B. Endoscopic repair of spontaneous esophageal rupture during gastroscopy: A CARE compliant case report. *Medicine (Baltimore)* 2018; **97**: e13422 [PMID: 30508951 DOI: 10.1097/MD.0000000000013422]
10 **Hashmi MAR**, El-Badawy M, Agha A. Suspecting a fatal condition on a plain chest radiograph; Boerhaave syndrome. *Scott Med J* 2021; **66**: 46-48 [PMID: 32981463 DOI: 10.1177/0036933020961181]
11 **Allaway MGR**, Morris PD, B Sinclair JL, Richardson AJ, Johnston ES, Hollands MJ. Management of Boerhaave syndrome in Australasia: a retrospective case series and systematic review of the Australasian literature. *ANZ J Surg* 2021; **91**: 1376-1384 [PMID: 33319446 DOI: 10.1111/ans.16501]
12 **Kanda Y**. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; **48**: 452-458 [PMID: 23208313 DOI: 10.1038/bmt.2012.244]
13 **Chang CW**, Hung YJ, Chan CP, Huang CL. Spontaneous esophageal rupture following perforated peptic ulcer: a report of two cases. *J Cardiothorac Surg* 2021; **16**: 57 [PMID: 33771196 DOI: 10.1186/s13019-021-01431-z]
14 **Pasternak A**, Ellero J, Maxwell S, Cheung V. Boerhaave's syndrome in an ultra-distance runner. *BMJ Case Rep* 2019; **12**

[PMID: 31399415 DOI: 10.1136/bcr-2019-230343]
15 **Bani Fawwaz BA**, Gerges P, Singh G, Rahman SH, Al-Dwairy A, Mian A, Khan N, Farooq A. Boerhaave Syndrome: A Report of Two Cases and Literature Review. *Cureus* 2022; **14**: e25241 [PMID: 35755521 DOI: 10.7759/cureus.25241]
16 **Ali N**, Abate G. Candida Empyema as a Red Flag for Esophageal Rupture: A Case Report and Literature Review. *Case Rep Infect Dis* 2020; **2020**: 3935691 [PMID: 32351745 DOI: 10.1155/2020/3935691]
17 **Alakkari A**, Sood R, Everett SM, Rembacken BJ, Hayden J, Sarela A, Mohammed N. First UK experience of endoscopic vacuum therapy for the management of oesophageal perforations and postoperative leaks. *Frontline Gastroenterol* 2019; **10**: 200-203 [PMID: 31205665 DOI: 10.1136/flgastro-2018-101138]
18 **Zhu C**, Castrodad A, Santos AP. Alternative management of delayed spontaneous oesophageal perforation by endoscopic stenting. *BMJ Case Rep* 2021; **14** [PMID: 34257131 DOI: 10.1136/bcr-2021-244122]
19 **Chen JJ**, Zhao W. Boerhaave's syndrome: A case of spontaneous oesophageal rupture. *Indian J Med Res* 2021; **154**: 156 [PMID: 34782544 DOI: 10.4103/ijmr.IJMR_1031_19]
20 **de Schipper JP**, Pull ter Gunne AF, Oostvogel HJ, van Laarhoven CJ. Spontaneous rupture of the oesophagus: Boerhaave's syndrome in 2008. Literature review and treatment algorithm. *Dig Surg* 2009; **26**: 1-6 [PMID: 19145081 DOI: 10.1159/000191283]
21 **Matsuura N**, Saitou K. Boerhaave's Syndrome. *Intern Med* 2022; **61**: 265-266 [PMID: 34219113 DOI: 10.2169/internalmedicine.7807-21]
22 **Xu H**, Huang D, He C. Boerhaave's syndrome with rupture of the right wall of the esophagus after oral administration of sulfate solution. *Rev Esp Enferm Dig* 2021; **113**: 677 [PMID: 33393326 DOI: 10.17235/reed.2020.7617/2020]
23 **Issa D**, Alwatari Y, Smallfield GB, Shah RD. Spontaneous transmural perforation in eosinophilic esophagitis: RARE case presentation and role of esophageal stenting. *J Surg Case Rep* 2019; **2019**: rjz190 [PMID: 31214326 DOI: 10.1093/jscr/rjz190]
24 **Sheshala K**, Kumar GN, Misra KC, Hemanth C, Appasani S. Bee Sting to Boerhaave's Syndrome. *Indian J Crit Care Med* 2021; **25**: 346-348 [PMID: 33790521 DOI: 10.5005/jp-journals-10071-23770]
25 **Matsumoto R**, Sasaki K, Omoto I, Noda M, Uchikado Y, Arigami T, Kita Y, Mori S, Maemura K, Natsugoe S. Successful conservative treatment of spontaneous intrathoracic esophageal perforation using a temporary covered esophageal stent with a check valve: a case report. *Surg Case Rep* 2019; **5**: 152 [PMID: 31650260 DOI: 10.1186/s40792-019-0717-3]
26 **Y K**, F AB, A T, D H. Boerhaave syndrome in an elderly man successfully treated with 3-month indwelling esophageal stent. *Radiol Case Rep* 2018; **13**: 1084-1086 [PMID: 30228849 DOI: 10.1016/j.radcr.2018.04.026]
27 **Awadelkarim A**, Shanah L, Ali M, Alhusain R, Adam O, Subahi A, Yassin AS, Lieberman R. Esophago-Pericardial Fistulae as a Sequela of Boerhaave Syndrome and Esophageal Stenting: A Case Report and Review of Literature. *J Investig Med High Impact Case Rep* 2021; **9**: 23247096211036540 [PMID: 34330166 DOI: 10.1177/23247096211036540]
28 **Chalikonda D**, Yoo J, Johnson D, Tofani C. Boerhaave Syndrome Causing Bilateral Empyemas. *ACG Case Rep J* 2019; **6**: e00203 [PMID: 31750375 DOI: 10.14309/crj.0000000000000203]
29 **Śnieżyński J**, Wilczyński B, Skoczylas T, Wallner GT. Successful Late Endoscopic Stent-Grafting in a Patient with Boerhaave Syndrome. *Am J Case Rep* 2021; **22**: e931629 [PMID: 34385411 DOI: 10.12659/AJCR.931629]
30 **Truyens M**, Hufkens E, Van Geluwe B, Vergauwe P, Van Moerkercke W. Boerhaave's syndrome: successful conservative treatment in two patients. *Acta Gastroenterol Belg* 2020; **83**: 654-656 [PMID: 33321024]
31 **Sato H**, Ishida K, Sasaki S, Kojika M, Endo S, Inoue Y, Sasaki A. Regulating migration of esophageal stents - management using a Sengstaken-Blakemore tube: A case report and review of literature. *World J Gastroenterol* 2018; **24**: 3192-3197 [PMID: 30065565 DOI: 10.3748/wjg.v24.i28.3192]
32 **Barakat MT**, Girotra M, Banerjee S. (Re)building the Wall: Recurrent Boerhaave Syndrome Managed by Over-the-Scope Clip and Covered Metallic Stent Placement. *Dig Dis Sci* 2018; **63**: 1139-1142 [PMID: 28948439 DOI: 10.1007/s10620-017-4756-y]
33 **Ahmad W**, Kwong WT. Boerhaave's Syndrome: A Window to the Heart. *Clin Gastroenterol Hepatol* 2018; **16**: e77-e78 [PMID: 28893681 DOI: 10.1016/j.cgh.2017.08.052]
34 **Teblick A**, Jansens H, Dams K, Somville FJ, Jorens PG. Boerhaave's syndrome complicated by a Saccharomyces cerevisiae pleural empyema. Case report and review of the literature. *Acta Clin Belg* 2018; **73**: 377-381 [PMID: 29103370 DOI: 10.1080/17843286.2017.1398439]
35 **Kauer WK**, Stein HJ, Dittler HJ, Siewert JR. Stent implantation as a treatment option in patients with thoracic anastomotic leaks after esophagectomy. *Surg Endosc* 2008; **22**: 50-53 [PMID: 17704867 DOI: 10.1007/s00464-007-9504-5]
36 **van Boeckel PG**, Dua KS, Weusten BL, Schmits RJ, Surapaneni N, Timmer R, Vleggaar FP, Siersema PD. Fully covered self-expandable metal stents (SEMS), partially covered SEMS and self-expandable plastic stents for the treatment of benign esophageal ruptures and anastomotic leaks. *BMC Gastroenterol* 2012; **12**: 19 [PMID: 22375711 DOI: 10.1186/1471-230X-12-19]
37 **Bi Y**, Wu Z, Yi M, Han X, Ren J. Three-tube method and covered metallic stent for the treatment of anastomotic leakage after esophagectomy. *BMC Gastroenterol* 2020; **20**: 330 [PMID: 33028222 DOI: 10.1186/s12876-020-01480-z]
38 **Felipe N**, King SA, Salerno A. 'Diagnosis of Boerhaave's Syndrome With Aid of Bedside Ultrasound. *J Emerg Med* 2021; **61**: 568-573 [PMID: 34193358 DOI: 10.1016/j.jemermed.2021.05.017]
39 **Ioannidis O**, Malliora A, Christidis P, Kotidis E, Pramateftakis MG, Mantzoros I, Ouzounidis N, Foutsitzis V, Angelopoulos S, Tsalis K. Conservative treatment of Boerhaave's syndrome in an octogenarian complicated with late distal esophageal stenosis and successfully treated by stent placement. *Cir Cir* 2021; **89**: 23-27 [PMID: 34762618 DOI: 10.24875/CIRU.20000882]
40 **Agrawal V**, Aggarwal D. Undiagnosed spontaneous oesophageal rupture presenting as right hydropneumothorax. *Indian J Thorac Cardiovasc Surg* 2019; **35**: 111-114 [PMID: 33060987 DOI: 10.1007/s12055-018-0719-y]
41 **Jones WG 2nd**, Ginsberg RJ. Esophageal perforation: a continuing challenge. *Ann Thorac Surg* 1992; **53**: 534-543 [PMID: 1489367 DOI: 10.1016/0003-4975(92)90294-e]
42 **Grillo HC**, Wilkins EW Jr. Esophageal repair following late diagnosis of intrathoracic perforation. *Ann Thorac Surg* 1975;

