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Geoepidemiologic variation in outcomes of primary sclerosing cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic, progressive, hepatobiliary disease characterized by inflammation and fibrosis of the intra- and extra-hepatic bile ducts. Its natural history is one that generally progresses towards cirrhosis, liver failure, cholangiocarcinoma, and ultimately disease-related death, with a median liver transplantation-free survival time of approximately 15-20 years. However, despite its lethal nature, PSC remains a heterogeneous disease with significant variability in outcomes amongst different regions of the world. There are also many regions where the outcomes of PSC have not been studied, limiting the overall understanding of this disease worldwide. In this review, we present the geoepidemiologic variations in outcomes of PSC, with a focus on survival pre- and post-liver transplantation as well as the concurrence of inflammatory bowel disease and hepatobiliary neoplasia.

Key words: Cholangiocarcinoma; Inflammatory bowel disease; Liver transplantation; Geography; Biliary tract; Autoimmune

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Core tip: There appears to be considerable geoepidemiologic variation in the outcomes of primary sclerosing cholangitis (PSC). Median liver transplantation-free survival in adults with PSC ranges from 14 to 21 years, depending on geographic region. Post-liver transplantation survival for PSC in North America and Europe appears to be nearly twice

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that found in Asia. The overall average risk of cholangiocarcinoma among patients with PSC is approximately 400 times that of the general population, occurring in roughly 7%-9% of all patients with PSC. However, these rates vary from region to region, with East Asia having rates roughly three-times higher compared to other regions. Studies from North America, Europe, and Oceania generally report worse clinical outcomes for patients with PSC-inflammatory bowel disease compared to patients with only PSC or inflammatory bowel disease; however, this association is less prominent in studies from Asia.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease of unclear etiopathogenesis with a wide spectrum of presentations^[1]. The natural history of PSC is one that generally progresses to cirrhosis, liver failure, and death^[2-5]. PSC most often affects males in the fourth decade of life, though males as well as females of all ages may be affected. It is also strongly associated with inflammatory bowel disease (IBD)^[6-8]. Though a rare disease, PSC is the fifth leading indication for liver transplantation (LT) in the United States and a major indication in other countries^[1,3-5]. Moreover, no medical therapy has been shown to significantly delay PSC progression; indeed, it has been suggested that PSC treatments are one of the greatest unmet needs in hepatology^[9,10].

Despite the global incidence of PSC, outcomes data are lacking from certain regions of the world. Additionally, few studies have looked at the specific subset of patients with PSC and concurrent IBD (PSC-IBD) with respect to the frequency of their concurrence and the impact on disease-related outcomes. To this end, we queried the PubMed and EMBASE databases on PSC and PSC-IBD related outcomes and abstracted the available relevant data. Based on our findings, we herein review the geoepidemiologic variation in the outcomes of PSC, focusing particularly on LT-free, overall, and post-LT survival, as well as the concurrence of PSC with IBD, and the association of PSC with hepatobiliary and other malignancies.

OUTCOMES IN PRIMARY SCLEROSING CHOLANGITIS

Geographic variations in survival

Survival in patients with PSC is highly variable with patient demographics and disease severity playing a large role in this variation. Global LT-free survival (survival free of liver-related death or LT) and global overall survival (OS) among patients with PSC has recently been reported to be 15-20 years from time of diagnosis, though significant variation exists (Table 1). Historically, European and North American studies have reported a median time from diagnosis to death or LT of 10 to 12 years^[1,8,11,12]. Recent studies have suggested longer survival times, though this may be due to the fact that until recently, there have only been a small number of outcomes-based studies examining survival in PSC^[6,11-14]. Technological advances in LT may also play a role in the metric of LT-free survival (as higher frequencies of LT and/or LT performed at younger ages can decrease LT-free survival). In Europe, Asia, and Oceania, median LT-free survival time appears to be 20 years or more^[1,15,16]. However, this statistic does not provide a complete picture. In a Netherlands-based study, Boonstra *et al*^[1] reported the median LT-free survival for all patients with PSC to be 21.3 years^[1]. However, median LT-free survival of the subset of patients with PSC treated at LT centers was only 13.2 years^[1]. In a Japan-based study, Kumagai *et al*^[17] noted a median LT-free survival and OS of 18 years, though these patients were recruited from a LT center. Median LT-free survival and OS in some regions, such as Israel, even reach as high as 23.5 and 26.3 years, respectively^[16]. Indeed, survival among patients with PSC may be increasing, but major confounding factors such as availability of LTs, patient criteria for LTs, as well as competing survival risks and

variable ages at disease presentation may disproportionately influence apparent LT-free survival in various regions. Furthermore, few if any studies have been performed in Central and South America, Africa, and much of Asia; thus, trends and comparisons of survival in these regions cannot be accurately performed at this time (Figure 1).

Overall, patients with PSC have a three- to four-fold increased risk of all-cause mortality compared to the general population^[1,18-20]. Across reported regions, the leading causes of death among patients with PSC are cholangiocarcinoma (CCA), liver failure, LT-related complications, and colorectal cancer^[1,8,21-23]. In Asia, liver dysfunction is reported as the most common cause of death in patients with PSC (40%-70%), whereas in Europe and North America the plurality (40%-50%) of PSC-related deaths are due to cancer^[16,17,24,25].

Variations in post-liver transplant survival

LT is the treatment of choice for patients with advanced PSC-related hepatobiliary disease. Current practice guidelines support referral for LT when patients develop a Model for End-stage Liver Disease score of 15 or greater, a Child-Pugh-Turcotte classification of C, or when LT may significantly improve quality of life, such as in the case of intractable pruritis^[22,26-29]. However, data regarding time to LT are often difficult to compare between populations because: (1) Studies at referral centers generally have patients with more severe disease, and thus may be more likely to receive a LT (Berkson's bias); and (2) Patients living in countries/regions with greater health care access may be more likely to receive LTs. For example, the increased availability of LT centers in Europe and North America has significantly altered clinical outcomes such that nearly 50% of patients with PSC treated in these countries receive LTs^[30]. In contrast, only approximately 4%-12% of patients in Asian countries receive LTs^[17,31]. A major reason for this is that certain countries, such as Japan, have significant shortages of brain death donors and thus rely heavily on living donor LTs^[17].

Various European and American studies have reported 1, 3, 5 and 10-year post-LT survival rates in the 70% to 90% range; however, post-LT survival in Asia appears lower with 5 and 10 year post-LT survival rates in the range of 55% to 75%^[22,31-38]. Regional differences in post-LT survival may, in part, be due to overall greater clinical experience with LTs in Europe and North America or variations in patient selection criteria across regions. However, other factors may also play a role. Genetic differences, such as human leukocyte antigen profiles, have been associated with LT success rates, and the genetic underpinnings of PSC may help to explain some of the observed differences^[32,39]. One North American study explored the risk of LT listing among patients with PSC and identified significantly different HLA associations among various ethnic groups. In particular, European Americans and Hispanics with PSC listed for LT had similar HLA profiles, but African Americans displayed a different HLA profile^[40]. In addition, African Americans were more likely to have severe PSC-related disease than other ethnic groups in this study independent of socioeconomic factors, suggesting that genetics may contribute to PSC phenotype^[40]. Unfortunately, linkage disequilibrium patterns, associations with HLA-DRB1, HLA-B, and other non-HLA genes as well as varying nomenclature and typing methodologies across regions over time currently preclude the clinical utility of PSC genotyping^[41]. Of note, limited data on post-LT survival in pediatric patients with PSC are available; one North American study reported the 5-year LT-free survival among children with PSC to be 78%^[42].

Geographic variations in post-transplant PSC recurrence

Approximately 20%-25% of patients with PSC experience disease recurrence post-LT, though this rate varies by cohort^[43]. Recurrent PSC (rPSC) carries the potential need for re-LT and increased risk of mortality. The etiology of rPSC is unknown, but various studies have attempted to identify possible risk factors for recurrent disease. Across regions, pre-LT colectomy has been associated with reduced risk of rPSC, whereas increased age, presence of IBD, increased Model for End-stage Liver Disease score, acute cellular rejection, and pre-LT CCA have been associated with increased risk of rPSC^[43]. Time-to-recurrence post-LT also appears to be similar across regions with a median time to recurrence of 5.1 years and a range spanning a few months to multiple decades^[43]. Of note, among studies examining rPSC, the median age at LT appears to be younger in Asian studies compared with the global average (approximately 33 years *vs* 45 years, respectively)^[32,36,43,44]. However, as stated previously, most of these data come from European and North American LT centers, possibly limiting prognostication to other regions. Analyses of LT-free survival, OS, and time to LT were conducted using weighted averages of studies from each reported geographic region (Table 1).

Table 1 Overall and regional primary sclerosing cholangitis clinical outcomes in terms of overall survival (measured in years) and incidence of cholangiocarcinoma

Region	Studies (n)	Total patients (n)	Age at diagnosis (yr)	PSC-IBD co-incidence (%)	Transplant free survival (yr)	Overall survival (yr)	Time to LT (yr)	Annual incidence CCA ¹
Africa	0	0	-	-	-	-	-	-
Asia	9	711	39	39%	20.8	23.6	3.5	1503
Europe	18	3993	35	74%	17.3	14.8	4.9	303
North America	14	1155	31	66%	14.5	13.8	3	642
South America	1	21	7	24%	-	-	-	433
Oceania	4	416	47	79%	23.3	10	8	439
International	1	7121	39	73%	14.5	-	-	-
Overall	47	13417	37	71%	15.9	15.3	4.6	500

¹Among PSC per 100000. PSC: Primary sclerosing cholangitis; IBD: Inflammatory bowel disease; CCA: Cholangiocarcinoma; LT: Liver transplantation.

PRIMARY SCLEROSING CHOLANGITIS AND INFLAMMATORY BOWEL DISEASE

Geographic variations in PSC-IBD

Long-established associations and complex interactions exist between PSC and IBD. The PSC-IBD phenotype is distinct with outcomes different from those seen in PSC or IBD alone. Moreover, geographic variations may exist in the PSC-IBD phenotype. In particular, studies from Oceania have noted patients with PSC-IBD to be at an increased risk of death and increased risk of gastrointestinal or hepatobiliary malignancies than patients with PSC alone^[45,46]. In contrast, multiple studies from Asia have not identified significant differences in these outcome measures between patients with PSC-IBD and PSC alone^[16,17]. A study from Iran even noted favorable outcomes for patients with PSC-UC relative to those with UC alone^[47]. However, there are also studies from Asia suggesting worse outcomes in PSC-IBD; one study from South Korea found an increased risk of colorectal neoplasia and a trend towards increased mortality in patients with PSC-UC compared to those with UC alone^[48]. Studies from North America generally report worse outcomes for patients with the PSC-IBD phenotype, with most studies suggesting a significantly increased risk of neoplastic disease, rPSC, and potentially earlier onset of rPSC post-LT^[49-54]. Studies from Europe appear to have similar findings to that of North America; patients with PSC-IBD appear to have an increased risk of neoplastic disease, particularly colorectal dysplasia, compared to patients with either PSC or IBD alone^[1,55]. However, European studies generally have not identified significant survival differences between patients with PSC-IBD and PSC alone^[11,55,56].

Differences concerning age at presentation of PSC and PSC-IBD appear to remain highly variable. Multiple studies from various regions have noted that patients with PSC-IBD present at an earlier age than patients with PSC alone, but there are also studies in similar regions that have not identified significant age differences^[11,16,17,45,46,49]. Whether this is due to IBD-related symptomatology leading to an earlier age of diagnosis and thus lead-time bias or if the PSC-IBD phenotype itself tends to present at an earlier age is unclear^[57].

PSC-IBD concurrence rates appear to vary between regions. Roughly 65% of patients with PSC in Western countries have concurrent IBD, whereas only 30% of patients with PSC in East Asian countries have concurrent IBD^[8,17,58,59]. Interestingly, among patients with PSC-IBD in Europe and East Asian countries, the concurrence of PSC-UC was similar at approximately 80%^[8,17,58,59]. However, studies from Central Asia and the Middle East have more variable results. Generally, PSC-IBD concurrence rates in these regions are reported as similar to those in Europe, but PSC-UC concurrence rates are much lower, often under 60%^[16,60,61]. Lastly, some regions, such as central and southern Europe, Alaska, and northern Canada have identified either very low or even no concurrence of PSC with IBD^[62-64].

Figure 1 Locations of all studies reporting liver transplantation-free and overall survival in primary sclerosing cholangitis.

PRIMARY SCLEROSING CHOLANGITIS AND NEOPLASIA

Geographic associations with cholangiocarcinoma

PSC is a major risk factor for the development of CCA. The risk of CCA among patients with PSC is roughly 400 times that of the general population^[4]. The global annual incidence of CCA is approximately 500 per 100000 patients with PSC, or 0.5% annually (Table 1).

The annual incidence of CCA among adult and pediatric patients with PSC is roughly 7%-9% across populations, though estimates in North America vary greatly, with reported incidences as low as 4% and as high as 20%^[1,11,42,65-67]. The highest annual incidence of CCA is in Asia, with incidences as high as three times the global average; the reason for this elevated incidence is unknown (Table 1)^[16,35,60,68,69]. Interestingly, the highest non-PSC related rates of CCA are also seen in Asia, suggesting another variable (*e.g.*, parasitic infections and chronic viral hepatitis) may be playing a role in the high rate of CCA^[70].

Data regarding duration of PSC and risk of CCA are variable, with several studies suggesting PSC increases the risk of CCA over time while other studies have not found the same association^[4,65]. This may be due to the fact that the presence of CCA in patients with PSC is often occult (with at least 10% of patients with PSC having “silent” CCA for significant lengths of time), thus the true time to development of carcinoma is unclear^[71]. Interestingly, both duration of IBD among PSC-IBD patients and colorectal neoplasia (CRN) among PSC-UC patients increase the risk of CCA development^[72].

Geographic associations with colorectal neoplasia

IBD confers an increased risk of CRN and PSC-IBD further increases the risk of CRN above that of IBD alone^[55]. Of note, some studies have reported an increased risk of CRN among PSC-UC patients compared to UC patients but not among PSC-IBD patients relative to IBD patients, implying a specific disease interaction between PSC and UC^[72-75].

While regional differences in PSC-IBD associated CRN are difficult to ascertain, it is known that post-LT colorectal neoplasia is of particular concern in patients with PSC and PSC-IBD^[22]. Among post-LT PSC-IBD patients, the risk of CRN rises by approximately 1% per year post-LT^[22,76]. As such, it is possible that rates of CRN among PSC-IBD patients may be greater in European and North American countries owing to the increased frequency of LT in these regions, though there is little evidence to support this directly. Annual endoscopic monitoring is considered standard of care among PSC-IBD patients^[77].

LIMITATIONS

Geographic reporting of PSC-related outcomes is heterogenous, with the majority of studies coming from Europe and North America, a limited number of studies from Asia and Oceania, and very few studies from South America and Africa, hence

summary estimates were not amenable to meta-analysis. Moreover, the reporting of results differs even within similar regions, making comparisons challenging. For example, within one region, one study may report LT-free survival while another study may report OS, limiting the ability to make comparisons. Additionally, PSC case identification, outcomes, and other factors may have changed over time. Therefore, when comparing studies from one region to another we may be comparing them not only based on where the studies took place, but when they took place, potentially confounding results. Lastly, our search was limited to studies available in English, which may have left out studies from non-English speaking regions.

CONCLUSION

Studies on global PSC-related outcomes have increased over the years allowing for novel analyses of regional differences. Causes of PSC-related death vary globally, with liver dysfunction being the primary cause of PSC-related death in Asia, and cancer being the primary cause in both Europe and North America. Although notably, there is a significantly greater rate of CCA in East Asia than the rest of the world. Interestingly, PSC-IBD concurrence rates vary across regions, yet the proportions of PSC-IBD subtypes are largely consistent across regions. Likewise, PSC-IBD related outcomes appear largely consistent across regions. As most studies of PSC have been conducted in the United States and Western European countries, with a paucity of data from other regions, the need for large population-based studies in under-reported regions is imperative to better understand global and regional PSC-related outcomes.

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Liver injury induced by paracetamol and challenges associated with intentional and unintentional use

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Abstract

Drug induced liver injury (DILI) is a common cause of acute liver injury. Paracetamol, also known as acetaminophen, is a widely used anti-pyretic that has long been established to cause liver toxicity once above therapeutic levels. Hepatotoxicity from paracetamol overdose, whether intentional or non-intentional, is the most common cause of DILI in the United States and remains a global issue. Given the increased prevalence of combination medications in the form of pain relievers and antihistamines, paracetamol can be difficult to identify and remains a significant cause of acute hepatotoxicity, as evidenced by its contribution to over half of all acute liver failure cases in the United States. This is especially concerning given that, when co-ingested with other medications, the rise in serum paracetamol levels may be delayed past the 4-hour post-ingestion mark that is currently used to determine patients that require medical therapy. This review serves to describe the clinical and pathophysiologic features of hepatotoxicity secondary to paracetamol and provide an update on current available knowledge and treatment options.

Key words: Paracetamol; Drug-induced liver injury; Hepatotoxicity; Acute liver failure

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Core tip: Paracetamol is a widely used anti-pyretic that has long been established to cause liver toxicity once above therapeutic levels. Given the increased prevalence of combination medications in the form of pain relievers and antihistamines, paracetamol can be difficult to identify and remains a significant cause of acute hepatotoxicity globally. This is especially concerning given that, when co-ingested with other medications, the rise in serum paracetamol levels may be delayed and alter medical management. This review serves to describe the clinical and pathophysiologic features of

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INTRODUCTION

Acute liver failure consists of severe liver dysfunction, as evidenced by coagulopathy, jaundice, and encephalopathy, usually in the absence of underlying liver disease^[1]. The incidence of acute liver failure (also termed fulminant hepatic failure) is roughly 10 per one million people annually in developed countries^[1] with over 2000 cases in the United States diagnosed each year^[2]. While viral hepatitis is among the most common cause of acute liver failure worldwide^[1], drug-induced liver injury (DILI) is another culprit of liver damage. Half of all cases of acute liver injury in the United States result from DILI^[3]. Paracetamol, also known as acetaminophen, is a widely used anti-pyretic that has known liver toxicity once above therapeutic levels in the blood^[4]. In fact, paracetamol is the most common cause of DILI in the United States^[5]. Given its ease of access as an over-the-counter medication, the United States Food and Drug Administration had stated it is safe to consume up to a maximum dose of 4000 mg within 24 h^[6,7] while experts recommend a dose of 2000 mg or less in patients with existing liver disease or with chronic alcohol use^[8-10]. Alternatively, dosing guidelines from drug inserts in European countries recommends maximum of a 3000 mg of paracetamol in older adults either < 50 kg or in those > 50 kg with additional risk factors for hepatotoxicity^[11,12]. However, toxicity from paracetamol has recently become more challenging to rapidly identify given the increased use of combination medications, such as over-the-counter cold medicine or prescription pain relievers, that also contain paracetamol. In addition, toxic ingestions with these medications or in combination with alcohol may have a delayed presentation of hepatotoxicity^[13-15]. Previously, only limited data on the mechanism and outlook of patients with acute liver injury existed. Because acute liver failure was poorly studied and understood, centralized data registries, such as the United States Acute Liver Failure Study Group, were formed to improve detection and patient outcomes. Additionally, the United States Drug-Induced Liver Injury Network was formed with the goal of creating a centralized registry for all acute liver failure cases that result from the use of prescriptions, over-the-counters, and herbal medications^[16]. Our aim is to describe the clinical and pathophysiologic features of hepatotoxicity secondary to paracetamol and provide an update on current available knowledge and treatment options.

PATHOPHYSIOLOGY

Paracetamol was first developed in 1878 from phenacetin and became widespread in the 1950s as an over-the-counter antipyretic and analgesic. Since that time, there have been numerous studies connecting paracetamol ingestion with liver injury in a dose-dependent fashion. These effects are compounded in the setting of concomitant alcohol abuse, starvation ketosis or concurrent infections. Hepatocytes metabolize paracetamol *via* microsomal cytochrome P450 (CYP450) into non-toxic byproducts. This metabolism pathway *via* CYP450, specifically cytochrome P450 2E1 (CYP2E1), produces reactive oxygen species^[17], originally thought to be the ultimate cause of liver injury in paracetamol overdose. After recent debunking^[18-20] of that long-standing belief, mitochondrial dysfunction has instead been attributed as the main source of free radicals and oxidative stress in paracetamol hepatotoxicity^[21]. Mitochondrial dysfunction begins with the formation of drug-protein adducts between the reactive paracetamol metabolite, N-acetyl-p-benzoquinone imine (NAPQI), and mitochondrial proteins involved in the electron transport chain^[22,23]. Additionally, increased activity of mitochondrial complex I, a known site of free radical generation^[24], occurs with paracetamol overdose, and the level of activity was found to correlate with the degree of liver injury^[23]. Oxidative stress induced by paracetamol overdose is mainly attributed to mitochondrial superoxide and peroxynitrite^[24]. The superoxide reacts

with nitric oxide to form the highly reactive peroxynitrite species that is main source of oxidative and nitrosative stress^[24].

Paracetamol has high bioavailability, with almost 80% of the drug being absorbed when taken orally^[25]. In individuals without liver injury, the half-life of paracetamol is roughly 2-3 h^[26]. At therapeutic levels in the blood, approximately 90% of paracetamol is broken down into non-toxic metabolites through sulfidation and glucuronidation pathways and then renally excreted^[27]. However, at overdose levels, these pathways become saturated, resulting in large amounts of paracetamol being converted by CYP450 into its toxic metabolite, NAPQI^[28]. NAPQI is subsequently excreted after glutathione conjugation renders it to harmless metabolites, as shown in **Figure 1**. Glutathione peroxidase activity is reduced by 60% in the setting of paracetamol^[29]. This is dose-dependent, with larger amounts of paracetamol resulting in prolonged depletion of glutathione^[21]. This reduction of glutathione in the mitochondria and cell cytosol results in decreased excretion of reactive oxygen species and peroxynitrite^[30]. Additionally, without glutathione, oxidative stress activates the opening of mitochondrial permeability transition pores that results in the destruction of the membrane potential and halts ATP synthesis^[21,30]. Ultimately, this results in the breakdown of DNA and cell membranes and the induction of apoptosis, resulting in cell death and acute inflammation^[30].

CLINICAL PRESENTATION

In the United States, paracetamol is the one of the most widely used over-the-counter analgesics. According to the Third National Health and Nutrition Examination Survey from 1988-1994, 36% of Americans reported using acetaminophen within a month timeframe^[31]. Due to its ease of access and availability in combination with other medications, such as opioids and antihistamines, paracetamol overdose can be accidental or in a suicide attempt. A thorough history and early recognition is key since long delays to the administration of treatment can result in worse outcomes for paracetamol-related hepatotoxicity. Depending on the severity of the liver damage, patients can present with a range of symptoms, from being initially asymptomatic to having overt signs of liver failure, including jaundice, confusion, ascites, nausea and vomiting.

