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REVIEW

Rise of sodium-glucose cotransporter 2 inhibitors in the management of nonalcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in the Western world. It is more prevalent in male gender, and with increasing age, obesity, and insulin resistance. Besides weight loss, there are limited treatment options. The use of anti-diabetic medications has been studied with mixed results. In this review, we discuss the use of anti-diabetic medications in the management of NAFLD with a specific focus on sodium-glucose cotransporter 2 inhibitors. We shed light on the evidence supporting their use in detail and discuss limitations and future directions.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Sodium-glucose cotransporter 2 inhibitors; Liver cirrhosis; Diabetes

Core tip: Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in the Western world. NAFLD is associated with obesity and insulin resistance. Weight loss is the cornerstone of therapy with no other proven pharmacologic therapy, Sodium-glucose co-transporter 2 (SGLT2) inhibitors may play a role in preventing and treating NAFLD. SGLT2 inhibitors reduce hepatic steatosis, steatohepatitis, and fibrosis in patients with NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in Western countries[1] and its prevalence worldwide is increasing substantially. NAFLD constitutes a spectrum of liver disease that extends from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), a more progressive form of the disease that can lead to advanced fibrosis or cirrhosis. The worldwide prevalence is approximately 10%-35%[2]. In the United States, it is estimated that NAFLD affects more than 20% of the population[3,4]. Cardiovascular disease remains the most common cause of death in patients with NAFLD[5].

The underlying pathophysiology of NAFLD is not fully understood, but genetics and insulin resistance seem to play key roles[6]. Certain risk factors have been identified in NAFLD. Gender, age, ethnicity, and the presence of obesity or type 2 diabetes mellitus (T2DM) are differentially associated with NAFLD. Males are affected more often than females with approximately a 2:1 ratio. Most patients are diagnosed in their 40 s and 50 s. Studies demonstrate a higher prevalence in Hispanics, medium prevalence in Caucasians, and relatively low prevalence amongst blacks[7]. Certain genetic polymorphisms (*i.e.*, PNPLA-3 and TM6SF2) have also been implicated in the disease process leading to more progressive form of NAFLD[8].

The multifaceted pathophysiologic nature of NAFLD has challenged the development of targeted therapeutic strategies for this growing disease. Thus far, weight loss is the most effective therapy with 3%-5% weight loss resulting in improvement of liver transaminases and reversal of steatosis[9,10], and 7%-10% weight reduction resulting in reversal of abnormal histologic features[11].

Pharmacologic therapies for NAFLD have not yet gained widespread use, mainly due to the poor quality of evidence supporting their use. Evaluated medications include those with anti-oxidative effects (Vitamin E)[12], anti-inflammatory effects (Ursodeoxycholic acid)[13], lipid-lowering effects (Atorvastatin)[14], anti-diabetic medications, and other nutritional supplements (Omega-3 fatty acids)[15].

In this review, we focus on the use of anti-diabetic agents in the treatment of NAFLD, more specifically on the newly emerging class of Sodium-glucose co-transporter 2 (SGLT2) inhibitors. We shed light on the evidence supporting their use in detail and discuss future directions.

SEARCH CRITERIA

MEDLINE search was conducted using the keywords "SGLT2 inhibitors" and "NAFLD" OR "NASH" and all the studies were included. There were no excluded articles. The studies were mainly focused on the role of SGLT2 inhibitors in NAFLD and were included up to December 2018.

ANTI-DIABETICS IN NAFLD

A cornerstone in the management of NAFLD is treating concomitant diabetes mellitus. The relationship between NAFLD and type-2 diabetes mellitus (T2DM) is well established and is often relayed as a bidirectional relationship. There is an association between the prevalence of NAFLD and T2DM, as multiple prospective observational studies shown NAFLD independently increases the incidence of T2DM[16-21]. In one study, NAFLD was independently associated with impaired glucose metabolism[22]. Previous reports show a high prevalence of NAFLD in patients with T2DM[23,24]. T2DM was also associated with worsening NAFLD and progression to NASH and hepatocellular carcinoma (HCC)[25-27]. The underlying mechanisms between NAFLD and T2DM is complicated, but stems from the critical role the liver plays in regulating glucose and lipid metabolism, where the inciting event is thought to be a fat-associated chronic low-grade inflammatory response[28,29]. As there is

overwhelming evidence that NAFLD and T2DM share a common pathogenesis[30], the treatment of T2DM had been suggested as an important key in the management of NAFLD.