20: 387-399 [PMID: 1180593 DOI: 10.1016/s0003-4975(10)64235-x]
43 **Gouge TH**, Depan HJ, Spencer FC. Experience with the Grillo pleural wrap procedure in 18 patients with perforation of the thoracic esophagus. *Ann Surg* 1989; **209**: 612-7; discussion 617 [PMID: 2705825 DOI: 10.1097/00000658-198905000-00014]
44 **Maki H**, Inoue S, Goto M, Nishino T, Yoshida T, Takizawa H. Spontaneous esophageal perforation within a hiatal hernia: A case report. *Int J Surg Case Rep* 2022; **98**: 107484 [PMID: 36030761 DOI: 10.1016/j.ijscr.2022.107484]
45 **Park SB**, Yum YJ, Cha JM. Cyanoacrylate injection treatment for postoperative leakage of Boerhaave's syndrome: A case report. *Medicine (Baltimore)* 2021; **100**: e28075 [PMID: 34889255 DOI: 10.1097/MD.0000000000028075]
46 **Nachiappan M**, Thota R, Gadiyaram S. Laparoscopic Repair of Spontaneous Esophageal Perforation After Multiple Endoscopic Failures. *Cureus* 2022; **14**: e26784 [PMID: 35967151 DOI: 10.7759/cureus.26784]
47 **Aref H**, Yunus T, Alhallaq O. Laparoscopic Management of Boerhaave's syndrome: a case report with an intraoperative video. *BMC Surg* 2019; **19**: 109 [PMID: 31409335 DOI: 10.1186/s12893-019-0576-7]
48 **Anand R**, Puckett Y, Ronaghan CA. Above and Below the Diaphragm: A Previously Undescribed Case of Recurrent Boerhaave Syndrome Diagnosed With Computerized Tomography Esophagram. *Cureus* 2022; **14**: e24015 [PMID: 35547434 DOI: 10.7759/cureus.24015]
49 **Rahman A**, Alqaisi S, Downing C. Unusual Presentation of COVID Pneumonia as Esophageal Rupture Ended With Successful Management. *Cureus* 2021; **13**: e17348 [PMID: 34567889 DOI: 10.7759/cureus.17348]
50 Kochar T, Dhingra PS, Khaliq MF, Mcjunkin B. Eosinophilic esophagitis presenting with spontaneous esophageal rupture: a case report. J Med Case Rep 2019; 13: 275 [PMID: 31477179 DOI: 10.1186/s13256-019-2207-4]
51 **Bury J**, Fratczak A, Nielson JA. Atypical Presentation of Boerhaave Syndrome With Hypoxia and Unresponsiveness. *Cureus* 2022; **14**: e27848 [PMID: 36110495 DOI: 10.7759/cureus.27848]
52 **Shennib H**, Baribault M, Heuser R. Bovine xenograft pericardial patch use for definitive single stage repair of a large esophageal defect: a case report. *J Cardiothorac Surg* 2021; **16**: 300 [PMID: 34645503 DOI: 10.1186/s13019-021-01670-0]
53 **Olivero R**. Boerhaave syndrome: A rare postoperative complication. *JAAPA* 2019; **32**: 1-3 [PMID: 31348107 DOI: 10.1097/01.JAA.0000558372.31728.05]
54 **He X**, He Z, Li H. Boerhaave syndrome: Challenges in diagnosis and treatment of the early presentation and its complication. *J Trauma Acute Care Surg* 2018; **84**: 1030-1032 [PMID: 29443861 DOI: 10.1097/TA.0000000000001830]
55 **Kita R**, Kobayashi H, Nakao K, Iwaki K, Kondo M, Kaihara S. Three Cases of Boerhaave's Syndrome Treated *via* Laparoscopic Transhiatal Esophageal Repair. *Case Rep Gastroenterol* 2022; **16**: 406-412 [PMID: 35949239 DOI: 10.1159/000525011]
56 **Sekiya S**, Ebihara Y, Yamamura Y, Tanaka K, Nakanishi Y, Asano T, Noji T, Kurashima Y, Murakami S, Nakamura T, Tsuchikawa T, Okamura K, Shichinohe T, Hirano S. Two emergency cases of spontaneous esophageal perforation treated using a minimally invasive abdominal and left thoracic approach. *Asian J Endosc Surg* 2020; **13**: 406-409 [PMID: 31531935 DOI: 10.1111/ases.12754]
57 **Tuñon C**, De Lucas J, Cubilla J, Andrade R, Aguirre M, Zúñiga Cisneros J. Endoluminal vacuum therapy in the management of an esophago-pleural fistula as a complication of Boerhaave syndrome in a patient with eosinophilic esophagitis. *BMC Gastroenterol* 2021; **21**: 484 [PMID: 34930127 DOI: 10.1186/s12876-021-02058-z]
58 **Lee SY**, Kim KW, Lee JI, Park DK, Park KY, Park CH, Son KH. Esophageal Endoscopic Vacuum Therapy with Enteral Feeding Using a Sengstaken-Blakemore Tube. *Korean J Thorac Cardiovasc Surg* 2018; **51**: 76-80 [PMID: 29430435 DOI: 10.5090/kjtcs.2018.51.1.76]
59 **Kim YE**, Do YW, Cho JY, Kim ES, Lee DH. Successful Treatment Using Endoluminal Vacuum Therapy after Failure of Primary Closure in Boerhaave Syndrome. *Korean J Gastroenterol* 2019; **73**: 219-224 [PMID: 31030459 DOI: 10.4166/kjg.2019.73.4.219]