Acute liver failure is defined by the presence of hepatic encephalopathy, jaundice and coagulopathy in individuals without any history of cirrhosis occurring for less than 26 wk^[32]. This includes individuals with Wilson disease, autoimmune hepatitis or viral hepatitis as long as the disease was diagnosed within the last 26 wk^[32]. An exclusion is severe alcoholic hepatitis, as this is likely accompanied with a history of prolonged alcohol abuse, resulting in chronicity of the liver injury.

There are four phases of acute paracetamol toxicity: Preclinical, hepatic injury, hepatic failure, and recovery^[33]. Phase one, or the preclinical phase, occurs shortly after ingestion of toxic levels of paracetamol and can last 12-24 h. Non-specific symptoms such as nausea, vomiting, diaphoresis or lethargy may be seen. One to two days following the ingestion, the second phase begins, as evidenced by hepatotoxicity in laboratory values [elevation in hepatic enzymes, lactate, international normalized ratio (INR)]^[33,34]. Clinically, right upper quadrant abdominal pain may be present. In some cases, liver injury will progress to phase three, typically occurring at days three to five. Here, nausea and vomiting may recur or worsen and are accompanied with fatigue, jaundice, and central nervous system depression, varying from confusion to a coma^[33]. Elevation in liver aminotransferases as high as 10000 IU/L can be seen^[35]. The resultant hepatic necrosis and failure can be fatal and associated with multiorgan failure^[33,34]. Lastly, phase four is recovery with normalization of laboratory values; roughly 70% of patients will fully recover, while 1%-2% will die from hepatic failure^[33]. Death from untreated paracetamol toxicity occurs 4 to 18 days later^[33].

Laboratory findings

Initial laboratory testing in acute liver failure will reveal prolonged prothrombin time, INR greater than 1.5, elevated aminotransferase and bilirubin levels, thrombocytopenia, electrolyte abnormalities, elevated ammonia levels and acid-base disturbances. Typically, aminotransferase levels are in the thousands in cases of paracetamol-induced acute liver failure. Paracetamol levels should always be drawn in acute liver injury cases. Since the time of ingestion is not always known, such as in accidental overdose, absent or low levels of paracetamol should not exclude paracetamol-induced liver injury in those cases where it is suspected. Laboratory variables most indicative of patient outcome were the peak bilirubin and prothrombin time levels with bilirubin directly correlated to survival^[36].

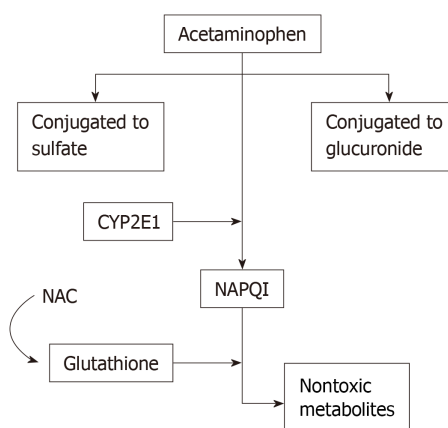


Figure 1 Paracetamol metabolism pathways and breakdown into N-acetyl-p-benzoquinone imine, by cytochrome P450 2E1. N-acetyl-p-benzoquinone imine is the toxic metabolite produced from paracetamol metabolism when the other two conjugation pathways become over-saturated. The resultant toxic N-acetyl-p-benzoquinone imine byproduct is converted into nontoxic metabolites by glutathione, which is regenerated by N-acetylcysteine. NAPQI: N-acetyl-p-benzoquinone imine; CYP2E1: Cytochrome P450 2E1; NAC: N-acetylcysteine.

Liver biopsy is not routinely performed in the diagnosis of acute liver failure as it is associated with a high risk of bleeding and mortality. In addition, in prior studies assessing the role and accuracy of liver biopsy in acute liver failure, the diagnosis changed in 18% of cases; there was no report on whether biopsy information altered the clinical course or treatment^[37]. In fact, the American Gastroenterological Association “suggests against routine use of liver biopsy” in the workup of acute liver failure^[37].

HEPATOTOXICITY RISK FACTORS

The dose of ingestion as well as the time span between ingestion of paracetamol and of the treatment drug N-acetylcysteine (NAC) are the most influential factors in the manifestation and severity of paracetamol hepatotoxicity^[4,38-40]. While acute liver injury can occur when used at or below the recommended daily maximum dose (4000 mg)^[4], paracetamol toxicity is often the result of ingestion of paracetamol over this maximum dose. In fact, the maximum daily dosage has been a topic of controversy, with some manufacturers voluntarily lowering this recommended threshold on their products in order to increase the safety of patients^[41,42].

Beyond exceeding the recommended daily dose, the risk for liver injury increases when paracetamol is used in combination with other drugs and substances, such as alcohol. The interplay between paracetamol and alcohol is an interesting one, because these compounds are competitive substrates for CYP2E1, which reduces the production of the reactive NAPQI species generated in paracetamol metabolism; as a result, acute alcohol ingestion may in fact act as a protective mechanism against paracetamol hepatotoxicity^[43-46]. On the other hand, paracetamol hepatotoxicity is augmented with chronic alcohol consumption through the up-regulation and increased synthesis and activity of CYP2E1 as well as the decreased production of glutathione; these activities result in enhanced liver necrosis and an exacerbated prognosis^[43,46]. While the risk of liver failure may be increased in the case of chronic alcoholism in combination with paracetamol overdose, alcoholism does not necessarily increase the risk of paracetamol hepatotoxicity when in combination with therapeutic doses^[43]. Beyond alcohol, there are various prescribed and over-the-counter medications that can predispose a patient to paracetamol hepatotoxicity, including opioids, anti-tuberculosis drugs^[47], and anti-epileptic drugs as well as herbs and dietary supplements, such as St. John’s wort, garlic and germander, through their effects on CYP450 metabolism (Table 1)^[7].

The risk for paracetamol hepatotoxicity is increased in patients with malnutrition, as glutathione stores are depleted and no longer available for conjugation with the reactive NAPQI species^[48]. Individuals at a particular risk for poor nutritional status include those with chronic alcoholism^[48], and while patients with anorexia nervosa are malnourished and have low glutathione reserves, they also have reduced CYP2E1 activity, which in fact does not exacerbate the risk of paracetamol toxicity in this subset of malnourished patients^[49]. Age also impacts hepatotoxicity risk, with

Table 1 Drugs and substances that affect cytochrome P450 2E1 activity and can interfere with paracetamol metabolism

Cytochrome P450	Inducers	Inhibitors
CYP2E1	Ethanol Isoniazid St. John's wort Garlic, Germander	Disulfiram

CYP2E1: Cytochrome P450 2E1.

advanced age (over 40 years old) being associated with a higher risk of acute liver failure, liver transplantation, and death from paracetamol overdose^[50]. The metabolism of paracetamol appears to be dependent on age^[51], and paracetamol use alone and in combination with opiates is widespread among advanced-age adults for treatment of chronic pain or cancer. Chronic liver disease patients are also at increased risk for hepatotoxicity, as paracetamol metabolism is decreased in patients with cirrhotic livers. While there is no evidence suggesting pregnancy as a predisposing risk factor for paracetamol toxicity^[7], the use of paracetamol during pregnancy should be carefully monitored, since paracetamol is the most common overdose during pregnancy, and toxicity in such cases can result in significant morbidity and mortality for both the fetus and mother^[52].

The aforementioned confounding factors that influence the development and acuteness of liver injury are summarized in the flowchart in [Figure 2](#).

PROGNOSTICATION

While the extent of liver injury has been found to be dose dependent, there are a few possible risk factors for DILI. One study has found that men and younger age was associated with an increased risk in hepatocellular damage^[53]. Traditionally, there are a few scoring systems available to prognosticate those with acute liver failure though none are considered gold standard criteria. The King's College liver failure criteria^[36] uses serum laboratory values to determine the prognosis of DILI and tested these prognostications by retrospectively analyzing those patients that had to undergo liver transplantation. The Roussel Uclaf Causality Assessment Method^[54] is a sensitive test but difficult to perform based on its complicated system. The Roussel Uclaf Causality Assessment Method score is based off of seven measures that include the time of DILI onset, concomitant risk factors or drug use, non-drug related liver injury, the patient's clinical course, prior liver injury toxicity and the response to re-challenge of the drug^[54]. A modification to this is the Digestive Disease Week-Japan scale^[55], which adds the lymphocyte stimulation test. Prior to transplantation, the finding of jaundice in DILI patients was associated with a poor prognosis with over 10% mortality prior to liver transplantation for paracetamol-induced liver injury^[56]. This prognostic finding of hepatocellular injury significant enough to alter bilirubin excretion (with elevations greater than two times the upper limit of normal) is referred to as "Hy's Law Cases"^[56].

Patient outcomes are dependent upon what phase of paracetamol poisoning that treatment is initiated in. If the antidote is given during phase one (in cases where medical history reveals a suspicion of paracetamol overdose), patients are expected to fully recover with only a transient period of liver injury^[57,58]. In fact, the administration of N-acetylcysteine will prevent most patients from progressing past phase two of hepatic injury^[34]. Additionally, the presence of other organ involvement, such as altered mental status or acute renal failure portends a worse prognosis and is often an indication for monitoring the patient in a critical care setting^[59].

TREATMENT

Early initiation of treatment is critical immediately following recognition of DILI. The Rumack-Matthew nomogram is a tool that uses serum paracetamol levels at a specific time point in the overdose, typically measured between 4- and 24-hours post-ingestion, to predict the risk of hepatotoxicity and guide medical management^[60,61]. If the paracetamol level is above a certain cutoff, also called the "treatment line" that

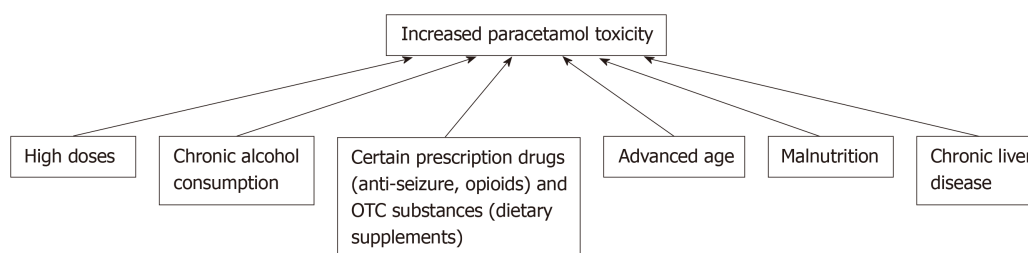


Figure 2 Factors that pre-dispose patients to increased paracetamol toxicity.

typically starts at 150 µg/mL at 4 h and extends to 4.7 µg/mL at 24 h, then treatment is indicated^[62,63] (outlined in Figure 3). If the time of ingestion is unknown but within 24 h, the earliest possible time of ingestion should be estimated and plotted on the nomogram to see if treatment with NAC should be initiated (*i.e.* if above the treatment line). The use of the nomogram should be avoided until 4 h or more after ingestion as the levels may be misleading during this timeframe from the point of acute ingestion and not be an accurate predictor of toxicity^[64,65]. Classically, the nomogram is used in conjunction with the patient's history and laboratory findings to determine medical management. If medication review reveals co-ingestion with opioids or anticholinergic medications, the post-ingestion level should be checked at 4 h and repeated at 6 h post-ingestion if the initial level falls below the treatment line to account for possible delay in maximum serum concentrations of paracetamol^[13]. However, other aspects of the history such as the reported dose in paracetamol toxicity, can be used to predict patient outcomes. A prospective study demonstrated that individuals who had a reported overdose with 50 g of paracetamol had a 90% probability of being over the treatment value cutoff, suggesting that dosing can help rapidly identify individuals that need treatment immediately initiated^[66].

Currently, the mainstay therapy is NAC, given intravenously as soon as the diagnosis of paracetamol hepatotoxicity is made. NAC acts by restoring glutathione levels that then allow for the removal of NAPQI from the body^[67]. Specifically, NAC is hydrolyzed to cysteine, which in turns restores glutathione as well as provides thiol groups that react directly with NAPQI in the hepatocytes^[57,68]. Administration of NAC is the mainstay treatment and standard of care in paracetamol overdose, with the most benefit seen if initiated within the first 8 h from the time of paracetamol overdose^[57,58]. However, it has been shown that mortality is significantly decreased by the administration of NAC even up to 36 h after the toxic ingestion and that this cohort of patients is less likely to progress to grade III/IV hepatic coma after receiving treatment with NAC^[69]. NAC is typically administered intravenously over three weight-based doses: The initial 150 mg/kg dose in the first 15-60 minutes, followed by 50 mg/kg over 4 h, and then 100 mg/kg over 16 h^[60,70]. In cases where NAC is administered orally, the typical dosing regimen is a loading dose of 140 mg/kg, subsequently followed by 70 mg/kg every 4 h until 18 doses are administered^[60,68]. After NAC dosing is complete, re-evaluation of the paracetamol level and liver function tests should be done to assess if repeat dosing is indicated. Dosing of NAC can be continued if the serum paracetamol level is above 10 µg/mL or if alanine aminotransferase (ALT) elevation persists, especially in the setting of acidosis, coagulopathy, acute kidney injury and hyperbilirubinemia as these patients have worse outcomes^[71].

With opioid use being more prevalent, medication interactions that slow gut motility have important implications in paracetamol toxicity. Recent studies have shown that there are limitations to the Rumack-Matthew nomogram in predicting the risk of hepatotoxicity in the setting of combination medications due to a delay in the onset of symptoms and laboratory abnormalities^[13-15]. In particular, paracetamol combined with antihistamines or opioids have been shown to have serum paracetamol levels below 150 µg at the 4-hour post-ingestion mark but would cross above the treatment threshold when levels were rechecked within the 24-hour period^[13]. In fact, a United States prospective cohort study^[14] showed that 6% of patients with an acute combination medication overdose of paracetamol with antihistamines or opioids had paracetamol levels that were initially low at the 4-hour time mark but were later found to be above the 150 µg/mL treatment threshold.

In conjunction with NAC therapy, activated charcoal has been proven to be beneficial in reducing the number of patients that develop toxic serum paracetamol levels^[72] and has been shown to decrease the extent of liver injury, as evidenced through a reduction in serum transaminase levels and prothrombin time^[72,73]. Since the

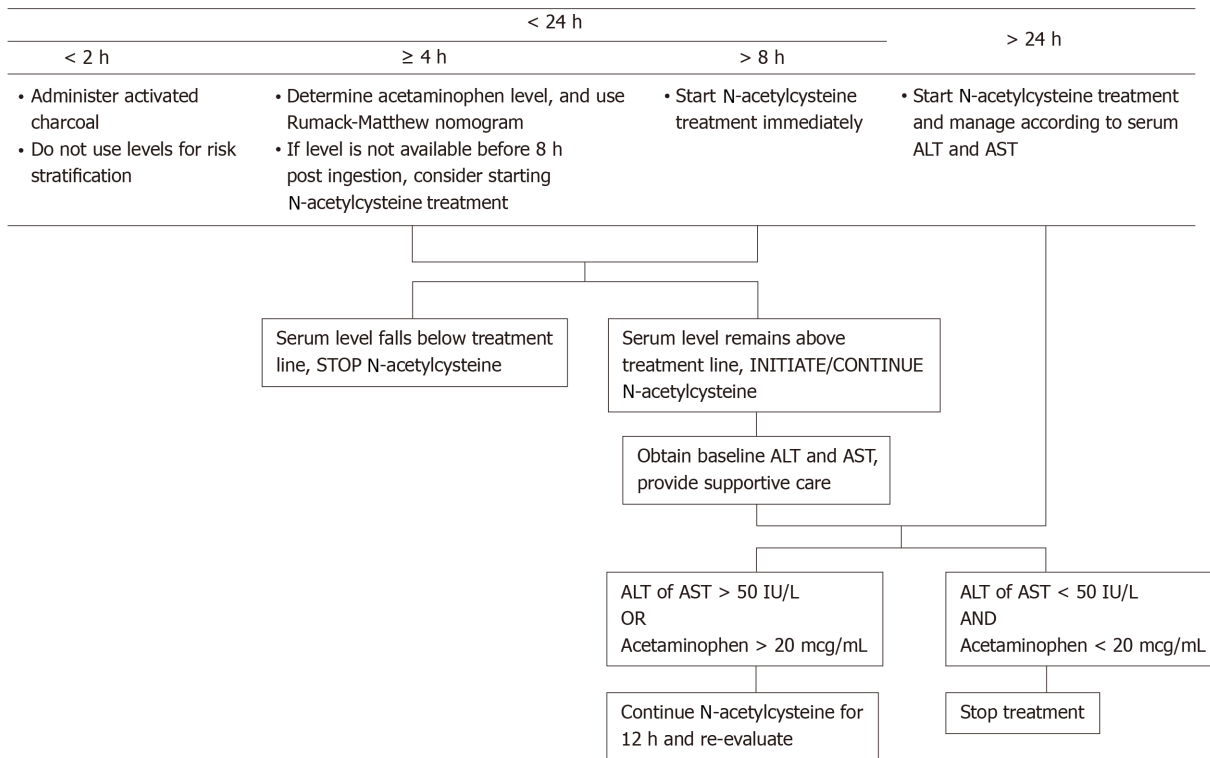


Figure 3 Flowchart depicting the management pathway for acute paracetamol overdose/ toxicity. ALT: Aminotransferase; AST: Aspartate aminotransferase.

majority of paracetamol absorption in the gastrointestinal tract occurs within the first 4 h^[40], activated charcoal is generally believed to be most beneficial if administered within that time period, as its mechanism of action is to interfere with paracetamol absorption. However, activated charcoal has been shown to provide some benefit even with later administration, suggesting an additional mechanism for improvement in hepatotoxicity^[72].

Treatment updates and alternatives

While the mechanism of toxicity in paracetamol overdose is thought to be due to glutathione depletion and subsequent buildup of harmful metabolites as previously mentioned, studies on the repletion of glutathione as a therapy option are few and in early stages but yielded positive results. In one animal study^[74], both free and niosomal (or encapsulated) glutathione administered intravenously had been shown to reduce hepatotoxicity in paracetamol overdose with serum concentration at 150 mg/kg. This promising finding may represent an avenue for treatment in the future after further investigations are performed. An additional novel therapy is N-acetylcysteine amide (NACA), which is a variant of NAC with an amide in place of a carboxyl group, which in turn increases the compound's lipophilicity^[75]. This allows NACA to more easily transverse cell membranes, meaning it is effective at lower doses when compared to NAC and potentially avoid some adverse side effects. NACA's therapeutic benefit is multifactorial: It acts as a precursor to glutathione, promotes intracellular metabolism of toxic compounds and is a free radical scavenger. In this study, NACA was dosed at 106 mg/kg every 12 h for a maximum of up to 72 h. With this dosing regimen, NACA was found to have increased survival in mice as well as improved ability to decrease damage from oxidation and paracetamol^[75].

Additionally, recent research has explored the effectiveness of lower doses of NAC in the treatment of hepatotoxicity from paracetamol overdose. The study by Shen *et al*^[76] demonstrated that NAC was still effective at an initial lower infusion rate (200 mg/kg over 9 h, or 23 mg/kg/h) followed by the third dose of the conventional treatment regimen. The lower initial infusion would allow for immediate treatment in suspected acute liver failure from overdose cases to prevent delay while awaiting serum paracetamol levels and liver function tests. This is beneficial as serious adverse events including hypersensitivity reactions, such as rashes to even anaphylaxis, can occur following high dose NAC infusions^[58,77,78]. Furthermore, gastric lavage and molecular adsorbent recirculating system (MARS) are two other treatment options for paracetamol overdose. While gastric lavage is used for numerous types of drug

overdose, its use for the treatment of paracetamol toxicity has fallen out of favor as there are more effective conventional treatments with better outcomes^[79]. A study looking at the use of MARS in acute liver failure patients showed that this system could increase the removal of paracetamol and was associated with improved survival times when compared to current standard therapy alone^[80].

CLINICAL OUTCOMES

Outcomes of paracetamol overdose have been reported from numerous countries. A study from Australia reported over 440 deaths from paracetamol in combination with codeine from accidental overdose, with roughly 25% of these cases also involving other sedating medications, such as antihistamines^[81]. While paracetamol has been the main cause of DILI in the United States and the England, it is less common in other European countries, such as Portugal and Germany, only making up roughly 10% of ALF cases according to the European Liver Transplant Registry (ELTR) database^[82]. In part, this could be from the increased usage of paracetamol intake in the United States in comparison to European countries. A summary of clinical outcomes from paracetamol-induced acute liver failure can be found in [Table 2](#).

Recently, a multinational study, the Study of Acute Liver Transplantation (SALT)^[86], identified cases where drug exposure, specifically nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol, had led to acute liver failure and resultant registration for liver transplantation. Among all the individuals in the study, there was no significant difference in the development of acute liver failure in the setting of exposure to various NSAIDs with incidence of patients registered for liver transplantation in these cases being rare. In comparison, paracetamol was associated with a three-fold higher risk of being registered for liver transplantation from associated acute liver injury in non-overdose levels and a seven-fold higher in overdose levels of paracetamol exposure^[86]. In a follow up study, Gulmez *et al*^[87] analyzed all the cases of individuals on the transplant registry and identified those that had drug overdose with resultant liver failure. Of those, paracetamol was responsible for one-sixth of all cases, and paracetamol overdose was responsible for 97% of all drug overdoses associated with acute liver failure. In response to the findings of the SALT study, the EPIHAM study^[88] was conducted to compare the risk of non-overdose levels of paracetamol versus NSAIDs resulting in admission for acute liver injury. However, the three-fold risk associated with paracetamol in transplantation registry was not seen for acute liver injury in this study^[88].

Acute liver failure from paracetamol toxicity has a high mortality rate of 30% if there is no liver transplantation available^[89,90]. Among intentional and accidental overdose, the liver transplant-free survival rate was not found to significantly differ. Prognostic criteria, such as the King's College criteria, can be used to determine appropriate candidates for liver transplantation referral based on those with expected high mortality of over 80%^[36,91]. As previously mentioned, those with phase three liver injury and signs of progressive organ dysfunction, severe acidosis or multiorgan failure have a poor prognosis and should be referred for possible liver transplantation. Those patients that undergo liver transplantation due to paracetamol liver failure have good clinical outcomes, with a 5-year survival of over 70%^[59].

CONCLUSION

Paracetamol toxicity, albeit accidental or intentional overdose, is an ongoing global problem that continues to result in cases of hepatotoxicity, acute liver failure, and even irreversible liver injury necessitating liver transplantation. Given the increased prevalence of combination medications in the form of pain relievers and antihistamines, paracetamol remains a significant cause of acute hepatotoxicity, as evidenced by paracetamol contributing to over half of acute liver failure cases in the United States. This is especially concerning given that when co-ingested with other medications, the rise in serum paracetamol levels may be delayed past the 4-hour post-ingestion mark that is currently used to determine patients that require medical therapy. Current research is exploring the outcomes of paracetamol-related DILI cases and its relationship with liver transplantation as well as other treatment modalities.