METFORMIN

Metformin is the most commonly used medication in the management of T2DM. It reduces hepatic glucose production and promotes skeletal muscle glucose uptake. Given the pathogenesis of NAFLD and T2DM, multiple investigations have been carried out regarding its use in NASH. However, a meta-analysis published in 2010 demonstrated that metformin failed to improve hepatic steatosis, inflammation, hepatocyte ballooning, Alanine aminotransferase (ALT) levels, liver fibrosis, or body mass index (BMI) in subjects with simple steatosis or biopsy-proven NASH[31]. As a result, metformin is not recommended for use in NAFLD, even in patients with T2DM.

THIAZOLIDINEDIONES

Thiazolidinediones are PPAR-gamma agonists that enhance insulin sensitivity[32]. A study investigating the effect of pioglitazone on patients with NASH but without T2DM showed a significant reduction in ALT levels and improvement in histological features of NAFLD such as steatosis, inflammation, and hepatocyte ballooning when compared to placebo[33], however it did not slow down the progression of hepatic fibrosis[33].

INCRETIN-BASED THERAPY

GLP-1 agonists are incretin-based therapies that are used in the management of T2DM by promoting glucose-dependent insulin secretion[34]. An investigation comparing liraglutide and placebo in patients with NASH showed that liraglutide led to a significant resolution of steatosis as determined by an end-of-treatment liver biopsy[35]. It was also shown to slow down the progression to fibrosis[35].

Dipeptidyl-peptidase 4 (DPP-4) inhibitors, such as sitagliptin, inhibit the degradation of incretins, which in turn stimulate secretion of insulin in patients with T2DM. They have been shown to have extra-pancreatic effects, including protective effects on hepatocytes against diet-induced steatosis and ultimately NAFLD[36]. Not only do they prevent the development of NAFLD, but they seem to exert an effect in treating it by influencing the serum levels of ALT, Aspartate aminotransferase (AST) and gamma-GT[37]. They were also found to be safe in patients with T2DM and NAFLD, and had been suggested as a potential mono-therapeutic agent for NAFLD[38]. However, there are yet to be randomized controlled trials showing their therapeutic effects in NAFLD.

SGLT2 INHIBITORS

SGLT2 inhibitors are a class of drugs that inhibit glucose reabsorption in the kidney *via* inhibition of the SGLT channels which are primarily located in the proximal convoluted tubules epithelial cells, thus promoting glucosuria. Their mechanism of action is independent of insulin secretion making the use of these drugs useful in patients with limited pancreatic beta cell activity. The hypothesized mechanism of SGLT2 inhibitors in NAFLD stems from their glycosuric effect leading to total loss of energy which results in increased pancreatic secretion of glucagon while suppressing insulin secretion. SGLT2 inhibitors also work as alpha-cells secretagogues by directly stimulating glucagon release *via* neuronal stimulation[39]. This mild hyper-glucagonemic state induces hepatic gluconeogenesis, ketogenesis and lipolysis, leading to an overall reduction in the amount of fatty acids. Furthermore, SGLT2 inhibitors exert a direct neurogenic effect that enhances gluconeogenesis and lipolysis in the liver[40]. The sum of such effects leads to reduction in hepatic steatosis and halts the progression of NAFLD (Figure 1). Albeit being of the same group of medications, different SGLT2 inhibitors demonstrated different effects on NAFLD. In the following section, we discuss the evidence that supports the use of different members of this family of drugs in SGLT2.