World Journal of Meta-Analysis

Submit a Manuscript: https://www.f6publishing.com

World J Meta-Anal 2023 April 18; 11(4): 125-133

DOI: 10.13105/wjma.v11.i4.125

ISSN 2308-3840 (online)

META-ANALYSIS

Role of baricitinib in COVID-19 patients: A systematic review and meta-analysis

Manisha Thakur, Akhil Babu, Gopal Lal Khatik, Ashok Kumar Datusalia, Ramchander Khatri, Anoop Kumar

Specialty type: Pharmacology and pharmacy

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Badri M, Iran; Mohammadi M, Iran

Received: October 31, 2022
Peer-review started: October 31, 2022
First decision: January 17, 2023
Revised: January 27, 2023
Accepted: March 29, 2023
Article in press: March 29, 2023
Published online: April 18, 2023

Manisha Thakur, Ashok Kumar Datusalia, Department of Regulatory Toxicology, National Institute of Pharmaceutical Education and Research, Raebareli, Raebareli 226002, India

Akhil Babu, Gopal Lal Khatik, Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Raebareli, Raebareli 226002, India

Ramchander Khatri, Department of Pharmacognosy, Delhi Pharmaceutical Sciences and Research University, New Delhi 110017, India

Anoop Kumar, Department of Pharmacology and Clinical Research, Delhi Pharmaceutical Sciences and Research University, New Delhi 110017, Delhi, India

Corresponding author: Anoop Kumar, PhD, Assistant Professor, Department of Pharmacology and Clinical Research, Delhi Pharmaceutical Sciences and Research University, New Delhi 110017, Delhi, India. abitmesra@gmail.com

Abstract

BACKGROUND

Recent studies have indicated the use of baricitinib in coronavirus disease 2019 (COVID-19) patients. However, the use of baricitinib in COVID-19 patients is unclear so far.

AIM

To determine the precise role of baricitinib in the mortality of COVID-19 patients.

METHODS

The relevant studies were searched in PubMed, Google scholar, and Clinical trials registries till July 13, 2021 and sorted out based on inclusion and exclusion criteria. The quality of studies was assessed using Newcastle-Ottawa Scale. A random-effect model was used, and the pooled estimate was calculated as the odds ratio with a 95% confidence interval using Rev Man 5.

RESULTS

A total of 11 studies (4 observational and 7 clinical trials) were found relevant for analysis. The overall estimate measure in terms of odds ratio for observational studies was 0.42 [0.11, 1.67], whereas for clinical trials it was 0.37 [0.09, 1.46], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group.

CONCLUSION

More studies are required to confirm the role of baricitinib in the deaths of COVID-19 patients.