Table 2 Outcomes of acute liver failure from paracetamol among selected countries

Country	Acute liver failure from paracetamol	Hepatic failure resulting in death or transplant	Concomitant medication use/ suicide attempts
Australia ^[81]	Not disclosed	Death in 8.8% of cases (39 deaths total)	79% of cases with co-ingestion of opioids or benzodiazepines
United Kingdom ^[83]	2163 cases (65% of total ALF cases)	Death in 36% of cases (778 deaths total), 147 transplant cases	Not disclosed
United States ^[5]	120 cases (39% of total ALF cases)	Transplantation in 6% of cases, mortality in 27% of cases	44 cases (37%) were suicide attempts
Portugal ^[84]	5 cases over 3 years (11% of total ALF cases)	1 liver transplant case	Not disclosed
Germany ^[85]	10 cases (9.2% of total ALF cases)	3 liver transplant cases, 1 death	Not disclosed

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Case Control Study

Interleukin-6-174G/C polymorphism is associated with a decreased risk of type 2 diabetes in patients with chronic hepatitis C virus

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Abstract

BACKGROUND

Chronic hepatitis C (CHC) is associated with type 2 diabetes mellitus. Although the pathogenesis remains to be elucidated, a growing evidence has suggested a

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statement: The protocol was approved by the Federal University of Minas Gerais Ethical Board (ETIC 0404.0.203.000-10).

Informed consent statement: The primary version (PDF) of the Informed Consent Form that has been signed by all subjects and investigators of the study, prepared in Portuguese was uploaded.

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Data sharing statement: Technical appendix, statistical code and dataset available from the corresponding author at lucianadinizsilva@ufmg.br.

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role of pro-inflammatory immune response. Increased serum concentrations of Interleukin 6 (IL-6) have been associated with insulin resistance, type 2 diabetes mellitus as well as advanced forms of liver disease in chronic hepatitis C infection.

AIM

To investigate the frequency of IL-6-174G/C (rs1800795) single nucleotide polymorphism (SNP) in CHC patients and in healthy subjects of the same ethnicity. Associations between type 2 diabetes mellitus (dependent variable) and demographic, clinical, nutritional, virological and, IL-6 genotyping data were also investigated in CHC patients.

METHODS

Two hundred and forty-five patients with CHC and 179 healthy control subjects (blood donors) were prospectively included. Type 2 diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association. Clinical, biochemical, histological and radiological methods were used for the diagnosis of the liver disease. IL-6 polymorphism was evaluated by Taqman SNP genotyping assay. The data were analysed by logistic regression models.

RESULTS

Type 2 diabetes mellitus, blood hypertension and liver cirrhosis were observed in 20.8% (51/245), 40.0% (98/245) and 38.4% (94/245) of the patients, respectively. The frequency of the studied IL-6 SNP did not differ between the CHC patients and controls ($P = 0.81$) and all alleles were in Hardy-Weinberg equilibrium ($P = 0.38$). In the multivariate analysis, type 2 diabetes mellitus was inversely associated with GC and CC genotypes of IL-6-174 (OR = 0.42; 95%CI = 0.22-0.78; $P = 0.006$) and positively associated with blood hypertension (OR = 5.56; 95%CI = 2.79-11.09; $P < 0.001$).

CONCLUSION

This study was the first to show that GC and CC genotypes of IL-6-174 SNP are associated with a decreased risk of type 2 diabetes mellitus in patients chronically infected with hepatitis C virus. The identification of potential inflammatory mediators involved in the crosstalk between hepatitis C virus and the axis pancreas-liver remains important issues that deserve further investigations.

Key words: Chronic Hepatitis C; Type 2 diabetes mellitus; Interleukin 6-174G/C gene promoter single nucleotide polymorphism; Blood hypertension; Healthy control subjects

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Core tip: Chronic hepatitis C is associated with type 2 diabetes mellitus. Previous studies have demonstrated associations between increased serum concentrations of Interleukin 6 (IL-6) and type 2 diabetes and advanced forms of liver disease. However, the role played by IL-6-174G/C single nucleotide polymorphism on the pathogenesis of hepatitis C virus-associated type 2 diabetes remains to be elucidated. To the best of our knowledge, this is the first study to demonstrate that the GC and GG genotypes of IL-6 are inversely associated with type 2 diabetes. We believe that our results may contribute to the understanding of the extra-hepatic manifestations in hepatitis C.

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INTRODUCTION



Globally, an estimated 422 million adults have diabetes mellitus^[1] and around 71 million people are living with hepatitis C virus (HCV) infection^[2,3]. Over the past two decades, an accumulating body of scientific evidence has been linked type 2 diabetes mellitus to HCV infection^[4-11]. Given the high prevalence and the worldwide distribution of these two comorbidities, their association have an utmost impact on public health^[1-3].

In pioneering study, in 1898, Naunyn firstly described an association between liver cirrhosis and diabetes mellitus that it is known as hepatogenous diabetes^[12]. Hence, cirrhosis *per se* might lead to glucose intolerance or diabetes mellitus. The prevalence of diabetes in cirrhotic patients with non-alcoholic fatty liver disease, cryptogenic, hepatitis C, and alcoholic hepatopathy ranges from 27.3% to 56.1%^[13]. Regarding the HCV and the non-alcoholic fatty hepatic disease we have to bear in mind that type 2 diabetes mellitus can be detected prior to the onset of hepatic cirrhosis^[13-15] promoting a vicious cycle of hyperglycaemia causing a worsening metabolic state. Thus, altogether, glucose disturbed metabolism and HCV enhance the chronic inflammation and might interact as a reciprocal feed-forward loop^[16-19].

The pathogenesis of type 2 diabetes mellitus encompasses both different degrees of insulin resistance and relative insulin deficiency^[20,21]. Although, some mechanisms underlying the modified glucose metabolism in HCV infection have been elucidated^[22-24], several aspects remain unknown. Additionally, Chronic hepatitis C (CHC) patients with type 2 diabetes mellitus are likely to have an accelerated liver disease progression, *i.e.*, hepatic fibrosis, cirrhosis and hepatocellular carcinoma^[25-28]. Various factors can be involved in this interaction including direct viral effects and host factors, such as overweight and pro-inflammatory markers^[16,17,29,30]. Among the inflammatory markers, increased serum concentrations of interleukin-6 (IL-6) have been associated with insulin resistance, type 2 diabetes mellitus as well as advanced forms of liver disease in chronic hepatitis C infection^[31-39].

Polymorphisms in the IL-6 gene, which may alter the expression of IL-6, have been investigated in the context of metabolic disease and CHC^[31,32,34-42]. The association between the single nucleotide polymorphism (SNP) of IL-6 located in the promoter region at the position-174G/C (rs1800795) and type 2 diabetes mellitus was first reported in United States Pima Indians and Spanish Caucasians^[43]. The C-allele was significantly associated with a decreased risk of type 2 diabetes. However, in further investigations these results have not been confirmed^[34,39]. In the setting of hepatitis C, IL-6 SNP polymorphisms have been associated with hepatic-and extra hepatic-related outcomes, such as cirrhosis, hepatocellular carcinoma and poor quality of life^[31,32,40-42]. Altogether, both *in vitro* experiments and clinical studies including healthy individuals have demonstrated that the presence of C allele is associated with lower levels of IL-6^[44-46]. The interrelationship between decreased concentration of this cytokine and IL-6-174 SNP is more pronounced in individuals carrying the CC genotype^[44-46].

Because the host's immune response play an important role in extrahepatic manifestations in subjects chronically infected with HCV, even before the onset of hepatic cirrhosis, we hypothesized that IL-6-174G/G genotype, the IL-6 high-producer phenotype, may be associated to a high inflammatory profile that negatively affects the course of type 2 diabetes mellitus in these patients. Additionally, these factors may accelerate the liver fibrosis that also affects the insulin resistance. Thus, we evaluated the frequency of IL-6-174G/C SNP in patients chronically infected with HCV and in healthy subjects of the same ethnicity. Associations between type 2 diabetes mellitus (dependent variable) and demographic, clinical, nutritional, virological and, IL-6 genotyping data were also investigated in CHC patients.

MATERIALS AND METHODS

Participants

From March 2017 to July 2019, we prospectively included 260 adult patients with confirmed CHC diagnosis attending the Viral Hepatitis Outpatient Clinic, University Hospital, Belo Horizonte, Brazil. The control group consisted of 179 consecutive volunteer blood donors from the hemocenter of Felício Rocho Hospital (Hemoter - Clínica Romeu Ibrahim de Carvalho), Belo Horizonte, Brazil. The Viral Hepatitis Outpatient Clinic is an outpatient care ambulatory of a metropolitan tertiary teaching hospital that admits patients for the treatment of viral chronic hepatitis. All participants signed the informed consent form. The study was designed and conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Federal University of Minas Gerais/UFGM (ETIC 0404.0.203.000-10).

The exclusion criteria were: Pregnancy, breastfeeding, hepatic encephalopathy, HBV/HCV or HCV/HIV co-infection, current antiviral, use of non-steroidal anti-inflammatory drugs or corticosteroids, and the presence of advanced disease such as chronic kidney disease, heart failure, chronic pulmonary disease, chronic pancreatitis and neoplasia, including hepatocellular carcinoma.

Clinical, biochemical, histological and radiological methods were performed for the diagnosis of the liver disease^[47,48]. The severity of liver dysfunction was assessed by the Child-Pugh-Turcotte score^[49]. Compensated cirrhosis was defined as the absence of variceal bleeding, ascites and oedema, jaundice or symptomatic encephalopathy on physical examination, and decompensated cirrhosis as the presence of any of these complications^[50]. The aspartate amino transferase to platelet ratio index^[51] was calculated for each participant based on medical data.

The diagnosis of type 2 diabetes mellitus was based on documented use of oral hypoglycaemic medication or insulin; random plasma glucose levels ≥ 200 mg/dL in the presence of classic symptoms of hyperglycaemia or hyperglycaemic crisis; fasting plasma glucose ≥ 126 mg/dL on two occasions; 2 h plasma glucose ≥ 200 mg/dL during oral glucose tolerance test or haemoglobin A1c $\geq 6.5\%$ on two occasions^[52].

Blood hypertension was diagnosed according to the 2018 European Society of Hypertension/European Society of Cardiology Guidelines^[53].

An expert nutritionist carried out all nutritional evaluations. Weight and height were measured with a mechanical platform scale (FILIZOLA®, São Paulo, Brazil). Body mass index was calculated using the formula, Body mass index = weight/height² and the nutritional status of the patients were determined according to the World Health Organization criteria^[54]. Elderly individuals were classified according to the Lipschitz classification^[55].

Furthermore, an in-person interview was conducted using instruments to assess the sociodemographic and clinical characteristics of the patients. Fifteen patients were not included: Twelve patients who had initially agreed to take part in this study failed to complete the questionnaires; three patients were excluded because blood sample was inadequate for genotyping. Two hundred and forty-five patients and 179 healthy subjects remained in the study.

All participants were from a similar socioeconomic level, as assessed by a previously validated questionnaire^[56], which was based on income and educational level, as well as similar cultural habits. All subjects were natives of Minas Gerais, state in the south-eastern region of Brazil with the following ethnic background: 56.0% of European ancestry, 32.0% of African ancestry and 12.0% of Amerindian ancestry homogeneously present in each patient, irrespective of their phenotype^[57].

Laboratory parameters

Blood samples were obtained from each subject after an overnight fasting for cytokine genotyping and biochemical assessments. Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase alkaline phosphatase, albumin, total bilirubin, prothrombin time and hemogram were evaluated by using Vitros® 5600 (Ortho Clinical Diagnosis, Raritan, NJ, United States).

HCV genotype was determined by a line probe assay (VERSANT HCV genotyping assays; Bayer's Diagnostic Corporation, Tarrytown, NY, United States) and viral load assessed by a commercial test (CobasTaqMan HCV test V.2.0; Roche Molecular Systems, Pleasanton, CA, United States). The assays were carried out according to the manufacturers' recommendations.

Aliquots of leukocytes and plasma were stored at -80 °C until analysis.

DNA extraction and genotyping of IL-6

DNA was extracted from the leukocytes with the QIAmp DNA mini kit (QIAGEN GmbH, Hilden, Germany) according to the manufacturer's recommendations. DNA concentration and purity were evaluated by spectrophotometry (NanoDrop Lite Spectrophotometer, Thermo Scientific, Waltham, MA, United States). DNA concentration was determined by absorbance at 260 nm and purity was assessed by the absorbance ratio at 260/280 nm. The DNA of the samples was stored at -20 °C before use.

IL-6-174G/C (rs1800795) genotyping was Taqman assayed by Real Time PCR System 7.500 (Applied Biosystems, Thermo Scientific, Foster City, CA, United States) by using oligonucleotide primers previously described by Fishman *et al.*^[44]. The sequence of synthetic probes and reaction conditions are described in [Table 1](#).

Statistical analysis

The Hardy-Weinberg equilibrium of alleles at individual loci was assessed by two-tailed χ^2 test or Fisher's exact test.

Data were analysed with SPSS statistical software package version 17.0 (SPSS Inc.,

Table 1 Probes and conditions used in the polymerase chain reaction to genotype interleukin 6 single nucleotide polymorphism at position-174 (rs1800795)

IL-6 Gene-174 (rs1800795)
ACTTTCCCCCTAGTTGTGCTTGC[C/G]ATGCTAAAGGACGTCACAT 60 °C-1 min; 95 °C-10 min; 50 cycles (95 °C-15 s, 60 °C-90 s) and 60 °C-1 min TGCACA

IL-6: Interleukin 6.

Chicago, IL, United States). Descriptive statistics were used to provide information regarding demographic, clinical, nutritional, virological, and genetic data. The Shapiro-Wilk test was used to evaluate whether the data were normally distributed. The asymptotic Pearson's χ^2 test was used to compare the percentages. The Student's *t*-test or ANOVA was used to compare the means and the two-tailed Mann-Whitney *U* test was used for medians.

The associations of each variable including IL-6-174G/C, sex, increasing age, blood hypertension, nutritional status, liver fibrosis stage (chronic hepatitis and cirrhosis) with type 2 diabetes mellitus were tested in univariate analysis. All variables with *P* values < 0.20 were included in the full model of logistic regression. Odds ratio and 95% CI were used as an estimate of the risk. The Hosmer-Lemeshow test was used to assess the adequacy of the models. Variables that had missing data > 10% were not selected for the models of multivariate analysis. *P* values ≤ 0.05 were considered significant.

RESULTS

Distribution of the IL-6 genotypes in CHC patients and controls (blood donors)

The frequencies of the IL-6 SNP did not differ between CHC patients and blood donors (Table 2). All alleles were in Hardy-Weinberg equilibrium in the control group (*P* > 0.95) and in the CHC patients (*P* > 0.38) as shown in Table 2.

Demographic and clinical characteristics of CHC patients

Among the 245 patients with CHC, 94 (38.4%) had cirrhosis [Child-Turcotte-Pugh score A5, 60 (63.8%); A6, 21 (22.3%); B7, 6 (6.4%); B8, 4 (4.3%); B9, 2 (2.1%); C10, 1 (1.1%)]. The mean age of the patients was 51.8 ± 11.4 years and 129 (52.7%) were males.

Cirrhosis was significantly more frequent (*P* = 0.03) in males (61.7%) than in females (38.3%). The patients with cirrhosis (53.5 ± 8.8 year) were older (*P* = 0.05) than those without (50.8 ± 12.7 year). Overweight tended to be more frequent (*P* = 0.08) in the CHC patients without (64.9%) than in those with cirrhosis (53.2%).

There was no significant difference (*P* = 0.11) in blood hypertension rate between CHC patients with cirrhosis (46.8%) and those without (35.8%). The frequency of type 2 diabetes did not differ (*P* = 0.33) between the two groups (24.5% in cirrhotic and 18.5% in non-cirrhotic patients).

HCV viral load and genotype in patients with CHC

There was no significant difference (*P* = 0.58) in the viral load between patients without [HCV-RNA log₁₀ (IU)/mL, 5.93 (interquartile range: 5.46-6.39)] and those with cirrhosis [5.86; (interquartile range: 5.34-6.20)]. Also, the frequency of HCV Genotype 1 in patients without cirrhosis [109/126 (86.5%)] did not differ (*P* = 0.25) from that of patients with [61/78 (78.2%)]. The quantification of viral load and HCV genotyping were available in 213/245 (86.9%) patients.

Characteristics of CHC patients with and without type 2 diabetes mellitus

Fifty-one (20.8%) patients had type 2 diabetes mellitus that was significantly more frequent in older patients (Table 3). The prevalence of blood hypertension was higher in type 2 diabetes mellitus than in those without the disease (Table 3). Lower frequency of IL-6-174G/C and C/C genotypes was observed in patients when compared to those without type 2 diabetes mellitus (Table 3).

Factors associated with type 2 diabetes mellitus in patients with chronic hepatitis C

In the univariate analysis, type 2 diabetes mellitus was associated with old age, blood hypertension, body mass index, and the GC and CC genotypes of IL-6-174 (Table 3). In the multivariate analysis, type 2 diabetes mellitus remained inversely associated with the GC and CC genotypes of IL-6-174 and positively associated with blood

Table 2 The interleukin genotype distribution in patients with chronic hepatitis C (*n* = 245) and healthy controls (*n* = 179)

Variables	CHC, <i>n</i> (%)	Control, <i>n</i> (%)	<i>P</i> value
IL-6 genotypes			
-174			0.81
C/C	18 (7.3)	13 (7.3)	
G/C	85 (34.7)	68 (38.0)	
G/G	142 (58.0)	98 (54.7)	
Total	245 (100)	179 (100)	
HWE (<i>P</i> value)	0.38	0.95	

The asymptotic Pearson's χ^2 test was used to compare categorical variables. $P \leq 0.05$ were considered significant. *n*: Number of subjects; CHC: Chronic hepatitis C; IL-6: Interleukin-6; HWE: Hardy-Weinberg Equilibrium.

hypertension (Table 4).

DISCUSSION

Impaired glucose tolerance and type 2 diabetes mellitus have been reported to frequently occur in patients with chronic HCV infection independently of the hepatic disease severity^[26,58,59]. In consonance with the literature, we found a high prevalence of the type 2 diabetes mellitus in our patients^[5,7,60,61]. Although there is a sizeable body of scientific evidence linking glucose disturbed metabolism and hepatitis C, the biological mechanisms behind the concurrence of these conditions have not been completely clarified yet.

To the best of our knowledge, this is the first study to demonstrate that the GC and GG genotypes of IL-6-174 are inversely associated with type 2 diabetes mellitus in patients chronically infected with HCV. In the current study, CHC patients with type 2 diabetes mellitus had lower frequency GC and CC IL-6-174 genotypes compared to those without diabetes. Although, several investigations have shown that subjects carrying the GC and CC genotypes of IL-6 SNP had a decreased risk of type 2 diabetes mellitus^[34-38], the association has not found by others^[34,39], which may be due to the differences in the study designs and/or genetic ancestry of the populations. Concerning the chronic liver diseases, the IL-6-174G/C polymorphism has been associated with both fibrosis progression and hepatocellular carcinoma development^[41,62,63] in patients with CHC. The majority of the studies has verified an association between the presence of the high producer genotype (GG) and poor outcome in patients with the hepatopathy^[31,32,40,41,62,63].

Patients with CHC, with insulin resistance or type 2 diabetes mellitus are likely to have a more complicated course of the infection^[24-27]. Based on previous reports, it is important to keep in mind, if on the one hand insulin resistance is recognized as a risk factor for the progression of HCV-related liver disease^[26-29,31,32], on the other hand, preceding HCV infection significantly increases the risk of developing type 2 diabetes mellitus^[7]. Additionally, diabetic patients are at an increased risk of acquiring HCV infection^[64-66]. Thus, this two-way interface, *i.e.*, the relationship linking HCV and type 2 diabetes mellitus, is possibly determined by complex and multifaceted interactions among the hepatitis virus, the environment and the host. Our current data show that neither different HCV genotypes nor viral load was significantly associated with type 2 diabetes mellitus. In this scenario, the host-related factors should be highlighted.

HCV infection and type 2 diabetes mellitus are associated with increased production of IL-6, a pro-inflammatory cytokine that plays a crucial role in viral induced liver damage^[17,29,31-41,61,62], and may cause insulin resistance in adipose tissue, skeletal muscle and liver by inhibiting insulin signal transduction^[67,68]. Therefore, the results of the current study pointed to the role of IL-6 pathway in mediating both liver injury and disturbed glucose metabolism in CHC patients. Furthermore, even in the era of direct antiviral agents (DAAs), that has been causing dramatic changes in the treatment of CHC^[69], the evidences of the current investigation should not be disregarded. Although most of the studies have demonstrated that HCV clearance by DAA treatment reverses or improves the insulin resistance^[11,28,69,70], in a more recent investigation, the authors observed that successful hepatitis C virus treatment among patients with type 2 diabetes significantly reduces glycated haemoglobin shortly after

Table 3 Demographic, clinical comorbidity, nutritional status, liver fibrosis stage, virological, cytokine genotyping data of the chronically hepatitis C virus-infected patients with (*n* = 51) and without type 2 diabetes (*n* = 194)

Variables	Type 2 diabetes, <i>n</i> (%)	Non-type 2 diabetes, <i>n</i> (%)	<i>P</i> value
Demographic			
Male	27 (52.9)	102 (52.6)	1.0
Female	24 (47.1)	92 (47.4)	
Age (yr) ¹	55.5 ± 9.6	50.9 ± 11.7	0.01
Clinical comorbidity			
Blood hypertension	36 (70.6)	62 (32.0)	< 0.001
Nutritional status			
Body mass index (Kg/m ²) ²	27.0 (24.1-29.7)	25.6 (23.5-28.4)	0.11
Stage of liver disease			
Chronic hepatitis C	28 (54.9)	123 (63.4)	0.34
Liver cirrhosis	23 (45.1)	71 (36.6)	
Virological parameters			
Viral load HCV-RNA [Log10 (IU/mL)] ²	5.98 (5.66-6.24)	5.84 (5.30-6.40)	0.38
Genotype 1	40/45 (88.9)	130/159 (81.7)	0.37
IL-6 polymorphism			
IL-6-174G/G genotypes			0.04
G/G	37 (72.5)	105 (54.1)	
G/C	13 (25.5)	72 (37.1)	
C/C	1 (2.0)	17 (8.8)	
Total	51 (100.0)	194 (100.0)	
HWE (<i>P</i> value)	0.65	0.47	

¹mean ± SD.²Median and IQR, 25th-75th percentile. HCV: Hepatitis C virus; *n*: Number of subjects; IL: Interleukin; HWE: Hardy-Weinberg Equilibrium. The asymptotic Pearson's χ^2 test was used to compare categorical variables. The *t* test and Mann-Whitney *U* test were used for comparison of means and medians, respectively. *P* ≤ 0.05 were considered significant.

treatment, but not for a long time^[71]. In addition, Hengst *et al*^[72] demonstrated that DAA-induced viral clearance does not fully re-establish the modified cytokine and chemokine milieu in CHC patients^[72]. These evidences aligned with our results reinforce the role played by the immune-mediated mechanisms in the pathogenesis of insulin resistance and diabetes in HCV chronic hepatitis.