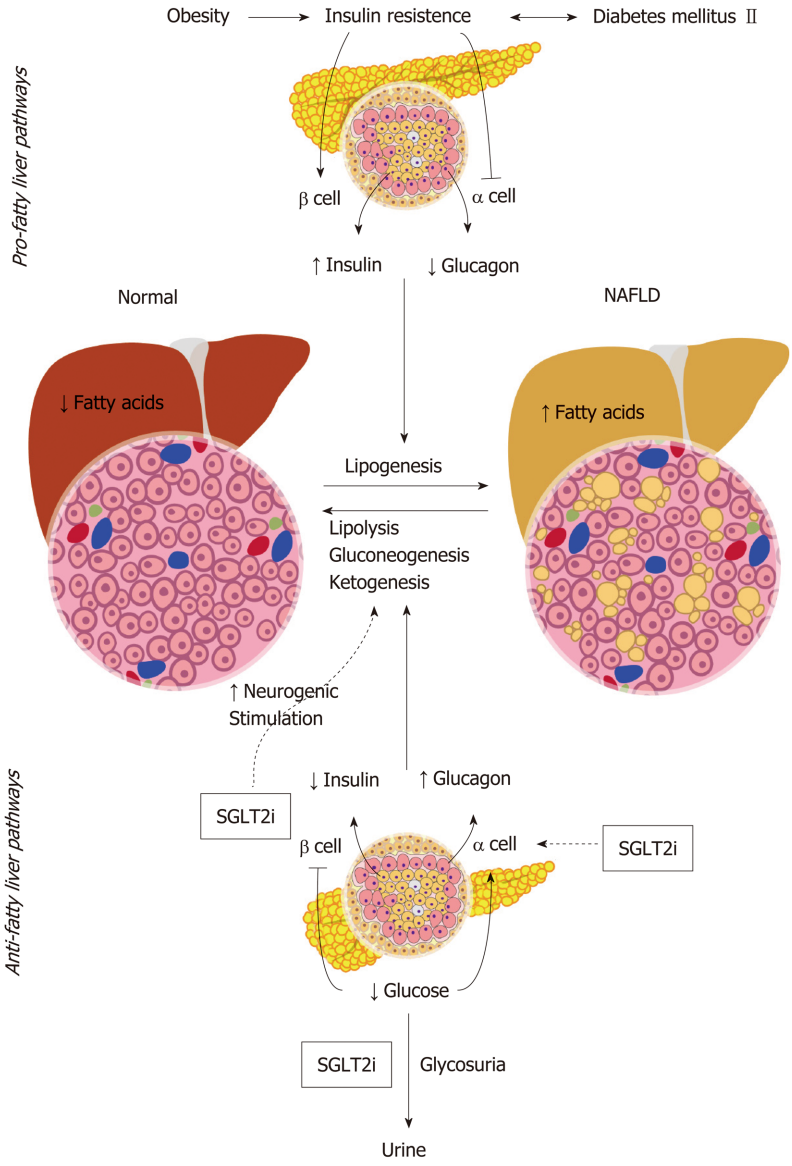

Figure 1 Mechanism of action of Sodium-glucose co-transporter-2 inhibitors in non-alcoholic fatty liver disease. Obesity-induced insulin resistance leading to diabetes are the major risk factors for non-alcoholic fatty liver disease (NAFLD). The increase in insulin secretion and inhibition of glucagon secretion by the islet cells in the pancreas ultimately leads to the stimulation of lipogenesis, ultimately shifting the balance towards hepatic steatosis and NAFLD. Sodium-glucose co-transporter inhibitors primary effect is inducing glycosuria causing lowering of the blood glucose levels. This inhibits the secretion of insulin and stimulates glucagon secretion, causing a higher insulin-to-glucagon ratio, which increases the lipolytic, gluconeogenetic, and ketogenetic pathways. This results in reduction in the hepatic steatosis in NAFLD.