Key Words: Janus kinase inhibitors; Baricitinib; COVID-19; Mortality; Systematic Review; Meta-analysis

Core Tip: Emerging reports have indicated the use of baricitinib in hospitalized coronavirus disease 2019 (COVID-19) patients. However, the use of baricitinib in COVID-19 patients is unclear so far. Current study aimed to find out the exact association of baricitinib in the mortality of COVID-19 patients.

Citation: Thakur M, Babu A, Khatik GL, Datusalia AK, Khatri R, Kumar A. Role of baricitinib in COVID-19 patients: A systematic review and meta-analysis. *World J Meta-Anal* 2023; 11(4): 125-133
URL: https://www.wjgnet.com/2308-3840/full/v11/i4/125.htm
DOI: https://dx.doi.org/10.13105/wjma.v11.i4.125

INTRODUCTION

According to the World Health Organization (WHO), multiple pneumonia episodes of unknown cause were reported in the central Metropolitan area of Wuhan in December 2019 in China. The causal infection was later identified as a novel coronavirus, tentatively termed coronavirus disease 2019 (COVID-19). This virus has been causing havoc on public health across the world since its outbreak in December 2019. More than 2000 incidents of COVID-19 infection were reported as of January 26, 2020, the majority of which were individuals living in or traveling Wuhan. The WHO claimed the COVID-19 pandemic was a Public Health Emergency of International Concern on January 30, 2020[1]. The cases of infection were highly associated with the seafood market in Wuhan[2]. Chinese officials announced 2835 confirmed cases in 2020, with 81 deaths. The causal agent has been identified as a novel coronavirus, COVID-19, a pathogen linked to severe acute respiratory syndrome (SARS), was quickly identified as the cause (SARS-CoV) by Chinese officials[3,4]. Coronaviruses (CoV) belongs to the family "coronaviridae". Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to be spread directly from bats to humans or by a single or several host species[3,5]. The treatment is based on the symptoms of the patients. Various classes of drugs are repurposed and are being used in the management of this infection.

Janus Kinase Inhibitors (JAKi) are also one of the repurposed drugs which are being used in the management of hospitalized COVID-19 patients due to their anti-inflammatory (inhibition of IL-6) and anti-viral effects (inhibit the entry of virus)[6]. Baricitinib is one of the JAKi approved for the treatment of rheumatoid arthritis. It has been observed that most SARS-CoV-2 infected patients were died due to cytokine storms, specifically the excess release of IL-6. Thus, baricitinib might be useful in the reduction of deaths of COVID-19 patients[7,8]. Meta-analysis is one of the quantitative analyses that help in clinical decision-making. The results of the individual studies are pooled and integrated using suitable statistical procedures[9-11]. In the current study, we performed a systematic review of clinical studies to determine the role of baricitinib in the deaths of COVID-19 hospitalised patients.

MATERIALS AND METHODS

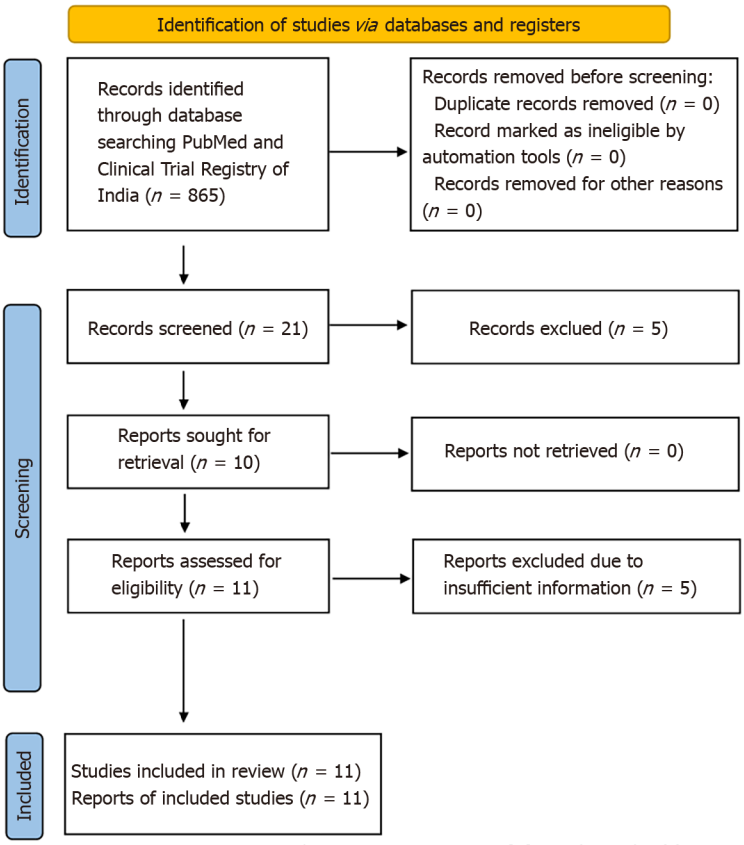
The study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Figure 1). The study is registered with the International prospective register of systematic reviews (PROSPERO, Registration number: CRD42021281366).

Search strategy

A search was conducted in PubMed, Google scholar, and Clinical trial registry for observational, randomized, and non-randomized controlled studies, cohort studies, and comparative cross-sectional studies with the following search strategies: "baricitinib", OR "immunosuppressants", OR "anti-rheumatoid", OR "Janus kinase inhibitor" OR "Disease-modifying antirheumatic drug" AND "COVID-19" OR "Coronavirus" OR "Acute respiratory distress syndrome" OR "SARS-CoV-2". The references of included studies were screened to boost the search.

Study selection

Two reviewers (MT and AB) separately screened all the titles and abstracts as per the inclusion and



DOI: 10.13105/wjma.v11.i2.125

Figure 1 Selection of studies as per the PRISMA guidelines.

exclusion criteria. The studies were included if participants were on baricitinib therapy, with all age groups, and all sexes. The case reports, case series, narrative review, systematic review, meta-analysis, studies of poor quality as per standard scale were excluded. The reviewers (MT and AB) separately screened the full-text studies for final inclusion. In the case of conflicts over the inclusion, the third reviewer (AK) was consulted.