In the present study, in addition to IL-6 SNP, arterial hypertension was associated with type 2 diabetes mellitus. Studies have demonstrated that cardiovascular diseases, hypertension and diabetes are strongly correlated to each other^[73]. Their powerful relationship have also been observed in patients chronically infected with HCV^[74,75].

The limitations of our study should also be considered. First, the subjects included were recruited from a referral centre and, consequently, may not be representative of all patients with CHC. Second, the cross-sectional nature of the investigation hindered the likelihood to recognize any cause-effect relationship between type 2 diabetes mellitus and IL-6 SNP in hepatitis C. Furthermore, another limitation is the lack of data on the serum concentrations of IL-6 of patients and controls; however, the functional significance of the studied polymorphism is well understood^[44-46].

In the current study, we demonstrated for the first time that the IL-6-174G/C gene promoter polymorphism is inversely associated with type 2 diabetes mellitus in patients with CHC. This finding reinforces the need for additional investigations focusing on the biological mechanisms of diabetes mellitus in patients chronically infected with HCV. The identification of potential inflammatory mediators involved in the crosstalk between HCV and the pancreas-liver axis remains important issues that deserve further investigations. Moreover, better understanding of these processes may positively affect the management strategies for reducing the extra-hepatic manifestations and their negative impact on health status in CHC patients.

Table 4 Variables associated with diabetes mellitus in patients with chronic hepatitis C

Variables	Multivariate analysis		
	OR	95%CI	P value
Age	1.01	0.98-1.05	0.43
Body mass index	1.03	0.96-1.09	0.45
Hypertension	5.56	2.79-11.09	< 0.001
IL-6-174 G/C (GC and CC)	0.42	0.22-0.78	0.006

CI: Confidential interval; IL-6: Interleukin 6; OR: Odds ratio.

ARTICLE HIGHLIGHTS

Research background

Chronic hepatitis C (CHC) is associated with an elevated prevalence of type 2 diabetes mellitus. Although, some mechanisms underlying the modified glucose metabolism in hepatitis C virus (HCV) infection have been elucidated, several aspects remain unknown. Growing scientific evidence has suggested a role of pro-inflammatory immune response. Increased serum concentrations of interleukin-6 (IL-6) have been associated with insulin resistance, type 2 diabetes mellitus as well as advanced forms of liver disease in chronic hepatitis C infection.

Research motivation

Patients with CHC, with insulin resistance or type 2 diabetes mellitus are likely to have a more complicated course of the infection. Based on previous reports, it is important to keep in mind, if on the one hand insulin resistance is recognized as a risk factor for the progression of HCV-related liver disease, on the other hand, preceding HCV infection significantly increases the risk of developing type 2 diabetes mellitus. Additionally, diabetic patients are at an increased risk of acquiring HCV infection. Thus, this two-way interface, *i.e.*, the relationship linking HCV and type 2 diabetes mellitus, is possibly determined by complex and multifaceted interactions among the hepatitis virus, the environment and the host.

Research objectives

The objectives of this study were therefore to investigate the frequency of IL-6-174G/C (rs1800795) single nucleotide polymorphism in CHC patients and in healthy subjects of the same ethnicity. Furthermore, the association between type 2 diabetes mellitus (dependent variable) and demographic, clinical, nutritional, virological and IL-6 genotyping data was also evaluated in patients chronically infected with HCV.

Research methods

Two hundred and forty-five patients with CHC and 179 healthy control subjects (blood donors) were prospectively included. Type 2 diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association. Clinical, biochemical, histological and radiological criteria were applied to make the diagnosis and staging of the liver disease. IL-6-174G/C (rs1800795) genotyping was Taqman assayed by Real Time PCR System 7.500 by using oligonucleotide primers previously described by Fishman *et al.*^[44]. The Hardy-Weinberg equilibrium of alleles at individual loci was assessed by two-tailed chi-square test or Fisher's exact test. The associations of each variable including IL-6-174G/C, sex, increasing age, blood hypertension, nutritional status, liver fibrosis stage (chronic hepatitis and cirrhosis) with type 2 diabetes mellitus were tested in univariate analysis. All variables with *P* values < 0.20 were included in the full model of logistic regression. Odds ratio (OR) and 95%CI were used as an estimate of the risk. *P* values ≤ 0.05 were considered significant.

Research results

Type 2 diabetes mellitus, blood hypertension and liver cirrhosis were observed in 20.8% (51/245), 40.0% (98/245) and 38.4% (94/245) of the patients, respectively. The frequency of the studied IL-6 single nucleotide polymorphism did not differ between the CHC patients and controls (*P* = 0.81) and the alleles were in Hardy-Weinberg equilibrium (*P* = 0.38). In the multivariate analysis, type 2 diabetes mellitus was inversely associated with GC and CC genotypes of IL-6-174 (OR = 0.42; 95%CI = 0.22-0.78; *P* = 0.006) and positively associated with blood hypertension (OR = 5.56; 95%CI = 2.79-11.09; *P* < 0.001).

Research conclusions

In the current study, we demonstrated for the first time that the IL-6-174G/C gene promoter polymorphism is inversely associated with type 2 diabetes mellitus in patients with CHC. This finding reinforces the need for additional investigations focusing on the biological mechanisms of diabetes mellitus in patients chronically infected with HCV.

Research perspectives

The identification of potential inflammatory mediators involved in the crosstalk between HCV and the axis pancreas-liver remains important issues that deserve further investigations. Moreover, better understanding of these processes may positively affect the management strategies for reducing the extra-hepatic manifestations and their negative impact on health status in CHC patients.

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Observational Study

Comparison of four non-alcoholic fatty liver disease detection scores in a Caucasian population

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a common disorder, with an estimated prevalence ranging from 20% to 35% in the general population. Several scores based on easily measurable biochemical and clinical parameters, including the fatty liver index (FLI), hepatic steatosis index (HSI), lipid accumulation product (LAP), and NAFLD liver fat score (LFS), have been developed for the detection of NAFLD. However, comparative information regarding the efficacy of these scores for predicting NAFLD in population-based samples comprising normal and high-risk individuals is lacking.

AIM

To evaluate four NAFLD detection scores in two samples with different NAFLD risks.

METHODS

NAFLD screening was performed in a population-based sample of 50-year-old individuals in Uppsala, Sweden [$n = 310$; Prospective investigation of obesity, energy and metabolism (POEM) study] and a high-risk population comprising patients with a body mass index $> 25 \text{ kg/m}^2$ and either high plasma triglycerides ($\geq 1.7 \text{ mmol/L}$) or type 2 diabetes ($n = 310$; EFFECT studies). NAFLD was defined as liver fat $> 5.5\%$ using magnetic resonance imaging-proton density fat

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fraction. FLI, HSI, LAP, and NAFLD LFS were assessed. A logistic regression model was used to evaluate the effectiveness of the different scores.

RESULTS

The prevalence of NAFLD was 23% in POEM. FLI showed the highest receiver operating characteristic area under the curve (ROC AUC; 0.82) and was significantly better than the LAP score ($P = 0.005$ vs LAP, $P = 0.08$ vs LFS, $P = 0.12$ vs HSI) for detection of NAFLD. The other three indices performed equally in POEM (0.77-0.78). The prevalence of NAFLD was 74% in EFFECT; LFS performed best (ROC AUC 0.80) in this sample. The ROC AUC for LFS (0.80) was significantly higher than that for FLI ($P = 0.0019$) and LAP ($P = 0.0022$), but not HSI ($P = 0.11$). We performed a sensitivity analysis with stratification for the two high-risk subgroups (patients with diabetes or hypertriglyceridemia) from the EFFECT studies. LAP performed best in patients with hypertriglyceridemia. No major differences were observed between the other scores.

CONCLUSION

The four investigated NAFLD scores performed differently in the population-based vs high-risk setting. FLI was preferable in the population-based setting, while LFS performed best in the high-risk setting.

Key words: Comparison; EFFECT studies; Fatty liver; Non-alcoholic fatty liver disease; Non-invasive indices; Screening

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Core tip: Several non-invasive indices based on routinely available biochemical and physical parameters have been developed for the detection of non-alcoholic fatty liver (NAFLD) disease. However, data comparing the efficacy of these indices within a population-based sample are lacking. Here we compared four non-invasive indices, namely, fatty liver index, lipid accumulation product, hepatic steatosis index, and liver fat score, in a population-based (Prospective investigation of obesity, energy and metabolism study) sample and a high-risk (EFFECT studies) sample. Our study demonstrated differences in NAFLD detection between the scores in the two samples. Of the four evaluated scores, fatty liver index was preferable in the population-based sample (NAFLD prevalence, 23%), whereas liver fat score performed best in the high-risk sample (NAFLD prevalence, 73%).

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common disorder, with an estimated prevalence ranging from 20% to 35% in the general population; the prevalence is approximately doubled in the obese population^[1-4]. NAFLD can be diagnosed using liver biopsies, ultrasound, magnetic resonance imaging (MRI), or spectroscopy; however, these investigations may not be readily available in primary care. Thus, the general physician should have simple tools available to use for screening, since not all obese subjects could be referred to imaging or biopsy.

In order to identify simpler and cost-effective approaches to diagnose NAFLD, several scores based on easily measurable biochemical and clinical parameters, such as the fatty liver index (FLI)^[5], hepatic steatosis index (HSI)^[6], lipid accumulation product (LAP)^[7], and NAFLD liver fat score (LFS)^[8], have been developed. However, only one study has evaluated these scores directly in the same population, using population-based NHANES data and ultrasound to diagnose NAFLD^[9]; this study found that LFS was the best score for NAFLD detection.

MRI-proton density fat fraction (PDFF) can quantitatively assess the degree of liver

steatosis as percent of the liver volume and can more accurately detect mild steatosis compared to ultrasound^[10]. Since the extent to which the different scores can predict NAFLD in a high-risk individual *vs* a non-selected individual is unknown, the present study was conducted to compare the ability of the abovementioned four scores to predict NAFLD in two sample sets, a population-based sample and a sample at high risk for NAFLD, using MRI-PDFF, which can accurately quantify liver fat values. In both the samples, NAFLD was diagnosed by MRI-PDFF using the median of the fat fraction values inside the delineated total liver volume. The hypothesis tested was that the different scores performed differently in the two samples.

MATERIALS AND METHODS

Study populations

The EFFECT studies: In the EFFECT I study (ClinicalTrials.gov NCT02354976)^[11], screened patients were eligible for inclusion in the treatment part of the study provided they were 40-75 years old and had a body mass index (BMI) of 25-40 kg/m², serum triglyceride level of 1.7 mM (150 mg/dL) or higher, and liver PDFF > 5.5% of liver volume. Exclusion criteria were as follows: Patients with diabetes mellitus, a history of other hepatic disease, an inability to undergo MRI scanning, and a significant alcohol intake (over 14 units per week for both women and men).

The EFFECT II study (ClinicalTrials.gov NCT02279407)^[12] had similar inclusion and exclusion criteria to the EFFECT I study, with the exception that eligible patients must have had a prior history of type 2 diabetes, and serum triglyceride levels were not considered for inclusion.

Thus, only data from the screening parts of the EFFECT I and II studies, including both patients who were randomized and screen failures, were used in the present study (Table 1). Data from 140 and 170 patients in the EFFECT I and EFFECT II studies, respectively, for whom a successful MRI liver scan was performed were pooled as a high-risk sample for NAFLD. Further details on the EFFECT I and II studies have recently been published^[11,12].

The prospective investigation of obesity, energy and metabolism study: The prospective investigation of obesity, energy and metabolism (POEM) study was a population-based study investigating individuals (all aged 50 years) from Uppsala^[13]. Of 502 individuals recruited (50% women), a successful MRI liver scan was performed in 310 individuals (Table 1).

None of these subjects reported a significant alcohol intake, as defined above for EFFECT I and II participants.

Liver fat measurement using MRI

MRI was used to determine PDFF using a water-fat separated scan with large liver coverage collected in a single breath hold as described earlier^[11,12]. The body coil was used to collect a spoiled, threedimensional, six-gradient echo with axial orientation. For the EFFECT studies, imaging was performed at seven different sites. Six of these used a 1.5T scanner and one used a 3T system. One of the sites used water-fat reconstruction supplied by the system vendor. Data from the other sites and from the POEM study were reconstructed using an in-house developed software that included T2 and a multi-peak lipid spectrum in the signal model. The POEM study data were collected on a 1.5T system. Images from the EFFECT studies were sent for centralized analysis at the imaging core laboratory at Antares Medical (Mölnådal, Sweden), and the POEM MRI data were analyzed at the Department of Radiology, Uppsala University. The liver was segmented by trained operators from the axial slices of the water image using the software ImageJ (National Institutes of Health, Bethesda, Maryland, United States, <https://imagej.nih.gov/ij/>). The border of the liver was avoided to reduce partial volume effects. Analysis of the EFFECT data was performed by one trained operator and POEM data by another operator. PDFF was determined using the median of the fat fraction values inside the delineated liver volume. The coefficient of variation for repeated examinations and analyses of liver PDFF was 5.3%, as determined by test-retest scanning and analysis of data from 10 healthy volunteers.

Blood analyses

The EFFECT studies: Fasting blood samples were collected in the morning. Patients were instructed to fast for a minimum of 10 h. Plasma glucose levels were analyzed using a hexokinase enzymatic method with a Glucose HK Gen.3 reagent kit (Roche Diagnostics, Indianapolis, IN, United States). Plasma insulin levels were measured using the Access Ultrasensitive Insulin assay (Beckman Coulter, Inc., Brea, CA, United

Table 1 Basic characteristics of the EFFECT and prospective investigation of obesity, energy and metabolism samples

Variable	EFFECT sample		POEM sample	
	<i>n</i>	mean ± SD or proportion	<i>n</i>	mean ± SD
Age (yr)	310	64.6 ± 7.2	310	50.1 ± 0.1
Sex (% female)	310	39	310	51
Systolic blood pressure (mmHg)	310	143 ± 17	310	125 ± 16
Weight (kg)	310	90 ± 13	310	80 ± 15
Height (cm)	310	172 ± 9	310	173 ± 10
Waist circumference (cm)	310	107 ± 11	310	92 ± 11
BMI (kg/m ²)	310	30.4 ± 3.4	310	26.4 ± 4.3
Diabetes medication (%)	310	41	310	2.2
Statin treatment (%)	310	39	310	4.1
Antihypertensive treatment (%)	310	57	310	7.3
Fasting glucose (mmol/L)	308	7.4 ± 2.0	310	5.09 ± 0.78
Fasting insulin (mU/L)	306	10.9 ± 6.9	309	6.49 ± 9.49
Serum cholesterol (mmol/L)	308	5.51 ± 1.41	310	5.29 ± 1
Serum triglycerides (mmol/L)	308	2.14 ± 1.16	310	1.15 ± 0.7
HDL-cholesterol (mmol/L)	308	1.34 ± 0.37	310	1.39 ± 0.37
LDL-cholesterol (mmol/L)	308	3.47 ± 1.23	310	3.39 ± 0.87
ALT (ukat/L)	307	0.62 ± 0.45	307	0.45 ± 0.15
AST (ukat/L)	301	0.51 ± 0.24	307	0.34 ± 0.15
Liver PDFF (%)	310	13.2 ± 9.5	310	4.2 ± 5.4
NAFLD (%)	310	75	310	23
Metabolic syndrome (%)	308	81	310	15

$P < 0.001$ for differences between the two samples for all variables except height, LDL and HDL-cholesterol, which did not show statistical significance. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NAFLD: Non-alcoholic fatty liver disease; PDFF: Proton density fat fraction; POEM: Prospective investigation of obesity, energy and metabolism; SD: Standard deviation.

States), a simultaneous one-step immunoenzymatic (sandwich) assay. Serum levels of total cholesterol and triglycerides were measured using the Cholesterol Gen.2 reagent and Triglyceride reagent, respectively (Roche Diagnostics). High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDLC) concentrations were measured using direct HDL-C and LDL-C assays (HDL-C3 third generation reagents and LDL-C plus second generation assay; Roche Diagnostics). Other analytes such as gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured in the local hospitals using conventional methods^[11,12].

The POEM study: All samples were collected in the morning after an overnight fast. Fasting plasma glucose and lipids were measured by conventional methods at the clinical chemistry laboratory at the University Hospital in Uppsala. Serum insulin was measured using a microtiter-based enzyme-linked immunosorbent assay (ELISA; 10-1113-01, Mercodia, Uppsala, Sweden). The assay was calibrated against the first international reference preparation 66/304 for human insulin^[13].

Fatty liver disease algorithms

FLI was calculated using the following formula^[5].

HSI was calculated using the following formula^[6]: $HSI = 8 \times ALT/AST \text{ ratio} + BMI (+ 2, \text{ if diabetes mellitus; } + 2, \text{ if female})$. LAP was calculated using the following formula^[7]: $LAP = (\text{waist} - 65) \times \text{triglycerides in men and } (\text{waist} - 58) \times \text{triglycerides in women}$. NAFLD LFS was calculated using the following formula^[8]: $LFS = -2.89 + [1.18 \times \text{MetS (Yes: 1, No: 0)}] + [0.45 \times \text{diabetes mellitus (Yes: 2, No: 0)}] + (0.15 \times \text{insulin}) + (0.04 \times \text{AST}) - [0.94 \times (\text{AST}/\text{ALT})]$.

Where MetS is the metabolic syndrome according to the International Diabetes Federation criteria^[14].

Both the EFFECT studies and the POEM study were approved by the Ethics

$$FLI = \frac{[e^{0.953 \times \log(\text{triglycerides})} + 0.139 \times BMI + 0.718 \times \log(GGT) + 0.053 \times \text{waist circumference} - 15.745]}{[1 + e^{0.953 \times \log(\text{triglycerides})} + 0.139 \times BMI + 0.718 \times \log(GGT) + 0.053 \times \text{waist circumference} - 15.745}]} \times 100$$

Committee of Uppsala University, and all participants have given their informed consent.

Statistical analysis

To evaluate the effectiveness of the four different scores in predicting NAFLD, a logistic regression model was used with liver PDF $> 5.5\%$ (binary) as the dependent variable and the score as the independent variable. From the logistic regression model, the area under the curve (AUC) for sensitivity *vs* 1-Specificity was calculated. To compare the AUC values from the two sample sets, their respective logistic regression models were compared by C-statistics.

For the exploratory analysis, a logistic regression model was used with NAFLD (binary) as the dependent variable and the variables included in the LFS equation as the independent variables. A backward stepwise procedure was used to eliminate independent variables with $P > 0.05$.

STATA14 (Stata Inc., College Station, TX, United States) was used for all analyses.

RESULTS

General population (POEM study)

Very few subjects ($n = 5$) with liver fat $> 5.5\%$, indicating NAFLD, had a BMI < 25 kg/m² (Figure 1). The prevalence of NAFLD was 23% in the population-based sample. FLI showed the highest receiver operating characteristic (ROC) AUC value (0.82), while the ROC AUC values for the other three indices were similar (0.77-0.78; Figure 2, Table 2). However, the ROC AUC for FLI showed a significant difference only with respect to the LAP score ($P = 0.005$), but not *vs* LFS ($P = 0.08$) or HSI ($P = 0.12$).

High-risk population (EFFECT studies)

The relationship between BMI and liver fat in the EFFECT studies is shown in Figure 3. The prevalence of NAFLD was 74% in the high-risk sample. LFS showed the highest ROC AUC value (0.80; Figure 4), and the ROC AUC for LFS was significantly higher than that for FLI ($P = 0.0019$) and LAP ($P = 0.0022$), but not HSI ($P = 0.11$).

Since the EFFECT studies consisted of two overweight/obese high-risk subgroups, namely, patients diagnosed with diabetes or hypertriglyceridemia, we performed a sensitivity analysis with stratification for these two subgroups.

No major differences in the detection of NAFLD were observed between the two subgroups, except for LAP, which performed best in patients with hypertriglyceridemia (Table 3).

Exploratory analysis

LFS showed the highest ROC AUC value in the high-risk population. Since LFS is rather cumbersome to calculate due to the many variables included in the LFS equation, we investigated whether the number of variables included could be reduced without any loss in ROC AUC. Using the regression coefficients from the logistic regression analysis, the formula $0.27 \times \text{fasting insulin (mU/L)} - 2.6 \times \text{AST/ALT ratio}$ resulted in a higher ROC AUC than that for the original LFS, but this was not statistically significant (simplified LFS ROC AUC, 0.8404; original LFS, 0.7994; $P = 0.12$) in the high-risk population. However, in the population-based sample, the simplified version of LFS resulted in a lower ROC AUC than that for the original LFS (simplified LFS ROC AUC, 0.7464; original LFS, 0.7774; $P = 0.33$). Furthermore, the ROC AUC for the simplified LFS was lower than that for FLI in the population-based sample ($P = 0.039$ for difference) but was not higher than that for the other scores.

DISCUSSION

In accordance with our hypothesis, the NAFLD scores investigated demonstrated different NAFLD detection abilities in the two samples. Of the four evaluated scores, FLI was preferable in the population-based sample (NAFLD prevalence, 23%), whereas LFS performed best in the high-risk sample (NAFLD prevalence, 73%). The prevalence of the NAFLD scores found in this study were similar to those found in other population-based studies^[1-4,9] and in high-risk groups, such as diabetes^[15,16].

FLI is a simple score that can be applied by the general practitioner and was found

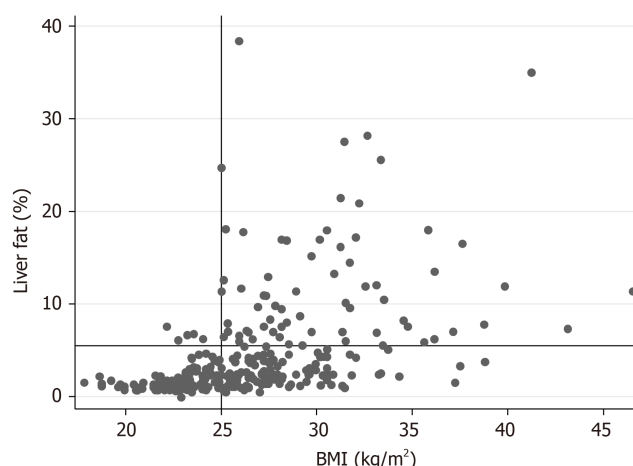


Figure 1 Relationship between body mass index and liver fat in the population-based prospective investigation of obesity, energy and metabolism study. The horizontal line indicates a liver fat of 5.5%, the limit for non-alcoholic fatty liver disease, while the vertical line indicates a body mass index of 25 kg/m². BMI: Body mass index.

to be useful in the general population as a screening tool. It should however be remembered that this would only be the first step in the characterization of NAFLD, demanding further investigations, for example, transient elastography or MR elastography, and eventually a biopsy.

In a study comparing three of the scores used in the present study *vs* liver histology (gold standard) in a sample of patients with a high prevalence of liver steatosis (95%)^[17], FLI, LFS, and HSI performed almost equally well to diagnose liver steatosis (AUC: 0.80-0.83). In another study comparing the different NAFLD diagnosis scores *vs* NAFLD diagnosed by imaging, LFS performed optimally in the population-based NHANES sample, with a NAFLD prevalence of 18% measured by ultrasound^[9]. In the NHANES-based study, use of LFS resulted in an AUC of 0.77 in the total sample, which is similar to the AUC for LFS in the population-based sample used in the current study; however, FLI showed a superior performance over LFS in this low-risk population. This difference in the performance of NAFLD scores between the two population-based sample sets could be due to differences in the sensitivity of the techniques used for NAFLD diagnosis in the two studies. The limited sensitivity of ultrasound for detecting mild steatosis might have led to an underestimation of NAFLD prevalence in NHANES^[9]. Further, the Scandinavian population included in the current population-based study was almost exclusively non-Hispanic Caucasians, which could have also influenced the performance of the NAFLD scores, since LFS and FLI performed almost equally in the non-Hispanic Caucasian subpopulation included in the NHANES study.

In the POEM study, very few cases of NAFLD were detected among subjects with a BMI < 25 kg/m², which is consistent with other studies^[18]. Thus, there is clearly a limited need to screen for NAFLD in subjects with normal weight. In the high-risk population (EFFECT studies), all patients had a BMI > 25 kg/m² and had either type 2 diabetes or elevated serum triglycerides (> 1.7 mmol/L). Not surprisingly, almost three-fourths of the population showed NAFLD measured with abdominal MRI-PDFF. In this high-risk population, LFS performed significantly better than FLI.

In the POEM study, 60% of subjects had a BMI > 25 kg/m², with a NAFLD prevalence of 35% in the overweight/obese subgroup of the population. In this moderate-risk population, the need for NAFLD screening is greater than that in the general population, as also suggested by other studies^[18]. Thus, future studies to determine an optimal screening tool for NAFLD should be performed in an overweight/obese population, which constitutes more than half of the middle-aged population in many countries.

Since LFS contains many variables and can be quite complicated to calculate in the clinical setting, we tried to simplify this score by using data on fasting insulin and AST/ALT only. This resulted in a simplified LFS score that performed at least as well as the original LFS in the high-risk sample but was less efficient in the population-based sample. However, if this finding of simplified LFS score could be reproduced by others in a high-risk group, the use of this simplified LFS score could be an attractive tool in the clinical setting for screening of NAFLD in high-risk individuals.

Another observation in the high-risk sample was that LFS performed almost

Table 2 Area under the curve of the receiver operating characteristic curves for the liver fat scores in the prospective investigation of obesity, energy and metabolism study

Liver fat scores	AUC
FLI	0.8190 (0.7661-0.8717)
LAP	0.7705 (0.7096-0.8271)
LFS	0.7774 (0.7106-0.8273)
HSI	0.7850 (0.7265-0.8458)

The 95% confidence interval for the total area under the curve is given in parenthesis. AUC: Area under the curve; FLI: Fatty liver index; HSI: Hepatic steatosis index; LAP: Lipid accumulation product; LFS: Liver fat score.

equally in the overweight/obese diabetes and hypertriglyceridemia subgroups. Thus, diabetes alone did not have a major impact on the predictive power of LFS, since many patients in the diabetes subgroup had hypertriglyceridemia.

The strength of this study is the evaluation and comparison of four different scores for NAFLD diagnosis in two different samples, high-risk and low-risk, using a validated, highly accurate, and reproducible method to quantify liver fat content, MRI-PDFF^[19]. The coefficient of variation for this method was found to be low (5.3%) in healthy volunteers. However, it is a limitation that we have not evaluated the coefficient of variation in populations with a high proportion of liver steatosis, in a similar manner to the sample based on the EFFECT studies. The C-statistics being used to evaluate the discrimination between the scores is known to be a rather weak test demanding large samples to be significant even if the difference in AUC is within the 2%-3% range. With sample sizes around 300 that were observed in the present study, we therefore have a limited power to detect significant differences regarding discrimination between the tests. In the present study, we performed a very detailed history of previous diseases and alcohol intake to exclude other causes of liver steatosis than NAFLD. Thus, although it cannot be excluded that we missed some cases of liver disease other than NAFLD, the vast majority of individuals included in the present study are not likely to have any liver disease other than NAFLD.

In conclusion, the four investigated scores for NAFLD diagnosis performed differently in the population-based setting compared with the high-risk setting. FLI was preferable in the population-based setting, while LFS, or a simplified version of LFS, performed best in the high-risk setting.

Table 3 Area under the curve of the receiver operating characteristic curves for the subgroups (diabetes and hypertriglyceridemia) in the high-risk population in the EFFECT studies

Liver fat scores	Diabetes	Hypertriglyceridemia	Total
FLI	0.6906	0.6896	0.6896 (0.6201-0.7591)
LAP	0.6744	0.7306	0.6844 (0.6171-0.7515)
LFS	0.8074	0.8168	0.7994 (0.7450-0.8538)
HSI	0.7457	0.7308	0.7450 (0.6768-0.8131)

The 95% confidence interval for the total area under the curve is given in parenthesis. FLI: Fatty liver index; HSI: Hepatic steatosis index; LAP: Lipid accumulation product; LFS: Liver fat score; ROC: Receiver operating characteristic.

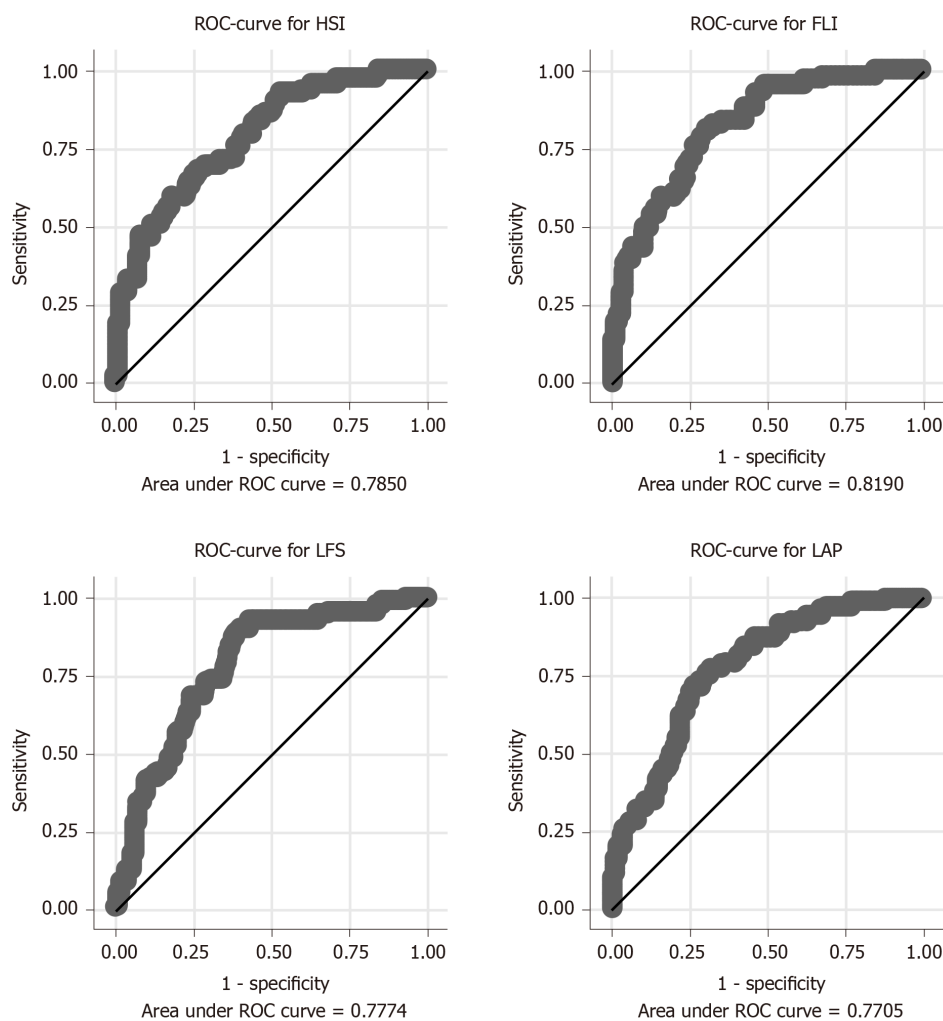


Figure 2 Relationship between the four scores in the detection of non-alcoholic fatty liver disease and measured liver fat > 5.5% given as receiver operating characteristic curves and area under the curve in the population-based prospective investigation of obesity, energy and metabolism study. FLI: Fatty liver index; HSI: Hepatic steatosis index; LAP: Lipid accumulation product; LFS: Liver fat score; ROC: Receiver operating characteristic.

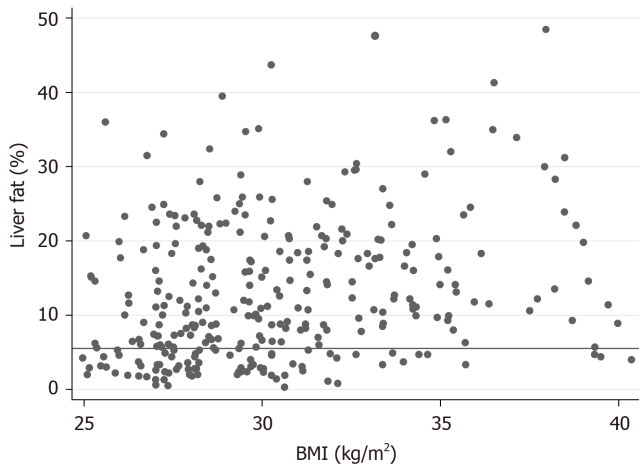


Figure 3 Relationship between body mass index and liver fat in the EFFECT studies. The horizontal line indicates liver fat 5.5%, the limit for non-alcoholic fatty liver disease. BMI: Body mass index.

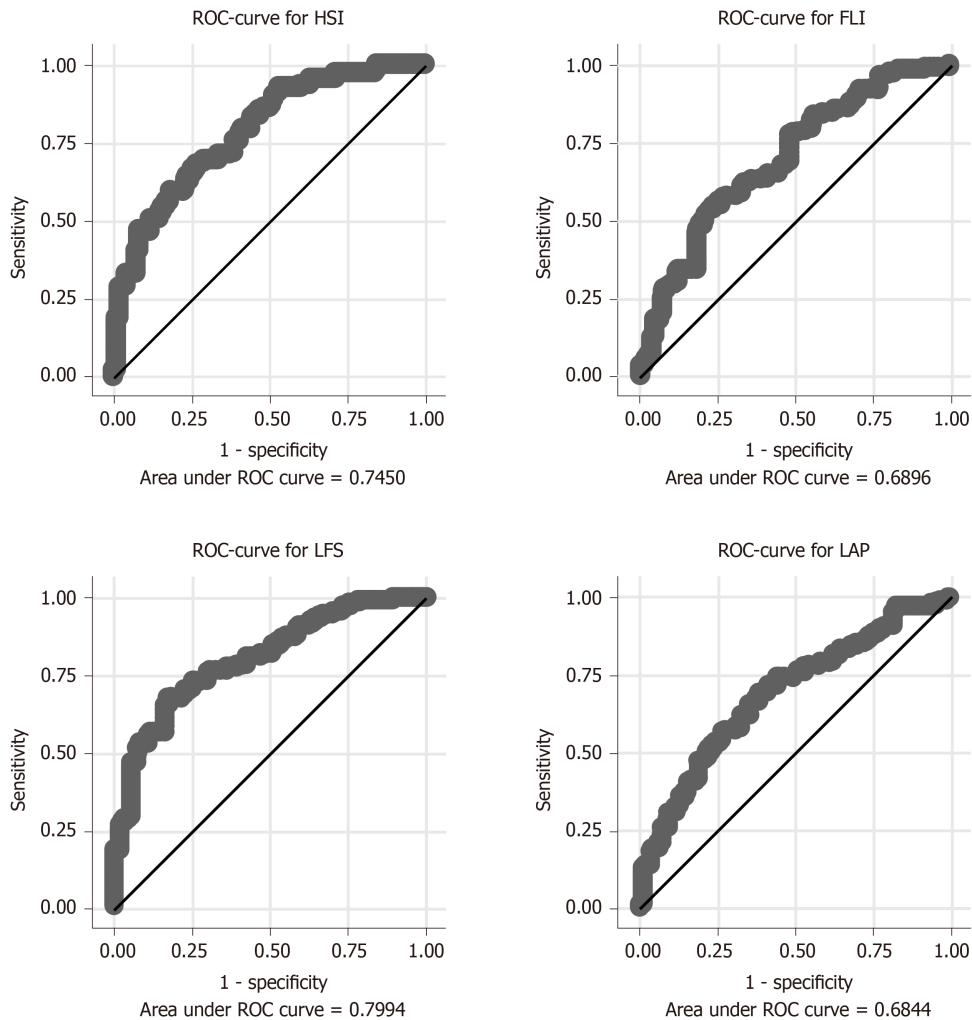


Figure 4 Relationship between the four scores in the detection of non-alcoholic fatty liver disease and measured liver fat > 5.5% given as receiver operating characteristic curves and area under the curve in the high-risk population investigated in the EFFECT studies. FLI: Fatty liver index; HSI: Hepatic steatosis index; LAP: Lipid accumulation product; LFS: Liver fat score; ROC: Receiver operating characteristic.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) is a common disorder, with an estimated prevalence of 20% to 35% in the general population. Several non-invasive indices based on routinely available biochemical and physical parameters have been developed for the detection of NAFLD. However, data comparing the efficacy of these indices within a population-based sample are lacking.

Research motivation

To better understand the applicability of different non-invasive indices for detecting NAFLD in a population-based sample [based on prospective investigation of obesity, energy and metabolism (POEM) study] *vs* a high-risk sample (based on EFFECT studies).

Research objectives

To compare the efficacy of four non-invasive indices, fatty liver index (FLI), hepatic steatosis index (HSI), lipid accumulation product (LAP), and NAFLD liver fat score (LFS), in predicting NAFLD in population-based samples comprising normal and high-risk individuals.

Research methods

NAFLD screening was performed in a population-based sample of 50-year-old individuals in Uppsala, Sweden ($n = 310$; POEM study) and a high-risk population comprising patients with a body mass index $> 25 \text{ kg/m}^2$ and either high plasma triglycerides ($\geq 1.7 \text{ mM}$) or type 2 diabetes ($n = 310$; EFFECT studies). NAFLD was defined as liver fat $> 5.5\%$ using magnetic resonance imaging-proton density fat fraction. FLI, HSI, LAP, and NAFLD LFS were assessed. A logistic regression model was used to evaluate the effectiveness of the different scores.

Research results

The prevalence of NAFLD was 23% in POEM. FLI showed the highest ROC AUC (0.82) and was significantly better than the LAP score ($P = 0.005$ *vs* LAP, $P = 0.08$ *vs* LFS, $P = 0.12$ *vs* HSI) for detection of NAFLD. The other three indices performed equally in POEM (0.77-0.78). The prevalence of NAFLD was 74% in EFFECT; LFS performed best (ROC AUC 0.80) in this sample. The ROC AUC for LFS (0.80) was significantly higher than that for FLI ($P = 0.0019$) and LAP ($P = 0.0022$), but not HSI ($P = 0.11$). We performed a sensitivity analysis with stratification for the two high-risk subgroups (patients with diabetes or hypertriglyceridemia) from the EFFECT studies. LAP performed best in patients with hypertriglyceridemia. No major differences were observed between the other scores.

Research conclusions

The four investigated NAFLD scores performed differently in the populationbased *vs* high-risk setting. FLI was preferable in the population-based setting, while LFS performed best in the high-risk setting.

Research perspectives

In the populationbased *vs* high-risk setting, the indices performed differently. FLI was preferable in the population-based setting, while LFS performed best in the high-risk setting.

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Combined endovascular-surgical treatment for complex congenital intrahepatic arterioportal fistula: A case report and review of the literature

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Abstract

BACKGROUND

Congenital intrahepatic arterioportal fistula (IAPF) is a rare vascular malformation in infants that causes severe portal hypertension (PH) with poor prognosis if untreated. Currently, radiological embolisation is considered the first-line therapy for simple IAPF; however, it might be not resolute for complex hepatic vascular lesions. When endovascular embolization is not sufficient to completely obliterate the IAPF, surgical intervention is needed, but it has been associated with severe morbidity and mortality in small children. Furthermore, indications are not defined.

CASE SUMMARY

We present the first case of a 6-month-old girl with trisomy 21 affected by a complex congenital IAPF, which caused severe PH, successfully treated with an endovascular-surgical hybrid procedure. The novel technique comprised a multi-step endovascular embolisation, including a superselective transarterial embolisation of the afferent vessels and a direct transhepatic embolisation of the dilated portal vein segment, combined with selective surgical ligation of the

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arterial branches that supply the fistula, which were too small to be embolised. The complex IAPF was also associated with severe cholestasis and intra/extrahepatic biliary tree dilatation, which was successfully treated by a temporary biliary drainage. At 24-mo follow-up, the hybrid endovascular-surgical procedure achieved complete occlusion of the complex IAPF and resolution of the PH. A comprehensive review of the literature on congenital IAPF management, focussed on alternative treatment strategies, is also reported.

CONCLUSION

The combined radiological-surgical approach is a safe and effective treatment option for complex IAPF and avoids major invasive surgery.

Key words: Liver; Intrahepatic arteriportal fistula; Congenital malformation; Portal hypertension; Radiological embolization; Hepatic surgery; Case report

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Core tip: Complex congenital intrahepatic arteriportal fistula (IAPF) is a rare vascular malformation causing severe portal hypertension, gastrointestinal hemorrhage and ascites in infants, for whom the therapeutic approach is challenging due to the children's small size and their poor clinical condition. Radiological embolization often isn't effective for complex lesions due to impossibility to embolize small afferent arterial branches, while surgical treatments (liver resection or liver transplantation) are associated with severe morbidity and mortality. We aimed to present a novel endovascular-surgical hybrid approach in an infant with complex congenital IAPF, providing a literature review on the treatment options and outcomes for congenital IAPF.

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INTRODUCTION

Intrahepatic arteriportal fistula (IAPF) is a rare vascular malformation characterized by abnormal intrahepatic communication between systemic arteries, commonly the hepatic artery (HA), and the portal venous system, without any communication with the systemic venous circulation^[1]. Less than 15% of IAPFs are congenital. The majority are secondary to liver trauma, surgery or liver puncture. In infancy, congenital IAPF may cause portal hypertension (PH) that manifests with severe gastrointestinal haemorrhage, ascites and hepatosplenomegaly. Various classifications have been proposed for congenital IAPF, based either on their location^[2] or supplying vessels^[3].

Although radiological embolisation of congenital IAPF is considered the first-line therapy^[4], it may be not resolute for complex lesions. When endovascular treatment is not sufficient to close the IAPF, surgical intervention is needed. Surgical options include ligation of the implicated arterial supply vessels, liver resection or liver transplantation (LT), all of which are associated with morbidity and mortality in small children with IAPF^[5-7].

In this report, we present the case of an infant girl with trisomy 21 affected by complex IAPF treated with a novel endovascular-surgical hybrid procedure. The literature of congenital IAPF was also systematically review.

CASE PRESENTATION

Chief complaints

A 6-month-old girl (4500 g of weight), with trisomy 21 and intraventricular septal defect, was referred for complex vascular lesion of the liver.

History of present illness

At presentation, the patient exhibited a poor clinical condition with gastrointestinal bleeding, severe PH with massive ascites (abdominal circumference: 49 cm), acute respiratory failure, fever, cholestasis (total/direct bilirubin: 18.1/13.6 mg/dL), thrombocytopaenia (platelets: 78.000/ μ L), coagulopathy (international-normalised-ratio: 1.5), vitamin-K under-supplementation and growth retardation (< 25th centile).

Abdomen Doppler ultrasonography (US) detected multiple intrahepatic shunts between the left portal vein (PV) and the left HA with turbulent flow characterised by arterial spikes (Figure 1A-C). The right and main PV were dilated with hepatofugal flow. A dilatation of the common biliary duct (6 mm) and the intrahepatic biliary tree were also detected.

A computed tomography (CT) scan confirmed a complex IAPF in segment IV of the liver formed by the connection of the left PV, left and right HA, left gastric artery, phrenic artery and numerous branches from an accessory right HA that arose from the superior mesenteric artery (SMA) (Figure 1D-F). Upper-gastrointestinal endoscopy showed esophageal varices grade 3 with red marks, which were treated by sclerotherapy. Due to massive ascites, diuretic treatment with furosemide (1 mg/kg/die) and spironolactone (2 mg/kg/die) was started. However, despite the maximization of the diuretic therapy, the ascites didn't improve and the patient presented acute respiratory distress due to abdominal distension. Therefore, daily paracentesis through a percutaneous abdominal pigtail drainage was required.

FINAL DIAGNOSIS

The patient had no history of previous liver procedure or abdominal trauma, and thus congenital complex IAPF was diagnosed and confirmed by arteriography of the celiac trunk, SMA and phrenic artery that supplied the hepatic vascular lesion (Figure 2A-C).

TREATMENT

After arteriography, radiological embolisation of multiple branches that originated from the right HA and the SMA was performed by glue cast, and by metallic coils [Guglielmi Detachable Coils (GDC) 360] from the phrenic artery (Figure 2D). After embolisation, the flow into the fistula decreased but the arterial-venous shunt persisted because it was supplied by an arterial network of dysplastic collaterals from the celiac trunk and SMA, which could not be catheterised due to their small size (Figure 2E and F). After 7 d, Doppler US showed a partial occlusion of the IAPF with persistent reverse pulsatile flow into the PV. As the clinical condition did not improve, a combined endovascular-surgical procedure was planned.

The hybrid procedure first used selective angiography to confirm a persistent flow into the intrahepatic fistula supplied by a dysplastic arterial network that originated from the right HA and the SMA, for which a selective embolisation was not feasible. Subsequently, though a midline xifo-umbilical laparotomy and under Doppler US guide, direct left PV puncture permitted a retrograde venous catheterisation of the fistula (by a microcatheter Excelsior SL 10) and multiple embolisations of the shunt using GDC 360 [4×15 ($n = 2$), 4×8 ($n = 1$), 3×8 ($n = 2$)]. After embolisation, persistent arterial flow into the vascular lesion was observed. Therefore, a second surgical phase was performed that consisted of ligation of multiple arterial branches from the right HA ($n = 2$) and SMA ($n = 2$) (Figure 3A-D). After the hybrid procedure, there was absence of flow into the IAPF as well as hepatopetal flow into the PV.

The post-operative course was uneventful; anticoagulant therapy was administrated for 3 mo to prevent PV thrombosis. Subsequently, PH progressively improved with gradual resolution of the ascites, allowing to suspend the daily paracentesis and to progressive withdraw diuretic drugs. However, US evidence of intra/extrahepatic biliary dilatation and hyperbilirubinaemia (total/direct bilirubin: 22.7/18 mg/dL) persisted. A percutaneous transhepatic cholangiography (PTC) revealed a uniform extrahepatic/intrahepatic biliary tree dilatation. Therefore, an internal-external biliary drainage (8 Fr) was inserted, and after 1 mo it was replaced by an internal biliary stent (Percuflex, 7 Fr, 7 cm; Figure 4A-C).