Quality assessment

The quality assessment of eligible observational studies was done using Newcastle-Ottawa Scale whereas quality assessment of clinical trials was done using NIH quality assessment scale for quality assessment of controlled intervention studies. The assessment was done by two reviewers (MT and AB) separately. The disagreement among authors was resolved after a discussion with four reviewers (GLK, AKD, RK, and AK). The studies were categorized into three categories, *i.e.*, good, fair, and poor quality.

Data extraction

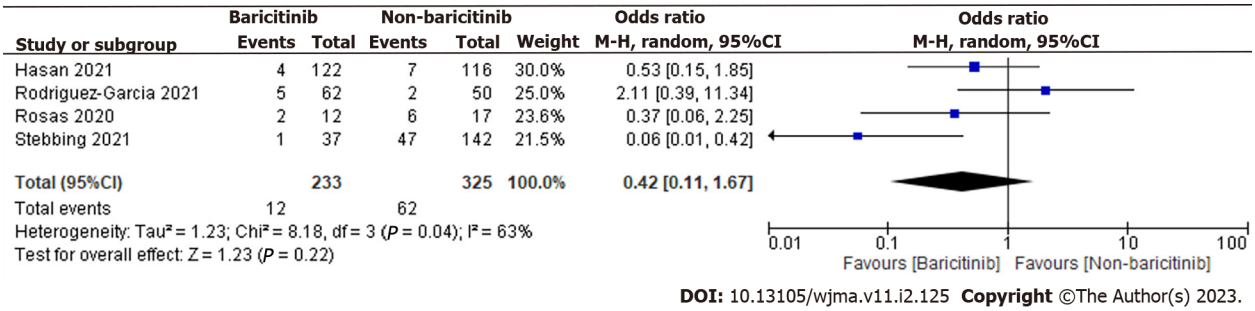
The data was extracted from studies by two reviewers (MT and AB) in an excel sheet. The information includes the name of the first author with publication year, the country where the study has been conducted, gender, study design, the total number of subjects, number of subjects, and deaths in baricitinib, non-baricitinib group.

Sensitivity analysis

The sensitivity analysis was done to check the effect of high or low sample size on the outcome to address the degree of heterogeneity.

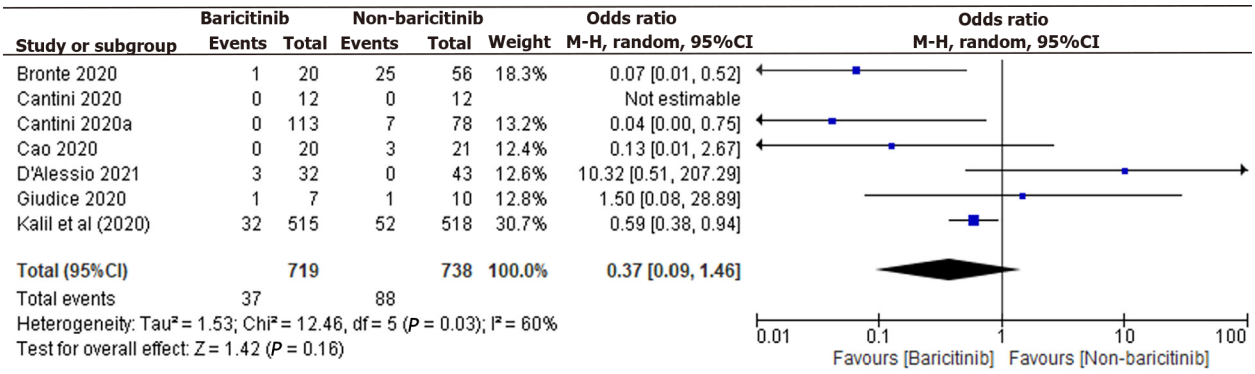
Statistical analysis

RevMan 5 was used for all of the analyses. Using a random-effect model, the overall estimate was calculated as an odds ratio with 95% confidence intervals. Cochrane Q and I square statistics were used to calculate study heterogeneity.



DOI: 10.13105/wjma.v11.i2.125

Figure 2 Forest Plot showing overall estimate measure of observational studies as odds ratio using random-effect model.



DOI: 10.13105/wjma.v11.i2.125

Figure 3 Forest Plot showing overall estimate measure of clinical trials as odds ratio using random-effect model.

RESULTS

Search results and study characteristics

We found 865 articles after the initial search. After primarily screening of titles, 21 relevant articles were found. Further, based on the screening of abstracts, 16 were retrieved, out of which 05 articles were excluded due to insufficient information. Finally, 11 articles[11-22] were included for qualitative and quantitative analysis. Figure 1 depicts the selection of articles. The full-text or secondary screening with bibliography searches yielded no additional articles for inclusion. Out of the 11 studies, 4 were observational studies whereas the remaining 7 studies were clinical trials. The four studies were conducted in Italy, two in Spain, one in Italy and Spain, and one each at, Omaha, Bangladesh, Germany, Wuhan. The characteristics of included observational studies were compiled in Table 1 whereas the characteristics of included clinical trials were compiled in Table 2.

Quality assessment

All observational studies on the Newcastle-Ottawa Scale were found to be of good to fair quality based on their scores in the selection, comparability, and outcome subscales. Three of the four studies were of high quality, while the fourth was of fair quality (Table 3). According to the NIH quality assessment scale, 5 studies were of good quality, while the remaining two were of fair quality (Table 4).

Analysis of observational studies

A total of 558 patients were found in selected 4 observational studies. 233 of the 558 coronavirus disease 2019 (COVID-19) cases were taking baricitinib, while the remaining 325 were not. The overall estimate was 0.42 [0.11, 1.67], indicating that the baricitinib group had a non-significant reduction in COVID-19 patient deaths compared to the non-baricitinib group (Figure 2).

Analysis of clinical trials

In total, 1457 patients were found in 7 clinical trials. 719 of the 1457 COVID-19 cases were taking baricitinib, while the remaining 738 were not. The overall estimate was 0.37 [0.09, 1.46], indicating that the baricitinib group had a non-significant reduction in COVID-19 patient deaths compared to the non-baricitinib group (Figure 3).