OUTCOME AND FOLLOW-UP

After 3 mo, angiography confirmed complete occlusion of the IAPF (Figure 3E and F).

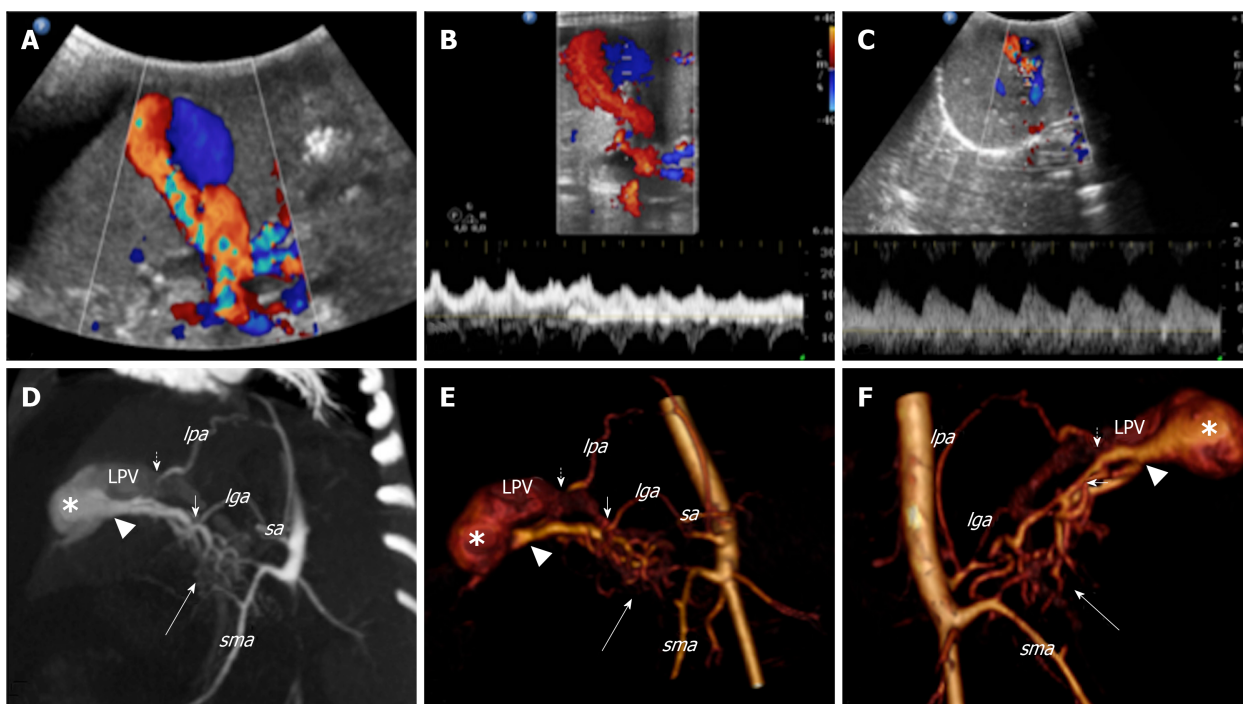


Figure 1 Colour Doppler ultrasound and computed tomography images that show the congenital intrahepatic arteriportal fistula. A: Colour Doppler ultrasound images of the liver revealed aneurysmal dilatation of the left portal vein with turbulent bidirectional flow; B: Particularly, the venous flow appeared arterIALIZED; C: Several dilated and tortuous branches of the hepatic artery with high flow rate supplied the dilated portal vein segment; D: Contrast enhanced multi-detector computer tomography images of the abdomen reformatted on both the left oblique: maximum intensity projection; E: 3D volume rendered; F: 3D-VR right oblique plane. Contrast enhanced multi-detector computer tomography shows the complex vascular malformation characterised by a dense dysplastic small arterial network that arose from the hepatic and superior mesenteric system (thick arrow) and directly converged to the left portal vein through one Y-shaped fistula within the Rex recess (arrow head). Two additional feeders to the vascular anomaly [from the phrenic (short dotted arrow) and left gastric (short arrow) artery, respectively] were also detected. lga: Left gastric artery; lpa: Left phrenic artery; sa: Splenic artery; sma: Superior mesenteric artery; LPV: Left portal vein.

Since the cholestasis was resolved, the biliary stent was endoscopically removed without complications. At 24-mo follow-up, the child is in good clinical condition with an appropriate growth [weight: 10.2 kg, height: 80 cm (> 50th centile)], normal liver function tests (total/direct bilirubin: 1.3/0.8 mg/dL), absence of biliary tree dilatation and ascites as well as free from drug treatment. The last Doppler US revealed total occlusion of the IAPF and absence of detectable intrahepatic portal flow, but there was patent extrahepatic PV without signs of PH. A summary of the patient's clinical course and therapeutic management is reported in [Figure 5](#).

DISCUSSION

IAPF is a rare cause of PH in infants; it presents by 2 years of age in approximately 70% of cases^[3]. Clinical presentation includes gastrointestinal bleeding (66%), splenomegaly (63%), chronic diarrhoea (50%), failure to thrive (50%), hepatomegaly (41%) and ascites (47%)^[2,3]. Doppler US is usually efficient for IAPF diagnosis. It reveals arterial pressure that peaks into the vascular lesion and pulsatile hepatofugal flow in the portion of the PV adjacent to the fistula. CT scan or magnetic resonance imaging is commonly used to define the vascular anatomy, and IAPF is identified by the early enhancement of the lesion in the arterial phase^[3]. Hepatic angiography permits accurate definition of the lesion's characteristics (location and afferent vessels) to make a differential diagnosis from other vascular anomalies (haemangioma or hepatic sinusoidal obstruction syndrome) and to treat the vascular lesion, usually during the same session.

Congenital IAPFs were usually classified according to their location^[2]: Small peripheral intrahepatic lesions, with minimal hemodynamic effects (type-1); central lesions, with consequent PH (type-2); diffuse intrahepatic lesions that compromise liver function (type-3). In 2006, Norton *et al*^[3] proposed a new IAPF classification based on the afferent vessels supplying the fistula: unilateral lesions (type-1) that involve only one between the right, left or main HA; bilateral lesions (type-2) that comprise both HAs; complex lesions (type-3) that involve both HAs and at least one non-HA.

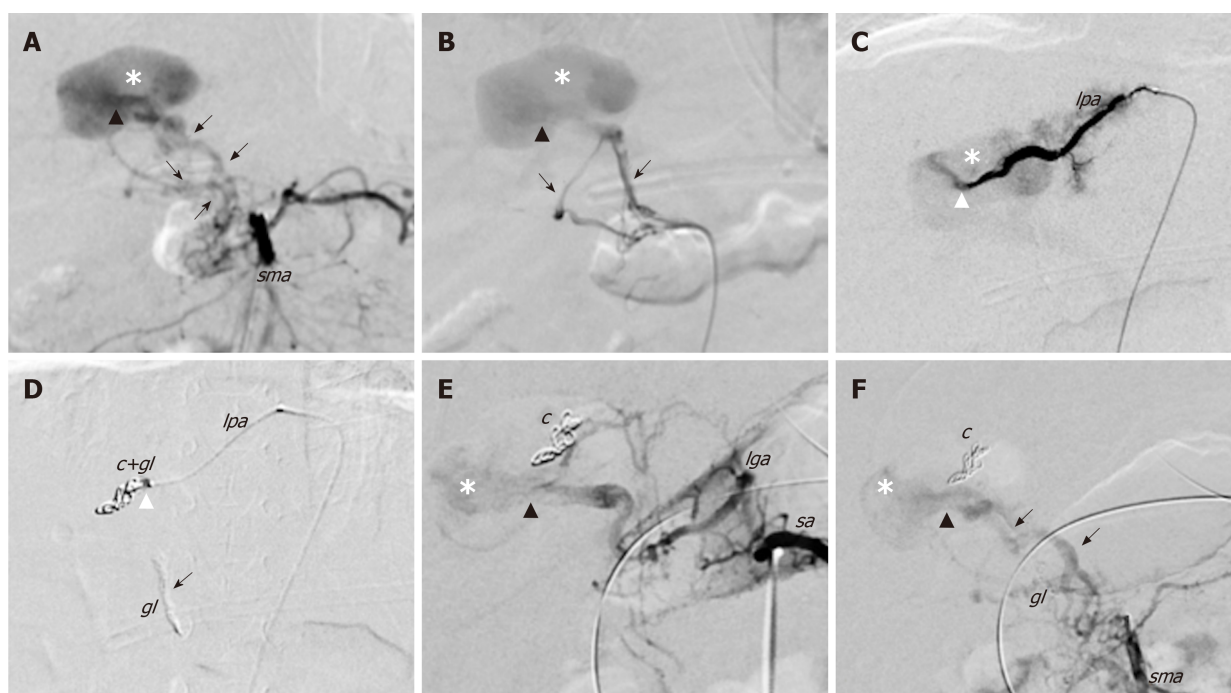


Figure 2 First angiography and endovascular embolization of the congenital intrahepatic arteriportal fistula. Initial endovascular treatment of the malformation (digital subtraction angiograms). A and B: Angiograms from the superior mesenteric artery show dilated and tortuous dysplastic arteries (black arrows) that converged into the left aneurismal portal vein through one Y-shaped fistula within the Rex recess (black arrow head); C: Superselective catheterisation of a distal branch of the left phrenic artery that shows the additional shunt (white arrow head) into the venous aneurism; D: Embolisation of the shunts with glue and coils with glue cast; E and F: Angiographic control images from celiac trunk (E) and superior mesenteric artery (F) that show persistent patency of the fistula after the embolisation. c: Coils; gl: Glue; lga: Left gastric artery; lpa: Left phrenic artery; sma: Superior mesenteric artery; sa: Splenic artery.

In the literature, the experience of congenital IAPF is limited to case report or small case series^[1,3,5,8-31]. To the best of our knowledge, of 44 congenital IAPF cases described so far, the majority of lesions were type-1 ($n = 19$; 43.2%) according to the Norton *et al*^[3] classification, followed by type-2 ($n = 10$; 22.7%) and type-3 ($n = 10$; 22.7%) IAPF. In 5 (11.4%) cases, the lesion type was not specified. The median age at diagnosis was 1 year (range: 17 d to 79 years), 43.2% ($n = 19$) were < 6 mo and 13.6% ($n = 6$) were > 18 years of age. As in our child, in 20.5% ($n = 9$) of cases the vascular anomaly was associated with trisomy 21. However, a relationship with this genetic anomaly has not yet been defined^[30]. The only other associated malformation was congenital heart disease ($n = 2$, 4.5%), with atrial/ventricular septal defects and patent ductus arteriosus.

Overall, endovascular embolisation was the primary treatment in 88.6% ($n = 39$) of congenital IAPF and 25.6% ($n = 10$) of patients required multiple endovascular procedures (range: 2-5), while 5 (11.4%) patients were initially treated with surgery (Table 1).

Radiological embolisation was successful for type-1/2 IAPF in 81.5% of cases (62.9% with one procedure, 18.5% with \geq two procedures). In complex type-3 IAPF, endovascular embolisation alone was effective in 62.5% of patients (37.5% with one procedure and 25% with \geq two procedures).

Of 10 patients with complex type-3 IAPF, embolisation was the first line-therapy in 8 (80%) cases, out of which 5 (50%) patients had complete occlusion of the IAPF (3 with one procedure and 2 with \geq two procedures), while in 3 (30%) cases radiological embolisation was not resolute due to the rapid re-collateralisation of the hepatic fistula after the endovascular treatment. This phenomenon required a secondary surgical treatment (1 end-to-side portocaval shunt, 1 LT and 1 patient had persistent PH). Finally, 2 (20%) patients with type-3 IAPF had surgery as the first therapeutic intervention: 1 child was successfully cured by liver resection, while 1 patient was treated by arterial ligation followed by radiological embolisation with subsequent only partial occlusion of the shunt. This patient died after cardiac surgery due to associated heart malformation.

After a median follow-up of 12 mo (range: 1-60), all patients with type-1/2 IAPF were alive with occluded shunt, while of the children with type-3 lesions, 7 (70%) were alive with occluded shunt, 2 (20%) were alive with persistent flow into the IAPF and 1 (10%) died after surgery.

In our case, the initial angiography detected a complex type-3 IAPF supplied by

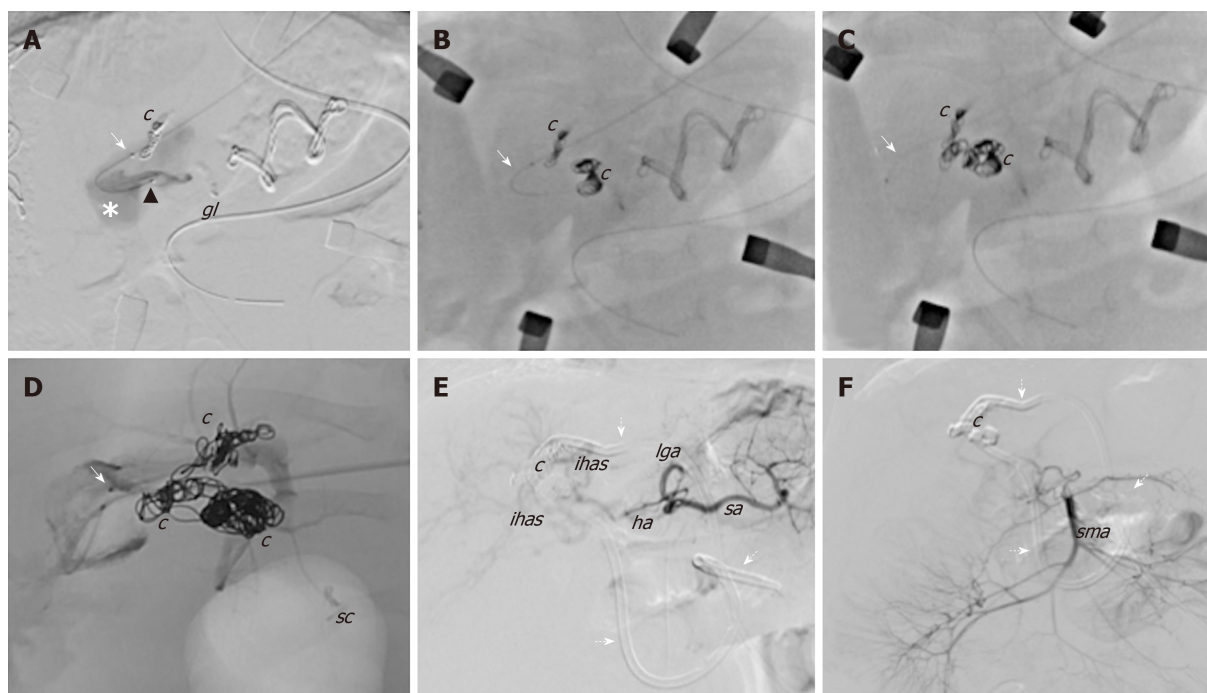


Figure 3 Angiographic images during the hybrid endovascular-surgical procedure of the congenital intrahepatic arteriportal fistula. A-D: The initial attempts of selective anterograde catheterisation of the vascular malformation failed due to the small size of the arterial branches, and thus a hybrid procedure was performed. It consisted of (1) retrograde venous catheterisation of the fistula through direct left portal vein puncture (white arrow) and embolisation of the shunt with coils; and (2) surgical exposure of the Rex and selective surgical ligation of the small dysplastic arteries feeding the fistula; E and F: Final angiographic images from the celiac trunk and the superior mesenteric artery, which revealed complete closure of the shunt without signs of revascularisation. c: Coils; gl: Glue; ha: Hepatic artery; ihas: Intrahepatic arteries; lga: Left gastric artery; lpa: Left phrenic artery; sma: Superior mesenteric artery; sa: Splenic artery; sc: Surgical clips; Dotted arrows: External internal biliary drainage.

major arterial vessels (celiac trunk, HA, SMA and phrenic artery). Only following embolisation of the dominant feeding arteries (from the celiac trunk and phrenic artery), a complex dysplastic network of small arterial vessels that supplied the fistula became apparent; however, they could not be embolised due to their small size. At this step, surgical options (including liver resection, portacaval shunt or LT) were considered, but we preferred a mini-invasive approach due to the infant's severe clinical condition. Therefore, an hybrid technique was chosen to allow: (1) Intraoperative transhepatic embolisation of the aneurysmal component of the PV under US guide, allowing for direct bleeding control; and (2) Selective surgical distal ligation of small arterial branches that supplied the shunt, which was not feasible for embolisation. This combined approach achieved complete occlusion of the IAPF, with consequent resolution of the PH, and also permitted preservation of the main HA trunk for possible future LT. A major complication of endovascular IAPF treatment involves PV thrombosis^[32], and thus prevention by anticoagulation was initiated soon after the procedure and maintained for 3 mo. Although no thrombosis was initially detected, the last follow-up revealed the absence of intrahepatic portal flow but well-compensated intrahepatic hemodynamics and patent extrahepatic PV. These findings suggest that the anticoagulant therapy might be prolonged after the procedure, but further data are needed to define the type and duration of anticoagulant regimen. Other embolisation-related risks include movement of the embolic agents to an incorrect site, pseudoaneurysm of the accessed artery and bile duct injury^[31], none of which were observed in the current case.

Nevertheless, in our infant the complex IAPF was associated with severe cholestasis and intrahepatic biliary tree dilatation with distal common bile duct stricture. The cause of the biliary complication was unclear (so far, no other case of congenital IAPF has been associated with biliary issues). We related it to ischaemic damage and/or compression by the vascular lesion. Therefore, we first chose to treat the vascular lesion. Subsequently, because the cholestasis did not improve after the IAPF occlusion, a biliary stent by PTC was inserted, and it was removed only after evidence of a complete resolution of the biliary dilatation.

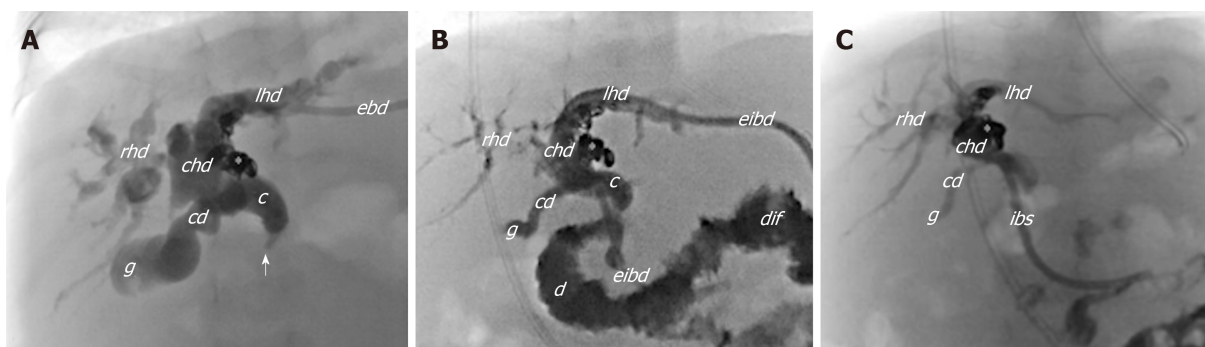


Figure 4 Cholangiogram. A: Cholangiogram from the external biliary drainage shows marked dilatation of both intra- and extrahepatic biliary tree with tortuous and convoluted appearance of ducts and the stricture (arrow) of the distal tract of the choledocus without passage of contrast medium into the bowel system; B: Cholangiogram after positioning the external-internal biliary drainage showing slight reduction of the biliary dilatation, particularly within the right system; C: Cholangiogram after 3 mo of internal biliary stent placement that shows almost complete resolution of the biliary dilatation. c: Choledocus; cd: Cystic duct; chd: Common hepatic duct; dif: Duodenojejunal flexure; ebd: External biliary drainage; eibd: External-internal biliary drainage; g: Gallbladder; ibs: Internal biliary stent; lhd: Left hepatic duct; rhd: Right hepatic duct; asterisk: Coils; Arrow: Stricture within the distal choledocus.

CONCLUSION

Since the first experience in 1996, endovascular embolisation is currently considered the first-line treatment for congenital IAPF. It presents an overall success rate of 79.5%, and it requires multiple endovascular procedures in 25.6% of cases. So far, radiological embolisation has been resolute in 81.5% of children with simple IAPF (type-1/2) and in 62.5% with complex IAPF (type-3). Yet, data on the optimal type of embolisation agent (coils or glue), post-procedure anticoagulant regimen and long-term complications and outcomes are lacking, and must be defined. Surgical procedures are rarely used as a first-line treatment and no definitive criteria can be drawn yet due to the lack of long-term outcomes. Although surgical ligation of arterial vessels that feed the IAPF is most commonly performed, it does not yet appear to be effective for complex IAPF when performed alone. Moreover, other surgical options (portacaval shunting, liver resection or LT), all of which were used as salvage treatments after embolisation, have no defined indication and limited to personal experience.

Although this study is limited to a single case, our experience suggests that for complex type-3 IAPF the hybrid approach that consists of a multi-step endovascular embolisation (embolisation of the afferent arterial vessels and direct transhepatic embolisation of dilated PV segment) combined with selective surgical ligation of arterial branches that feed the fistula (too small to be embolised) may be a safe and resolute treatment to avoid major invasive surgery as portacaval shunting, liver resection or LT.

Table 1 Treatments and outcomes of congenital intrahepatic arteriportal fistula reported in literature, *n* (%)

Type of first-line treatment	Overall (<i>n</i> = 44, 100%)	Type-1 IAPF (<i>n</i> = 19, 43.2%)	Type-2 IAPF (<i>n</i> = 10, 22.7%)	Type-3 IAPF (<i>n</i> = 10, 22.7%)	Type not specified (<i>n</i> = 5, 11.4%)
Radiological embolization	39 (88.6)	17 (89.5)	10 (100)	8 (80)	4 (80)
-Overall success rate	31 (79.5)	15 (88.2)	7 (70)	5 (62.5)	4 (100)
-Success rate for one procedure	21 (53.8)	13 (76.5)	4 (40)	3 (37.5)	1 (25)
-Success rate for multiple procedures	10 (25.6)	2 (11.8)	3 (30)	2 (25)	3 (75)
-Patients requiring subsequent surgery	8 (20.5)	2 (11.8) (liver resection)	3 (30) (1 LT, 1 liver resection/arterial ligation, 1 end-to-side porto-caval shunt)	3 (37.5) (1 endo-to-side portocaval shunt, 1 LT, 1 persistent PH)	-
Surgery	5 (11.4)	2 (10.5)	-	2 (20)	1 (20)
Arterial ligation	4 (9.1)	2 (10.5)	-	1 (10)	1 (20)
-Success rate	2 (50)	2 (100)	-	0 (0) (persistent shunt)	0 (0) (required subsequent embolization)
Liver resection	1 (2.3)	-	-	1 (10)	-
-Success rate	1 (100)	-	-	1 (100)	-

IAPF: Intrahepatic arteriportal fistula; LT: Liver transplantation; PH: Portal hypertension.