Table 1 Characteristics of included observational studies

Ref.	Country	Study design	Sample size	Sex		Baricitinib group		Non-baricitinib group	
				Male	Female	Number of patients	Death	Number of patients	Death
Hasan *et al*[14], 2021	Bangladesh	Cohort study	238	159	79	122	4	116	7
Stebbing *et al*[15], 2021	Italy, Spain	Observational	790	438	352	37	1	142	47
Rodriguez-Garcia *et al*[16], 2020	Spain	Cohort study	112	78	34	62	5	50	2
Rosas *et al*[19], 2020	Spain	Case control study	29	20	9	12	2	17	6

Table 2 Characteristics of included clinical trials

Ref.	Country	Study design	Sample size	Sex		Baricitinib group		Non-baricitinib group	
				Male	Female	Number of patients	Death	Number of patients	Death
Bronte *et al*[13], 2020	Italy	Clinical trial	76	38	38	20	1	56	25
Kalil *et al*[12], 2020	Omaha	Clinical trial	1033	652	381	515	32	518	52
Cantini *et al*[17], 2020	Germany	Clinical trial	24	20	4	12	0	12	0
Cantini *et al*[18], 2020	Italy	Clinical trial	191	119	72	113	0	78	7
Cao *et al*[20],2020	Wuhan	Clinical trial	41	24	17	20	0	21	3
D'Alessio *et al*[21],2021	Italy	Clinical trial	75	52	23	32	3	43	0
Giudice *et al*[22], 2020	Italy	Clinical trial	17	13	4	7	1	10	1

Table 3 Quality assessment of observational studies using new castle Ottawa scale

Ref.	Selection	Comparability	Exposure	Total score	Quality of the study
Hasan *et al*[14], 2021	****	**	***	9	Good
Stebbing *et al*[15], 2021	***	*	***	7	Good
Rodriguez-Garcia *et al*[16], 2020	****	*	***	8	Good
Rosas *et al*[19], 2020	**	**	***	7	Fair

*For each numbered item within the selection and outcome categories.

Heterogeneity

The I^2 (90%) and chi^2 statics have shown high heterogeneity among studies.

Sensitivity analysis

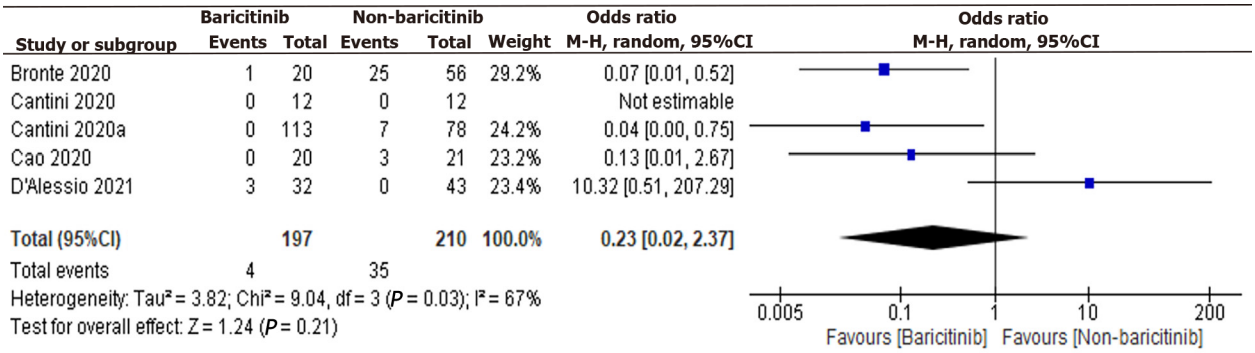
We have analyzed the forest plots of both observational and clinical trials and found that there is a study with high and low sample sizes, particularly in clinical trials. Therefore, analysis was also done again to check the effect of these studies on the outcome. The studies with a high and low sample sizes *i.e.*, Kalil *et al*[12] and Giudice *et al*[22], were excluded, and analysis was done again. The overall estimate was 0.23 [0.02, 2.37], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group (Figure 4). Overall, results were not affected by the studies with high and low sample sizes.

DISCUSSION

The current analysis was done to find out the role of baricitinib in the reduction of deaths of COVID-19 hospitalized patients. To the best of our knowledge, very few meta-analyses have been done so far on the use of baricitinib in COVID-19 treatment. Recently, Chen *et al*[23], have performed a meta-analysis

Table 4 Quality assessment of clinical trials using NIH scale

No.	Ref.	Type of study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality of the study
1	Bronte *et al*[13], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
2	Kalil *et al*[12], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Good
3	Cantini *et al*[17], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
4	Cantini *et al*[18], 2020	Clinical trial	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	Fair
5	Cao *et al*[20], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
6	D'Alessio *et al*[21], 2021	Clinical trial	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
7	Giudice *et al*[22], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	NO	Yes	NR	Good



DOI: 10.13105/wjma.v11.i2.125

Figure 4 Forest Plot showing overall estimate measure of clinical trials as odds ratio after exclusion of studies with high (Kalil *et al*[12], 2020) and low sample size (Giudice *et al*[22], 2020) using random-effect model.

of 11 studies and reported the safety and efficacy of JAK-inhibitors including baricitinib in COVID-19 patients. Another JAK inhibitor *i.e.*, ruxolitinib is also used in hospitalized patients. The meta-analysis results of Wijaya *et al*[24], have demonstrated a significant clinical improvement and decrease in the risk of mortality of COVID-19 patients. The potential of baricitinib in the reduction of deaths of hospitalized COVID 19 patients is also indicated by a meta-analysis conducted by Walz *et al*[25]. Recently, Putman *et al*[26], have also performed a meta-analysis to find out the efficacy of anti-rheumatoid therapy, including baricitinib and steroids for the treatment of COVID-19. However, number of available studies regarding the use of baricitinib in COVID-19 patients at that time was very less. The already published meta-analysis have also analyzed different design of studies together which make less valid conclusion. In the current meta-analysis, we have analyzed observational and clinical trials separately. However, the results of both observational and clinical trials have shown the non-significant deaths of COVID-19 hospitalized patients in the baricitinib group as compared to non-baricitinib group. Further, the sensitivity analysis results have also shown no effect of outliers on the outcome.

CONCLUSION

In conclusion, more research is needed to draw a valid conclusion about the use of baricitinib in the reduction of COVID-19 patient deaths.

ARTICLE HIGHLIGHTS

Research background

More research is needed to draw a valid conclusion about the use of baricitinib in the reduction of coronavirus disease 2019 (COVID-19) patient deaths.

Research motivation
More research is needed to confirm the role of baricitinib in COVID-19 patient deaths.

Research objectives
A total of 11 studies (4 observational and 7 clinical trials) were found relevant for analysis. The overall estimate measure in terms of odds ratio for observational studies was 0.42 [0.11, 1.67], whereas for clinical trials it was 0.37 [0.09, 1.46], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group. The degree of heterogeneity among studies was also discovered to be high.

Research methods
The study was conducted as per the PRISMA guideline using RevMan 5 software.

Research results
To investigate the role of baricitininb in the reduction of COVID-19 patient deaths.

Research conclusions
Can baricitinib reduce the deaths of COVID-19 patients?

Research perspectives
Emerging reports have indicated the use of baricitinib in hospitalized COVID-19 patients. However, the use of baricitinib in COVID-19 patients is unclear so far.

ACKNOWLEDGEMENTS

The authors are thankful to Vice-Chancellor, Prof. R.K. Goyal, Delhi Pharmaceutical Sciences & Research University, New Delhi, and Director, National Institute of Pharmaceutical Education and Research, Raebareli, India for their constant encouragement, motivation, and provision of the necessary resources to carry out this work.

FOOTNOTES

Author contributions: Thakur M and Babu A contributed to searching and selection of studies, extraction of data; Khatik GL, Datusalia AK, and Khatri R contributed to cross verification of data; Khatik GL contributed to first draft of the manuscript; Datusalia AK and Khatri R contributed to revision; Kumar A contributed to design, analysis and final rthe evision of manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: India

ORCID number: Anoop Kumar 0000-0002-7806-9986.

S-Editor: Liu JH
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus:

implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: 32007145 DOI: 10.1016/S0140-6736(20)30251-8]

2 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

3 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]

4 **Backer JA**, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. *Euro Surveill* 2020; **25** [PMID: 32046819 DOI: 10.2807/1560-7917.ES.2020.25.5.2000062]

5 **Lam TT**, Jia N, Zhang YW, Shum MH, Jiang JF, Zhu HC, Tong YG, Shi YX, Ni XB, Liao YS, Li WJ, Jiang BG, Wei W, Yuan TT, Zheng K, Cui XM, Li J, Pei GQ, Qiang X, Cheung WY, Li LF, Sun FF, Qin S, Huang JC, Leung GM, Holmes EC, Hu YL, Guan Y, Cao WC. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* 2020; **583**: 282-285 [PMID: 32218527 DOI: 10.1038/s41586-020-2169-0]

6 **Mehta P**, Ciurtin C, Scully M, Levi M, Chambers RC. JAK inhibitors in COVID-19: the need for vigilance regarding increased inherent thrombotic risk. *Eur Respir J* 2020; **56** [PMID: 32631841 DOI: 10.1183/13993003.01919-2020]

7 **Spinelli FR**, Conti F, Gadina M. HiJAKing SARS-CoV-2? *Sci Immunol* 2020; **5** [PMID: 32385052 DOI: 10.1126/sciimmunol.abc5367]

8 **Napolitano M**, Fabbrocini G, Patruno C. Reply: Potential role of Janus kinase inhibitors in COVID-19. *J Am Acad Dermatol* 2020; **83**: e65 [PMID: 32339701 DOI: 10.1016/j.jaad.2020.04.098]

9 **Srivastava R**, Kumar A. Use of aspirin in reduction of mortality of COVID-19 patients: A meta-analysis. *Int J Clin Pract* 2021; **75**: e14515 [PMID: 34118111 DOI: 10.1111/ijcp.14515]

10 **Thakur M**, Datusalia AK, Kumar A. Use of steroids in COVID-19 patients: A meta-analysis. *Eur J Pharmacol* 2022; **914**: 174579 [PMID: 34678244 DOI: 10.1016/j.ejphar.2021.174579]

11 **Sharma R**, Kumar A, Majeed J, Thakur AK, Aggarwal G. Drugs acting on the renin-angiotensin-aldosterone system (RAAS) and deaths of COVID-19 patients: a systematic review and meta-analysis of observational studies. *Egypt Heart J* 2022; **74**: 64 [PMID: 36068392 DOI: 10.1186/s43044-022-00303-8]

12 **Kalil AC**, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, Ruiz-Palacios GM, Hsieh L, Kline S, Tapson V, Iovine NM, Jain MK, Sweeney DA, El Sahly HM, Branche AR, Regalado Pineda J, Lye DC, Sandkovsky U, Luetkemeyer AF, Cohen SH, Finberg RW, Jackson PEH, Taiwo B, Paules CI, Arguinchona H, Erdmann N, Ahuja N, Frank M, Oh MD, Kim ES, Tan SY, Mularski RA, Nielsen H, Ponce PO, Taylor BS, Larson L, Rouphael NG, Saklawi Y, Cantos VD, Ko ER, Engemann JJ, Amin AN, Watanabe M, Billings J, Elie MC, Davey RT, Burgess TH, Ferreira J, Green M, Makowski M, Cardoso A, de Bono S, Bonnett T, Proschan M, Deye GA, Dempsey W, Nayak SU, Dodd LE, Beigel JH; ACTT-2 Study Group Members. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med* 2021; **384**: 795-807 [PMID: 33306283 DOI: 10.1056/NEJMoa2031994]

13 **Bronte V**, Ugel S, Tinazzi E, Vella A, De Sanctis F, Canè S, Batani V, Trovato R, Fiore A, Petrova V, Hofer F, Barouni RM, Musiu C, Caligola S, Pinton L, Torroni L, Polati E, Donadello K, Friso S, Pizzolo F, Iezzi M, Facciotti F, Pelicci PG, Righetti D, Bazzoni P, Rampudda M, Comel A, Mosaner W, Lunardi C, Olivieri O. Baricitinib restrains the immune dysregulation in patients with severe COVID-19. *J Clin Invest* 2020; **130**: 6409-6416 [PMID: 32809969 DOI: 10.1172/JCI141772]