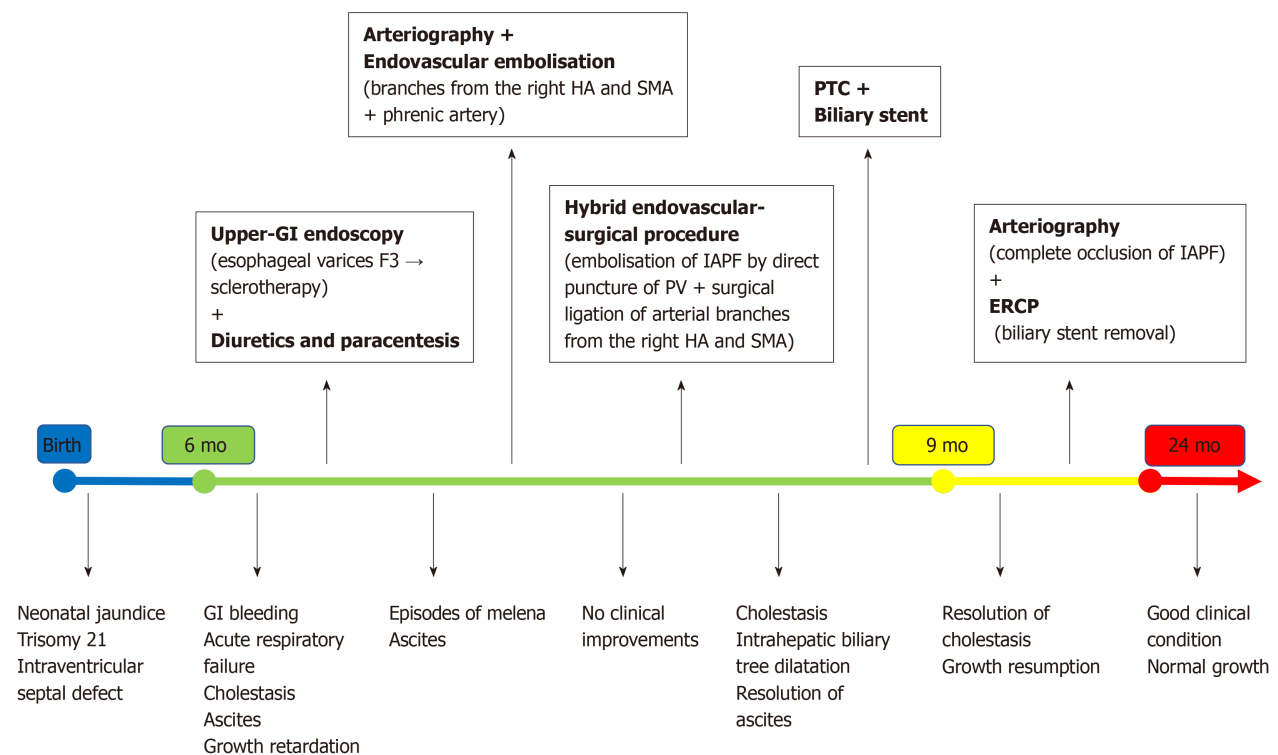


Figure 5 Summary of the patient's clinical course and the therapeutic management. Upper-GI: upper-gastrointestinal; ERCP: endoscopic retrograde cholangiopancreatography; HA: Hepatic artery; IAPF: Intrahepatic arteriportal fistula; PV: Portal vein; PTC: Percutaneous transhepatic cholangiography; SMA: Superior mesenteric artery.

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Inflammatory myofibroblastic tumor of the liver: A case report and review of literature

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Abstract

BACKGROUND

Inflammatory myofibroblastic tumors of the liver (IMTL) are extremely rare neoplasms and very little is known about their clinical presentation, pathogenesis, and biological behavior. Due to their absolute rarity, it is almost impossible to obtain a definite diagnosis without histological examination. Because of their intermediate biological behavior with the risk for local recurrence and metastases, surgical resection is recommend whenever IMTL is suspect.

CASE SUMMARY

We herein present a case of an otherwise healthy 32-year-old woman who presented with intermittent fever, unclear anemia, malaise and right flank pain 4 mo postpartum. The liver mass in segment IVa/b was highly FDG avid in the positron emission tomography-computed tomography. Hepatic resection was performed achieving a negative resection margin and an immediate resolution of all clinical symptoms. Histological analysis diagnosed the rare finding of an inflammatory myofibroblastic tumor of the liver and revealed cytoplasmic anaplastic lymphoma kinase expression by immunohistochemistry. Twelve months follow-up magnetic resonance imaging showed no recurrence and no metastases in the fully recovered patient.

CONCLUSION

IMTLs are extremely rare and difficult to diagnose. Due to their intermediate biological behavior, surgical resection should be perform whenever feasible and patients should be followed-up in order to detect recurrence and metastasis as early as possible.

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Core tip: In summary of the literature and with the experience from our own recent case, complete surgical resection of suspected inflammatory myofibroblastic tumors of the liver should be the preferred treatment of choice in order to rule out malignancy, avoid long-term medical treatment and to be able to recommend an appropriate follow-up for the patient.

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INTRODUCTION

Inflammatory myofibroblastic tumors (IMT) are rare diagnostic findings and little is known about their etiology, pathogenesis and clinical behavior. First described in the lungs, this rare neoplasm can occur in various tissues and organs of the human body^[1-4]. Whereas IMTs were originally considered as inflammatory pseudo tumors, they are now recognized as true neoplasms in the histological typing of the soft tissue tumors classification of the World Health Organization with intermediate biological potential due to their ability to recur and to metastasize^[1,4]. IMTs of the liver (IMTL) are even more seldom and most published literature are case reports (Table 1) or small case series (Table 2). Most patients present with either abdominal pain or fever, in others the tumor is detected incidentally^[5]. A systemic inflammatory process with leukocytosis, elevated C-reactive protein (CRP) and other systemic inflammatory markers often accompanies the clinical presentation^[3,5-11]. Although this type of neoplasm can occur in individuals of all ages, it seems more common in children and young adults^[4,12]. The etiology of IMTL is unclear^[4], but cytogenetic alterations suggest a clonal origin of these lesions^[3,4]. Proof of diagnosis is difficult since no tumor markers are available and radiological findings are often not specific^[6,8,13]. Surgical resection is usually considered as the treatment of choice for these rare findings. IMTLs mostly present as solitary lesions with typical firm surfaces. Histopathologically, they can have three basic patterns, which are often combined in one tumor: (1) A myxoid/vascular; (2) Spindel cell; and (3) Hypocellular fibrous pattern^[4]. The tumor is frequently infiltrated by eosinophils, lymphocytes and plasma cells^[4]. Rearrangements of the anaplastic lymphoma kinase (ALK) gene locus are common in IMTs supporting its neoplastic origin. ALK overexpression and its positive immunohistochemical staining is reported in 50%-60% of the cases^[14]. Differential diagnoses of IMTL include metastatic sarcomatoid carcinoma, spindel cell sarcoma or melanoma, gastrointestinal stromal tumor, sarcoma, solitary fibrous tumor and calcifying tumors besides the large group of inflammatory pseudotumors^[6]. Although these lesions generally show a benign behavior, there is the possibility of malignant transformation and development of metastases^[15,16]. Some small case series of IMTs described the anatomic location, size and age as potential risk factors correlated with recurrence^[2,13,17]. In addition, ALK reactivity in the primary tumor was associated with a non-metastatic course of the disease^[6]. In the liver, a malignant transformation is extremely rare and only very few cases with local recurrence or metastases have been described^[1,18]. Due to the scarcity of this disease, the role of a preoperative biopsy is unclear, but because of the difficulty to obtain a proper histopathological diagnosis and the risk of malignant transformation, surgical resection is usually recommended whenever technically feasible^[5,8,9,19,20].

We herein report the case of a 32-year-old woman who received an immediate hepatic resection for a large IMTL causing intermittent fever 4 mo postpartum.

CASE PRESENTATION

Chief complaints

A 32-year old woman presented herself to her family doctor with intermittent fever, unclear blood loss, malaise and pain in the right flank 4 mo postpartum.

History of present illness

The patient reported that the symptoms began 4 mo after she gave birth to her healthy child. She complained about fatigue and right upper quadrant abdominal pain. She had recurrent episodes of fever up to 38.5 °C, but no jaundice or pruritus.

History of past illness

There was no significant history of past illnesses.

Personal and family history

Personal and family history was unremarkable. She gave birth to a healthy child 4 mo before she was treated at our institution.

Physical examination upon admission

Vital signs were within the normal range, body temperature was 38.5 °C. On examination, the patient had a right upper quadrant tenderness, without jaundice or hepatosplenomegaly.

Laboratory examinations

Urine and most blood analyses were without any pathological findings including a normal liver function and normal ferritin levels. While the white blood cell count was normal, CRP was elevated to 181 mg/L. The liver enzymes (aspartate-aminotransferase 31 U/L, alkaline-aminotransferase 49 U/L) and cholestasis parameters (alkaline-phosphatase 466 U/L, γ -glutamyl transferase 424 U/L) showed an increase while the serum bilirubin (6 μ mol/L) stayed normal.

Imaging examinations

An ultrasound of the abdomen (**Figure 1A**) revealed a round, encapsulated liver lesion in segment IVa/b of unclear dignity, a non-contrast computed tomography of the abdomen ruled out urolithiasis, but confirmed the suspicious lesion of 8 cm in the liver as an incidental finding. The computer tomography (CT) and, same day magnetic resonance imaging (MRI) of the upper abdomen (**Figure 1B-F**) showed an 8 cm \times 8 cm tumor in segment IVa/b of the liver suspected to be a liver adenoma. Additional serological tests for hepatitis, the tumor markers carbohydrate-antigen 19-9 and alpha-fetoprotein, and markers for echinococcosis were all negative. After discussion of the case in our interdisciplinary liver tumor board on the next day, we performed a positron emission tomography-computed tomography (PET-CT) which showed the known lesion as a metabolically active tumor resembling an inflammatory pseudotumor of the liver or a malignant tumor of unclear origin. No other lesions were detected in any of the performed scans.

Further diagnostic work-up

The pathologist macroscopically (**Figure 2**) described the size of the resected specimen as wedge-shaped and nodular, 9.5 cm \times 7.0 cm \times 7.5 cm. The capsule of the liver was about unremarkable on one-half of the specimen. An area of 7.5 cm \times 7.5 cm \times 6.2 cm was sharply circumscribed, whitish/creamy and fibrous. No clearly definable capsule. The remaining liver tissue was inconspicuous and showed no further hereditary findings. The total weight of the tumor was 198 g. Immunohistochemistry showed a clear expression of cytoplasmic ALK and a weak expression of smooth muscle actin. Cytokeratin-PAN (CK Pan), Cytokeratin 18 (CK18), signal transducer and activator of transcription protein 6 (STAT6), Desmin, tyrosin-protein (C-kit), discovered on gastrointestinal stromal tumors 1 (DOG1), ETS related gene (ERG), family of calcium binding protein (S100) and SRY-related HMG-box 10 Protein (SOX10) showed no expression. The intra-tumoral immunoglobulin G4 (IgG4)-positive plasma cells were slightly increased, but displayed only a very small percentage of all plasma cells (**Figure 3**). The pathological diagnosis revealed an IMTL with no fibrosis and no malignancy.

FINAL DIAGNOSIS

The final diagnosis of the presented case is an IMTL.

Table 1 Case reports

Ref.	n	Age (yr)	Gender	Clinical and laboratory findings	Radiology	Localization	Tentative diagnosis	Treatment	Histology	Follow up
Watanabe <i>et al</i> ^[23] , 2019	1	70	Female	Incidental finding	CT unenhanced, low density	Right lobe	HCC	Right partial hepatectomy	Unencapsuled, partly ill defined expansive mass, myofibroblast-, fibroblast after 7 mo cells, inflammatory cells, SMA+, cytokeratins AE1/AE3+; CK7, CK18+, Desmin-, CD68-, IgG4+, ALK-	No recurrence
Al-Hussaini <i>et al</i> ^[24] , 2019	1	8	Male	FUO, weight loss, hepatomegaly, normal liver enzymes, CRP↑	MRI: Contrast-enhancing, hyper-intense, well-defined lesion	Right lobe	Infection DD malignancy	Right lobe hepatectomy	Multinucleated giant cells, inflammatory cells, SMA-, ALK-1-, CD-21- CD-23- CD-68+	No recurrence after 4 mo
Lu <i>et al</i> ^[23] , 2018	1	20	Male	FUO, jaundice, abdominal pain, CA 19-9↑	MRI: Multiple lesions, intrahepatic bile duct was significantly dilated	Left lobe	CCC	Biopsy, patient declined operation, PTCD	Spindle cells proliferation and infiltration by mixed inflammatory cells, ALK+, SMA+	NM
Jin <i>et al</i> ^[23] , 2017	1	42	Female	Fatigue, fever, pale conjunctivae; Hb↓, Lc↑	U/S: Hypochoic mass with unclear border; CT: Low density lesion with mild enhancement	Right lobe	Liver abscess	Right posterior segmentectomy	Chronic inflammatory cells, spindle cells; CD68+, smooth muscle actin, ALK-	No recurrence after 32 mo
Mulki <i>et al</i> ^[23] , 2015	1	50	Male	Abdominal pain, anorexia, mild fever, hepatomegaly	U/S: 2 hypodense masses, CT: + hepatic vein thrombus	Right lobe	Abscess with septic thrombus	Initial treatment: Biopsy, pigtail, antibiotics, secondary operation	Plasma cells, inflammatory cells, ALK, IgG4+	No residual disease
Obana <i>et al</i> ^[23] , 2015	1	69	Male	FUO, CA 19-9 48 ng/mL (<i>ni</i> : < 37 ng/mL), Diabetes mellitus II, Dyslipidemia, hypertension	U/S: Irregularly shaped, low-echoic mass; CT: Peripherally enhanced, MRI: T1W, central portion hyperintense	Right lobe Seg VI	CCC/HCC	Partial hepatectomy	Whitish-yellow mass 2 cm in size, inflammatory cell infiltrates, cholesterol cleft granuloma with focal abscess were observed in the central compartment, IgG4 -	NM
Guerrero Puente <i>et al</i> ^[24] , 2015	1	75	Male	Weight loss, fever, intermittent night sweat, abdominal pain, CRP↑, leukocytosis, cholestasis hypertension, hypercholesterinemia	CT: 8 cm heterogeneous focal lesion, portal branch thrombosis, lymphadenopathy; MRI: T2W isointense, T1W discretely hypointense, cystic-necrotic areas, perilesional edema	Left lobe	Inflammatory disease	CT-guided biopsy followed by antibiotic therapy	Inflammatory pseudotumour, vimentin+, AML+, desmin-, CD68-, ALK-, with no light chain restriction and a low proliferative index (15%)	Partial remission after 1 mo, almost complete remission after 6 mo
Onieva-González <i>et al</i> ^[27] , 2015	1	70	Male	Low-grade fever, asthenia, weight loss and oligoarthritis, lung tuberculosis, diabetes, gouty arthritis, renal lithiasis and colon diverticulitis	CT: Thickened gallbladder wall, poorly-defined hypodense lesion of 17 mm in the gallbladder bed, U/S: Nodule; MRI: Hypointense in T2 sequences, PET: No metabolism	Seg. V	Liver abscess	Antibiotic therapy, after 4 mo later fine needle biopsy followed by laparoscopic biopsy and cholecystectomy with the lesion in the gallbladder bed	Lymphoid infiltration without malignancy signs, compatible with an inflammatory pseudotumour	NM
Chang <i>et al</i> ^[29] , 2014	1	38	Male	Fatigue, abdominal distension and weight loss, jaundice, hepatomegaly, bilateral ankle edema	U/S: Complex mass; CT: Large cystic or necrotic mass; MRI: T2W: Cystic portion hyperintense to liver parenchyma, surrounded by a hypointense rim. T2W: Hyperintense compared to liver parenchyma	Bilateral	N/A	Ultrasound-guided and open biopsy, followed by resection	Cellular spindle-cell proliferation with heavy inflammatory infiltrate consisting primarily of plasma cells and lymphocytes	Recurrence after 2.5 yr

You <i>et al</i> ^[33] , 2014	1	43	Male	Chronic cough, right-upper-quadrant pain, anorexia for 3 mo, leukozytosis, elevated platelet count	U/S: 18 cm mass with slightly echogenic center; MRI: Large mass with central dark area and some peripheral spokes; CT: Mass, 20 cm × 17 cm × 18 cm, with extensions into the medial segment of the left hepatic lobe, hypervascular nodular area with enhanced density at the periphery and hypoattenuating density centrally	Right lobe	Fibrolamellar hepatocellular carcinoma or CCC	Percutaneous needle core biopsy > NM	Bland spindle cell proliferation amidst small mature lymphocytes, numerous plasma cells, histiocytes, and few neutrophils. Spindle cells showed a storiform pattern with large areas of necrosis; cytokeratin (CAM 5.2), cytokeratin 5/6-, actin-, CD34-, CD117-, DOG-1-, desmin-, CD68-, S100-, Pan-melanoma-. Spindle cells were negative for CD21, CD23, CD35, ALK-1. Epstein-Barr virus-encoded small RNA in situ hybridization (EBER) showed large numbers of Epstein-Barr virus positive cells, including some spindle cells	NM
Durmus <i>et al</i> ^[36] , 2014	1	67	Female	Moderate diffuse abdominal tenderness, focus over epigastrium	U/S: Heterogeneous hypoechogenic tumor; CT: Contrast enhancing mass with irregular confluent non-enhancing areas in the center with a hypodense late enhancing rim and no wash-out in the late phase, MRI: In T1W hypointense borders, well defined without fatty components. T2W showed a heterogeneous slightly hyperintense lesion with an ill-defined hyperintense rim	Segment IV	Malignancy	Left hemihepatectomy with partial excision of the adherent abdominal wall and diaphragm	Tumor with fibrosis and partially necrotic tissue infiltrated by inflammatory cells, predominantly plasma cells, and also pigmented macrophages and granulocytes	NM
Wong <i>et al</i> ^[37] , 2013	1	56	Female	Right-upper-quadrant abdominal pain, renal transplant	U/S: 2 cm × 2.4 cm mass in the left hepatic lobe with associated biliary duct dilatation, MRI: atrophic left liver lobe with multiple strictures and distal duct dilatation. 2-cm lesion at the origin of the left hepatic duct	Left lobe	Primary hepatic tumor	Surgical resection	Dense hyalinised stroma and scattered, histiocytic and lymphocytic inflammation	NM
Kruth <i>et al</i> ^[38] , 2012	1	NM	NM	FUO CRP†	Gastroscopy, CT lung and abdomen, MRI: 3.3 cm lesion	Seg. VI	Adenoma, focal nodular hyperplasia or HCC	Surgical resection	NM	No recurrence after 1 yr
Chablé-Montero <i>et al</i> ^[39] , 2012	1	23	Female	Fever, diaphoresis, right-upper-quadrant abdominal pain	U/S and CT: Heterogeneous rounded hepatic lesion of 7 cm in greatest dimension	Right lobe	Pyogenic hepatic abscess	Antibiotics, later right hepatic lobectomy	Grossly a non-encapsulated but well demarcated hepatic tumor with central necrosis of 11 cm in greatest dimension microscopically: Spindle myofibroblastic cells arranged in fascicles. Leukocytes, lymphocytes, plasma cells, SMA+	NM

Kayashima <i>et al</i> ^[30] , 2011	57	Female	Asymptomatic laparoscopic calculous cholecystectomy 3 yr ago	U/S: 3 liver masses, CT: 1 intra- and 2 extrahepatic lesions; MRI: three high-intensity lesions; PET: Abnormal accumulation in all lesions	Right lobe	CCC	Surgical resection (tiny black-colored nodules within the abdominal cavity and spilled gallstones)	Inflammatory granuloma located at liver parenchyma	No recurrence after 6 mo
Huang <i>et al</i> ^[40] , 2012	30	Male	Right upper abdominal pain; CEA†; 2 yr after renal transplant	CT: Low-density mass, about 30 mm in diameter, well defined, and with peripheral enhancement CT: Numerous hypodense lesions scattered throughout the liver	Caudate lobe	HCC or liver abscess	Hepatic caudate lobectomy with complete resection of the mass Liver biopsy	Mixture of spindle-shaped myofibroblastic cells and chronic inflammatory cells; SMA+	NM
Beauchamp <i>et al</i> ^[41] , 2011	74	Female	FUO	U/S: Ill-defined area, CT: multiple low attenuation lesions	NM	NM		IMT	NM
Al-Jabri <i>et al</i> ^[23] , 2010	69	Male	Right upper quadrant pain, nausea, vomiting, recent weight loss, rheumatoid arthritis and bronchiectasis, CRP†, cholestasis (normal Bilirubin)	U/S: Ill-defined area, CT: multiple low attenuation lesions	Right lobe	Cholecystitis, malignancy	Fine needle biopsy	Presence of benign hepatocytes, acellular debris and a mixture of acute and chronic inflammatory cells	No recurrence after 3 mo
Salakos <i>et al</i> ^[43] , 2010	10	Male	Fever, weight loss, fatigue, tachycardia, hepatomegaly, leukocytosis, platelet count ↑	U/S: Space occupying lesion in the liver; CT: Large lesion with solid and cystic parts and heterogeneous enhancement	Right and left lobe	NM	Biopsy followed by conservative treatment (ceftriaxone, clindamycin, NSAR)	Hyperplastic cholangioles, myofibroblasts and fibroblasts, infiltrate of lymphocytes, eosinophils and neutrophils; ALK+ response	Partial response after 2 mo, complete response after 18 mo
Ueda <i>et al</i> ^[45] , 2009	79	Male	Leukocytosis	U/S: Hypoechoic lesion, 3 cm in diameter, with several stones. CT: Low density area in segment V; MRI: Lesion of slightly low signal intensity; MRCP: Lesion of moderate-to-high signal intensity on T2W	Right lobe	Inflammation due to cholangitis with intrahepatic bile duct stones	1. ERCP: Sphincterotomy, antibiotics because of common bile duct stone. 2. Relapse of symptoms 4 wk later > resection	Grossly gray, fibrotic, solid tumor, intrahepatic bile duct stones. Proliferation of diffuse myofibroblastic and mesenchymal cells in a mixed myxoedematous, dense fibrotic stroma, with many small vessels and marked infiltration by various acute and chronic inflammatory cells	No recurrence after 2 yr
Stürer <i>et al</i> ^[7] , 2009	48	Female	Weakness, fever, weight loss, right upper abdominal pain, Lc-, neutrophil 75.3%, liver function normal	U/S: Single hypoechoic lesion in right lobe	Right lobe	NM	Resection	No capsule, light brown, no necrosis, spindle cells, granulation-tissue type vessels, chronic inflammatory cells on loose, edematous, myxoid stroma, CD 38+, SMA+, ALK+, desmin, EMA-	2 yr no recurrence after 2 yr
Manolaki <i>et al</i> ^[47] , 2009	9	Female	Fever, mild anorexia, intermittent epigastric pain	U/S: Hypoechoic lesion, lymph node at porta hepatitis, CT: hypodense space-occupying lesion	Left lobe	NM	Biopsy, secondary left lateral segmentectomy with lymph node excision	Pale and firm lesion (3.5 cm × 2.5 cm × 3.0 cm) with whitish solid infiltrations extending to the capsule of the liver. Proliferation of spindle-shaped cells arranged in short fascicles with an ill-defined mark. Inflammatory cells, predominantly lymphocytes, plasma cells and eosinophils; vimentin+, SMA+, CD68+, TBC+	No recurrence after 3 yr

CT: Computed tomography; MRI: Magnetic resonance imaging; FUO: Fever unknown origin; CRP: C-reactive protein; CCC: Cholangiocarcinoma; HCC: Hepatocellular carcinoma; PT/CD: Percutaneous transhepatic cholangio drainage; NM: Not mentioned; U/S: Ultrasonography; Hb: Haemoglobin; LC: Leukocytes; TC: Thrombocytes; TTW: T2-Weighted; T2W: T2-Weighted; Chron Hep B: Chronic Hepatitis B; Seg: Segment; †: Increase; ‡: Decrease; WBC: Wight blood cells; SMA: Smooth muscle actin; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Clinical studies of > 2 patients

Ref.	n	Age (yr)	Gender	Clinical and laboratory findings	Radiology	Localization	Tentative diagnosis	Treatment	Histology	Follow up
Park <i>et al</i> ^[28] , 2014	45	65 (29-84)	Male/female (26/19)	Abdominal pain (n = 16), fever (n = 11), malaise (n = 5), weight loss (n = 4); CRP↑ (n = 31), leukocytosis (n = 10), CEA (n = 1) CA 19-9 (n = 1); hypertension, tuberculosis, chronic Hepatitis B	CT scan: Hypo-attenuating lesions in 40 patients, MRI: Low signal intensity lesion at T1W image in 86.4% and relatively homogenous high signal intensity lesion at T2W image in 76.2%	Right lobe (n = 27), left lobe (n = 14), both (n = 4)	Malignancy (n = 26, 57.8%), abscess (n = 11, 24.4%)	Percutaneous needle biopsy (n = 35), surgical resection (n = 9), both (n = 1)	Chronic infiltration of various inflammatory cells (plasma cells, lymphocytes, neutrophils, and eosinophils) and fibrous stroma	No recurrence after median follow-up of 8 mo
Ahn <i>et al</i> ^[4] , 2011	22	34-76	Male/female (16/6)	Abdominal pain (n = 12), febrile (n = 5), malaise (n = 1), asymptomatic (n = 4), leukocytosis (n = 6), hyperbilirubinaemia (n = 3), alkaline phosphatase↑ (n = 10), liver enzymes ↑ (n = 5), CA 19-9 ↑ (n = 5), AFP↑ (n = 1); associated biliary disease (n = 15), malignancy (n = 4)	Solitary (n = 17); multiple (n = 5), median size 3 cm (1.1-9.6 cm), non-enhanced CT: Hypoattenuating lesions (n = 22), enhanced CT: Central hypoattenuating areas and a delayed hyperattenuating periphery (n = 18), multiseptate appearance with hyperattenuating internal septa and periphery (n = 3), hypoattenuation up to the equilibrium phase (n = 1)	Right lobe n = 10, left lobe n = 9, both n = 3, (mostly seg. IV n = 12)	IPT (n = 12), both malignancy (n = 4), recurrence of malignancy (n = 2), abscess (n = 4)	Percutaneous needle biopsy (n = 18), incisional biopsy (n = 1) --> surgical resection (n = 3); liver resection (n = 3) without prior biopsy, 16 patients conservatively, 6 patients with surgical resection	Histiocytic cell infiltration with negative IgG4 (n = 17), lymphoplasmacytic type (n = 5) with positive IgG4 (n = 4)	Post conservative treatment: 10 complete remission after 15 mo; 5 partial remission after 4 mo, post resection: Mortality n = 2 (myocardial infarction, peritoneal seeding)
Geramizadeh <i>et al</i> ^[44] , 2009	2	14	Male	Chills, fever, anorexia > 8 kg weight, leukocytosis	CT: Well-defined heterogeneous mass with central areas of necrosis and a slightly hyperdense rim	Left lobe	Abscess	Resection	Creamy grey mass with a vague whorling appearance. Plasma cells with varying degrees of fibroblastic proliferation admixed with lymphocytes, eosinophils and macrophages	No recurrence after 1 yr
Yamaguchi <i>et al</i> ^[27] , 2007	3	15	Male	Hepatitis B positive, weight loss	Well defined liver mass	NM	Malignancy	Fine needle biopsy	6 cm liver mass, fibroblastic proliferation, many plasma cells and eosinophils	No recurrence after 2 yr
		52	Male	Epigastric pain, appetite loss, weight loss, fever	U/S and CT: Hepatic mass in left lobe	Left lobe	IPT	Follow up	NM	Complete remission after 1 yr
		58	Male	Auxiliary finding	CT: Low density mass in the right lobe enhanced during the delayed phase	Right lobe	CCC	Biopsy > no treatment, follow up	IMTL	NM
	57		Female	Sigmoid cancer planned for resection	MRI: 2 metastases with low-intensity signal on T1, a slightly high-intensity signal on T2	Right lobe	Hepatic metastasis	Intraoperative right portal vein embolization	NM	NM

Millas *et al*^[6], 2009

Age	Sex	Abdominal and bone pain, fatigue, malaise, hematuria, WBC [†]	CT: Liver abscess right upper abdominal quadrant	Right lobe	Liver abscess	Drainage followed by right hepatectomy	Many plasma cells, densely collagenous bundles between a plasma cell-rich infiltrate	NM
35	Male							
56	Male	Right upper abdominal pain, malaise	CT: Liver abscess	Right lobe	Liver abscess	Drainage followed by right hepatectomy	Inflammatory response to hepatic abscess	
75	Female	Moderate upper quadrant pain, nausea, and vomiting	U/S: Cystic lesion, CT: Cystic lesion, slight dilatation of intrahepatic bile ducts	IVB	Cholangitis/Cystadenoma	Biopsy followed by Seg. IVB resection	Central granulation, fibrosis and chronic lymphoplasmacytic infiltrate, no features of neoplasia.	
47	Female	Right upper quadrant pain, jaundice, fever, pruritus	CT: Marked dilatation of the intrahepatic biliary tree	Right lobe	CCC	Seg. III resection, secondary right hepatectomy	Inflammatory pseudotumor Widespread chronic inflammatory infiltrate with lymphocytes and plasma cells, numerous lipid-laden macrophages, no malignancy	

CT: Computed tomography; MRI: Magnetic resonance imaging; FUO: Fever unknown origin; CRP: C-reactive protein; CCC: Cholangiocarcinoma; HCC: Hepatocellular carcinoma; PTCD: Percutaneous transhepatic cholangio drainage; NM: Not mentioned; U/S: Ultrasonography; Hb: Haemoglobin; LC: Leukocytes; TC: Thrombocytes; TIW: T1-Weighted; T2W: T2-Weighted; Chron Hep B: Chronic Hepatitis B; Seg: Segment; ↑: Increase; ↓: Decrease; WBC: Wight blood cells; SMA: Smooth muscle actin; ERCP: Endoscopic retrograde cholangiopancreatography.

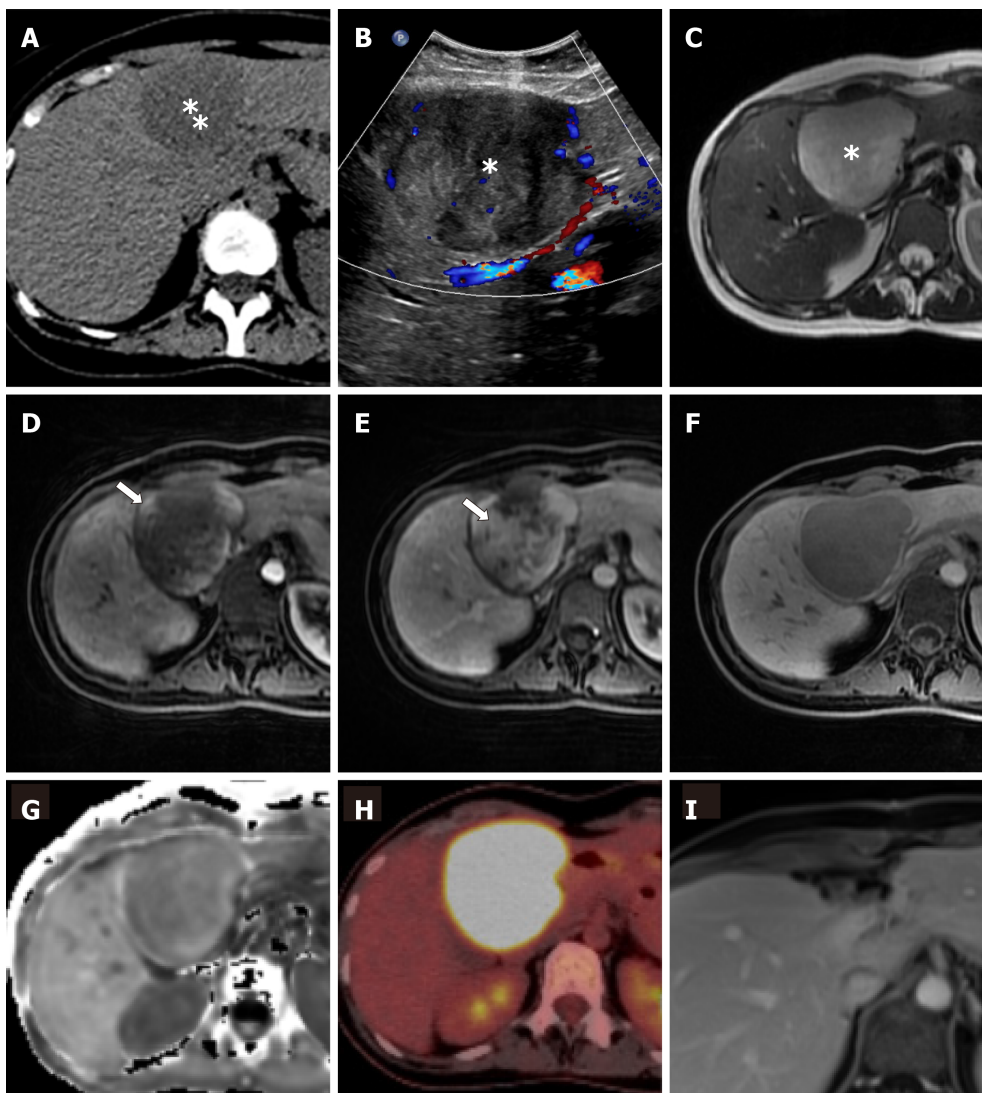


Figure 1 Imaging features within the liver lesion in segment IV. A: The lesion was first detected as an incidental finding in an unenhanced abdominal computed tomography to rule out kidney stones (asterisk); B: Conformed with an ultrasound examination (asterisk); C: In a following magnetic resonance imaging the lesion showed a homogeneous high signal in T2-weighted imaging (asterisk); D: After the application of intravenous hepatocyte specific contrast medium (gadoteric acid, Primovist®/Eovist®, Bayer Healthcare Pharmaceuticals, Leverkusen, Germany) there was an early enhancement at the rim in the arterial phase (arrow); E: Followed by a strong enhancement in the venous phase (arrow); F: In the hepatobiliary phase after 20 min, the lesion appeared with a low intracellular uptake of the contrast medium compared with the adjacent liver tissue; G: In the diffusion-weighted imaging there was no clear diffusion restriction detection within the lesion (apparent diffusion coefficient); H: In an additional positron emission tomography-computed tomography examination the lesion showed an intensively increased tracer uptake; I: A follow-up magnetic resonance imaging examination after 3 mo confirmed a complete surgical resection (with multiple artifacts at the resection margin due to multiple clips) and ruled out new hepatic lesions.

TREATMENT

Due to the unclear situation with fever and the suspicion of a large adenoma or malignant tumor of the liver, an immediate surgical resection was performed. Intraoperatively, the solitary central lesion could be confirmed by intraoperative ultrasound, which also excluded additional liver lesions. An open resection of the liver segment IVa/b was performed achieving a negative resection margin. While no intra-operative complications occurred, the patient developed a bilioma, which had to be drained interventionally 7 d after the surgery accompanied by an endoscopic retrograde cholangiopancreatography with stent insertion.

OUTCOME AND FOLLOW-UP

The case was discussed postoperatively in our interdisciplinary liver tumor board to determine the postoperative management. While no adjuvant therapy was indicated, it was recommended to follow the patient clinically by MRI imaging every 3 mo after

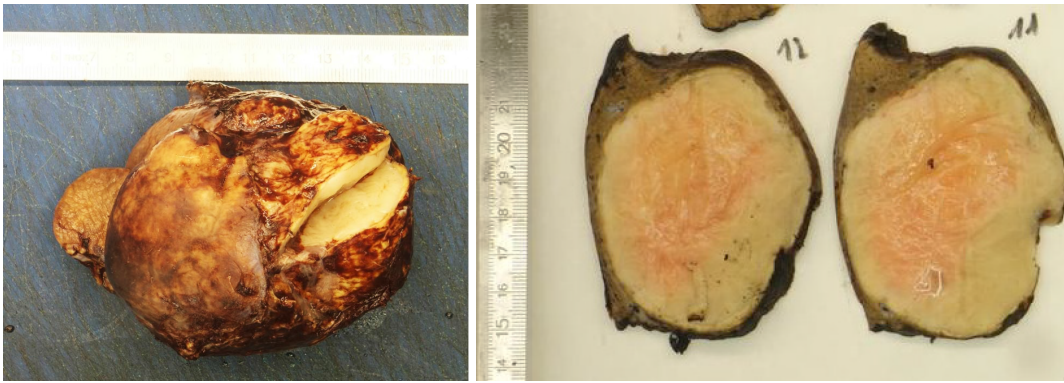


Figure 2 Postoperative macroscopic pathology of the inflammatory myofibroblastic tumors.

the surgery for the duration of at least one year.

The patient returned to work and MRIs of the liver 3, 6 and 12 mo after resection showed no local recurrence and no novel liver lesions.

DISCUSSION

We herein present and discuss the case of a 32-year-old woman who presented with a suspicious and symptomatic liver mass consequently diagnosed as IMTL.

IMTs of the liver are extremely rare findings that can sometimes mimic malignant lesions^[6]. In terms of demographics, the tumor seems to be more common in men than in women (M/F: 1.5/1) with a mean age at diagnosis of 37 years^[7]. IMTL usually occur in the right liver lobe, in close proximity to the gallbladder or central biliary system^[7,8]. Typical clinical findings reported in the literature are fever, abdominal pain, lack of strength and weight loss^[7], which all occurred in our case (intermittent fever, unclear blood loss, malaise and pain in the right flank) and led to the ultimate diagnosis. In addition to the fever, laboratory findings often suggest inflammation due to leukocytosis, neutrophilia and elevated CRP^[5,6,8,10]. More rarely, anemia and sometimes also elevated liver enzymes are reported^[6]. According to the clinical signs of infection, some individual cases were reported to be correlated with different active (virus) infections^[5,18,19,21,22]. In our patient, the antibody to Epstein-Barr virus was positive in the serological findings without any signs of an active Epstein-Barr virus infection. A clear association between IMT and infectious organisms seems to be doubtful since in most reported series, including our own case, no acid-fast organisms, fungi, parasites or bacteria could be identified in the tumor^[10,19].

Radiological features of IMTLs are nonspecific and a definite radiological diagnosis seems to be impossible. Due to the small cases (Tables 1 and 2) we could see, that the tumor in ultrasonography mostly was hypoechogenic. An IMT may be suspected if a defined soft tissue mass and a heterogeneous enhancement with invasive or non-invasive growth are present on adjacent structures in CT or MRI^[6,8,23]. Not all patients underwent a MRI for diagnostic treatment, only in eight cases^[17,24-29]. Al-Hussaini *et al.*^[24] and Kayashima *et al.*^[30] described a contrast-enhancing, hyper-intense well defined lesion without going into details. In four cases the lesion in T1W was mostly hypointense and T2W hyperintense^[17,25,26,28]. Despite its rarity, lack of diagnostic signs and symptoms, IMTL should not be ruled out as a differential diagnosis in liver lesions like focal nodular hyperplasia, hepatocellular adenoma, carcinoma and echinococcosis especially in young patients with normal tumor markers^[7]. In addition IMTL can sometimes mimic a liver abscess^[22]. Although many synonyms have been used for this lesion, including plasma cell granuloma, postinflammatory tumor, xanthomatous pseudotumor, inflammatory pseudotumor, and inflammatory fibrosarcoma^[31], the new classification clearly suggests the term inflammatory myofibroblastic tumor of its suitable origin or organ, in our case an IMTL^[4].

Due to the small number of cases worldwide (Tables 1 and 2), no clear diagnostic tests or radiographic features exist that help to make a definite diagnosis without a histopathological examination of the tissue^[10]. We performed a comprehensive literature search and studied the cases published during the last 10 years^[5,7,17,24-30,32-47]. There were more men affected than women. The most common localization of the tumor was on the right lobe of the liver. All patients in the described cases had at least an ultrasonography and/or a CT. In some cases, the diagnostic work-up was completed with MRI, MRCP or PET-CT. Due to the different radiological findings the

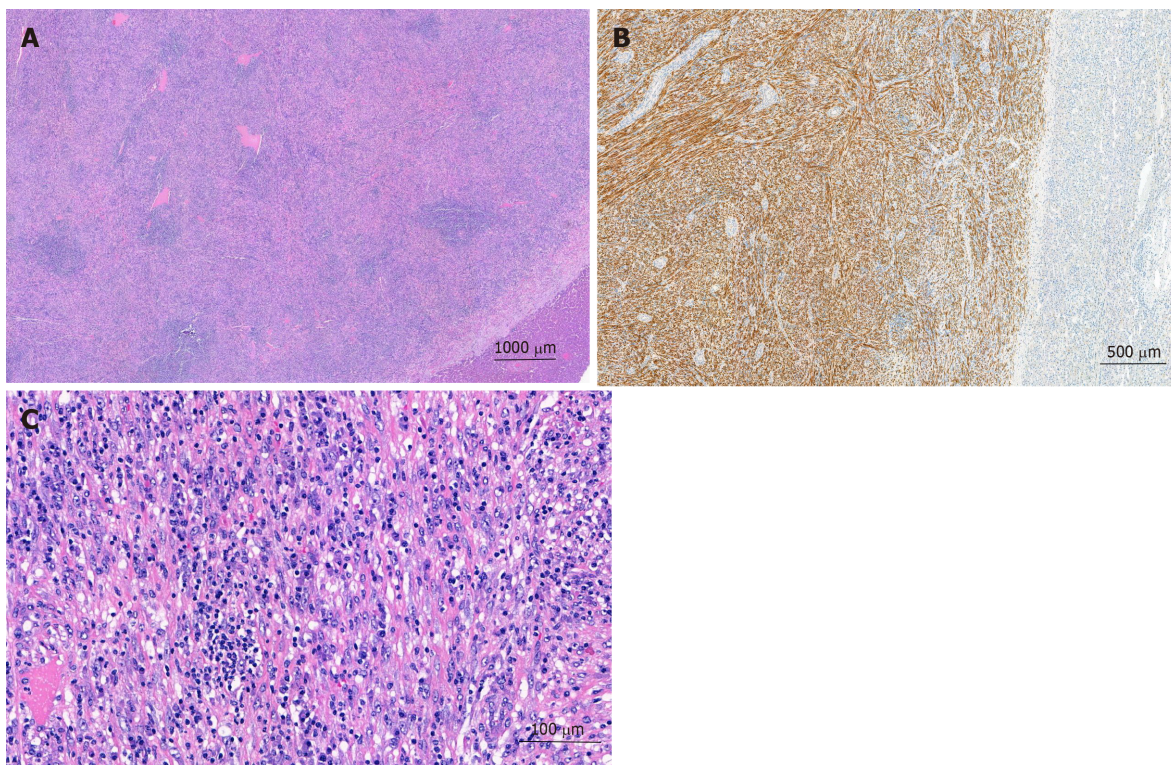


Figure 3 Postoperative microscopic pathology of the inflammatory myofibroblastic tumors. A: Well demarcated firm vascularized tumor mass with spotty inflammatory infiltrate; B: Bland proliferation of spindle cells in broad fascicles at higher magnification. Scattered lymphocytes and plasma cell; C: Intense positivity of the spindle cells for anaplastic lymphoma kinase.

tentative diagnose showed a large variation from liver abscess, inflammatory process and also malignancy.

In the gross examination of the resected specimen, most findings showed the similar finding of a well-demarcated, unencapsulated, yellow-whitish mass. Histologically infiltrations of chronic inflammatory-cells like lymphocytes, neutrophils, eosinophils, and macrophages were often described. Whenever immunohistochemical analyses were performed, ALK expression showed a similar distribution. The performed treatment of the different cases varied according to the initially suspected diagnose. In summary, more patients were treated conservatively, although there is no clear indication for such a treatment. Surgical resections were performed according to the size and location of the suspected tumor and varied from small atypical resections to major hepatectomies. In most of the cases the definite histology report of the resected specimen then showed the diagnosis of an IMTL. Unfortunately, follow-up was not described in all published cases. Except for one reported recurrence after 2.5 years, most patients stayed tumor-free during a follow-up ranging from X-Y months^[48].

Surgical resection is usually recommended so that a proper pathological work-up can be performed and malignancy can be ruled out. Nevertheless, several different treatment strategies have been published including conservative approaches with steroids, high-dose steroids, radiation and chemotherapy^[6-8,11]. Interestingly, one case with a spontaneous regression has also been reported^[17]. A typical pathological finding is that the IMTL's are unencapsulated. They are usually solid or gelatinous on the intersection and have a white color. Hemorrhage, calcification or necrosis are rarely described^[6,12], similar to the pathological findings in our case. As described by Elpek *et al*^[6], chromosomal translocations leading to the activation of ALK can be detected in IMTLs. Although immunohistochemistry for ALK expression in immunohistochemistry can reliably predict the presence of ALK gene rearrangement, its prognostic relevance is still unclear^[14,49]. IMTLs differ from IgG4-related liver disease in terms of ALK expression, low IgG4 positive cell infiltration, and lack of obstructive phlebitis^[6].

The natural course of IMTL without curative surgical therapy is unclear. To date, only a few cases have been described in which patients had local recurrence or metastases after liver resections^[15,16,48]. Due to the small numbers published worldwide, no recommendations for the follow-up are available and patients is treated according to the decisions made in the local interdisciplinary tumor boards. In

our case, the finding of the pseudotumor was 4 mo postpartum. Due to the rather large size of the lesion it was considered an advanced lesion. The pregnancy may have masked general symptoms such as nausea, vomiting, and abdominal pain. So far, only one case of newly diagnosed IMTL has been reported during pregnancy^[18].

CONCLUSION

In summary of the literature and with the experience from our own recent case, complete surgical resection of a suspected IMTL should be the preferred treatment of choice in order to rule out malignancy, avoid long-term medical treatment and to be able to recommend an appropriate follow-up for the patient.

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