14 **Hasan MJ**, Rabbani R, Anam AM, Huq SMR, Polash MMI, Nessa SST, Bachar SC. Impact of high dose of baricitinib in severe COVID-19 pneumonia: a prospective cohort study in Bangladesh. *BMC Infect Dis* 2021; **21**: 427 [PMID: 33962573 DOI: 10.1186/s12879-021-06119-2]

15 **Stebbing J**, Sánchez Nievas G, Falcone M, Youhanna S, Richardson P, Ottaviani S, Shen JX, Sommerauer C, Tiseo G, Ghiadoni L, Virdis A, Monzani F, Rizos LR, Forfori F, Avendaño Céspedes A, De Marco S, Carrozzi L, Lena F, Sánchez-Jurado PM, Lacerenza LG, Cesira N, Caldevilla Bernardo D, Perrella A, Niccoli L, Méndez LS, Matarrese D, Goletti D, Tan YJ, Monteil V, Dranitsaris G, Cantini F, Farcomeni A, Dutta S, Burley SK, Zhang H, Pistello M, Li W, Romero MM, Andrés Pretel F, Simón-Talero RS, García-Molina R, Kutter C, Felce JH, Nizami ZF, Miklosi AG, Penninger JM, Menichetti F, Mirazimi A, Abizanda P, Lauschke VM. JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality. *Sci Adv* 2021; **7** [PMID: 33187978 DOI: 10.1126/sciadv.abe4724]

16 **Rodriguez-Garcia JL**, Sanchez-Nievas G, Arevalo-Serrano J, Garcia-Gomez C, Jimenez-Vizuete JM, Martinez-Alfaro E. Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study. *Rheumatology (Oxford)* 2021; **60**: 399-407 [PMID: 33020836 DOI: 10.1093/rheumatology/keaa587]

17 **Cantini F**, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. *J Infect* 2020; **81**: 318-356 [PMID: 32333918 DOI: 10.1016/j.jinf.2020.04.017]

18 **Cantini F**, Niccoli L, Nannini C, Matarrese D, Natale MED, Lotti P, Aquilini D, Landini G, Cimolato B, Pietro MAD, Trezzi M, Stobbione P, Frausini G, Navarra A, Nicastri E, Sotgiu G, Goletti D. Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study. *J Infect* 2020; **81**: 647-679 [PMID: 32592703 DOI: 10.1016/j.jinf.2020.06.052]

19 **Rosas J**, Liaño FP, Cantó ML, Barea JMC, Beser AR, Rabasa JTA, Adsuar FM, Auli BV, López IF, Sainz AMG, Ramis PE, Pérez LR, Rebollo MLN, Lorido RH, Escolar LG; COVID19-HMB Group. Experience With the Use of Baricitinib and Tocilizumab Monotherapy or Combined, in Patients With Interstitial Pneumonia Secondary to Coronavirus COVID19: A Real-World Study. *Reumatol Clin (Engl Ed)* 2020; **18**: 150-156 [PMID: 33358361 DOI: 10.1016/j.reuma.2020.10.009]

20 **Cao Y**, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Wang N, Zhou X, Luo H, Mao Z, Chen X, Xie J, Liu J, Cheng H, Zhao J, Huang G, Wang W, Zhou J. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19):

A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020; **146**: 137-146.e3 [PMID: 32470486 DOI: 10.1016/j.jaci.2020.05.019]

21 **D'Alessio A**, Del Poggio P, Bracchi F, Cesana G, Sertori N, Di Mauro D, Fargnoli A, Motta M, Giussani C, Moro P, Vitale G, Giacomini M, Borra G. Low-dose ruxolitinib plus steroid in severe SARS-CoV-2 pneumonia. *Leukemia* 2021; **35**: 635-638 [PMID: 33173161 DOI: 10.1038/s41375-020-01087-z]

22 **Giudice V**, Pagliano P, Vatrella A, Masullo A, Poto S, Polverino BM, Gammaldi R, Maglio A, Sellitto C, Vitale C, Serio B, Cuffa B, Borrelli A, Vecchione C, Filippelli A, Selleri C. Combination of Ruxolitinib and Eculizumab for Treatment of Severe SARS-CoV-2-Related Acute Respiratory Distress Syndrome: A Controlled Study. *Front Pharmacol* 2020; **11**: 857 [PMID: 32581810 DOI: 10.3389/fphar.2020.00857]

23 **Chen CX**, Wang JJ, Li H, Yuan LT, Gale RP, Liang Y. JAK-inhibitors for coronavirus disease-2019 (COVID-19): a meta-analysis. *Leukemia* 2021; **35**: 2616-2620 [PMID: 33990684 DOI: 10.1038/s41375-021-01266-6]

24 **Wijaya I**, Andhika R, Huang I, Purwiga A, Budiman KY, Bashari MH, Reniarti L, Roesli RMA. The use of Janus Kinase inhibitors in hospitalized patients with COVID-19: Systematic review and meta-analysis. *Clin Epidemiol Glob Health* 2021; **11**: 100755 [PMID: 33969237 DOI: 10.1016/j.cegh.2021.100755]

25 **Walz L**, Cohen AJ, Rebaza AP, Vanchieri J, Slade MD, Dela Cruz CS, Sharma L. JAK-inhibitor and type I interferon ability to produce favorable clinical outcomes in COVID-19 patients: a systematic review and meta-analysis. *BMC Infect Dis* 2021; **21**: 47 [PMID: 33430799 DOI: 10.1186/s12879-020-05730-z]

26 **Putman M**, Chock YPE, Tam H, Kim AHJ, Sattui SE, Berenbaum F, Danila MI, Korsten P, Sanchez-Alvarez C, Sparks JA, Coates LC, Palmerlee C, Peirce A, Jayatilleke A, Johnson SR, Kilian A, Liew J, Prokop LJ, Murad MH, Grainger R, Wallace ZS, Duarte-García A; COVID-19 Global Rheumatology Alliance. Antirheumatic Disease Therapies for the Treatment of COVID-19: A Systematic Review and Meta-Analysis. *Arthritis Rheumatol* 2021; **73**: 36-47 [PMID: 32741139 DOI: 10.1002/art.41469]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com