CANAGLIFLOZIN

Canagliflozin is the most commonly prescribed SGLT2 inhibitors for patients with T2DM. In animal models of NAFLD, canagliflozin used in high-fat diet fed mice reduced ALT levels and prevented the development of cirrhosis as evident by reduced steatosis on histologic examination[41]. Canagliflozin also showed favorable outcomes when pitted against sitagliptin, a DPP4-inhibitor, in the management of Japanese patients with biopsy-proven NAFLD[42]. It demonstrated reductions in BMI, fasting blood glucose, body weight, HbA1c, and ALT levels[42]. It is worth noting that the study was a retrospective cohort study and the results could not be directly attributed to canagliflozin[42]. Canagliflozin used for 24 wk in patients aged 20-64 years with biopsy-proven NAFLD complicated with T2DM showed significant reductions in BMI, fasting blood glucose, waist circumference, ferritin level, gamma-glutamyltransferase (GGT) level, and type IV collagen 7S[43]. Furthermore, there was a

decrease in the NAFLD score in all patients included in the study[43]. However, the study was a single center, single arm study and only involved 5 patients. Hence, extrapolation to the general population was difficult[43]. A systemic analysis pooled the results of 4 studies in which canagliflozin was used for 26 or 52 wk *vs* placebo or sitagliptin, and showed significant reductions in HbA1c, body weight, ALT, AST, alkaline phosphatase and gamma-glutamyl transferase. The favorable changes in liver function tests were attributed to reductions in HbA1c and body weight[44]. In western-diet fed murine models, canagliflozin showed significant improvements in hyperglycemia, hyperinsulinemia and liver function tests as early as 8 wk after initiation, and significant improvements in hepatic fibrosis after 20 wk of treatment. There was additionally a significant reduction in the number of liver tumors after 1 year of canagliflozin treatment[45]. More recent evidence emerged on the positive effect of canagliflozin with a human study demonstrating significant reductions in hepatic steatosis, hepatocyte ballooning, fibrosis, and inflammation after 24 wk of treatment in patients with T2DM and NAFLD[46]. Another prospective cohort study also demonstrated significant reductions in ALT, AST, GGT, triglycerides, HbA1c, and body weight[47].

IPRAGLIFLOZIN

Ipragliflozin used in high fat diet fed murine models that had streptozocin nicotanamide-induced T2DM showed improvement in glucose tolerance, blood glucose, insulin, and lipid levels[48]. Moreover, there were reductions in hepatic steatosis and liver levels of oxidative stress biomarkers as well as improvement in aminotransferase levels after 4 wk of treatment[48]. Another murine based study demonstrated similar results by demonstrating improvement in insulin resistance, free fatty acids, AST and ALT levels, and liver fat content with an 8 wk course of ipragliflozin[49]. Murine models fed a choline-deficient l-amino acid-defined diet developed liver triglyceride increase, liver fibrosis, and mild inflammation[50]. These changes were prevented with 5 wk of ipragliflozin therapy which suggests that SGLT2 inhibitors might play a role in the prevention of hepatic fibrosis[50]. In human subjects, ipragliflozin used for 16 wk in patients with T2DM showed significantly reduced fatty liver index, fasting plasma glucose, HbA1c, body weight, visceral adipose tissue, and subcutaneous tissue and fat mass[51]. When ipragliflozin was compared to pioglitazone, a PPAR agonist, in patients with T2DM, similar effects were observed with regards to blood glucose, HbA1c, liver to spleen ratio, AST and ALT levels. There was a significantly reduced body weight and fat area with ipragliflozin[52]. The co-administration of ipragliflozin with incretin-based drugs such as GLP-1 analogs or DPP-4 inhibitors showed significant reductions in HbA1c, body weight, serum ALT levels, and fibrosis-4 index[53]. The most important aspect observed here is that ALT levels were not normalized with incretin-based therapies until combined with iprafliglozin, which suggests a synergistic effect between incretin-based therapies and SGLT2 inhibitors[53]. In a larger multicenter prospective study involving patients with T2DM and NAFLD, ipragliflozin administration for 24 wk showed significant reductions in HbA1c, AST, ALT, body weight, and steatosis[54]. It further suggests that SGLT2 inhibitors can help in the management of patients with T2DM with metabolic syndrome[55].

DAPAGLIFLOZIN

Dapagliflozin is a highly selective competitive inhibitor of SGLT2. In genetic murine models of obesity and diabetes, such as db/db, dapagliflozin was shown to improve markers of liver injury such as MPO and reactive oxygen species[56]. Even in diet-induced obesity, dapagliflozin showed decreased serum ALT, AST, hepatic lipid accumulation, and hepatic fibrosis in mice that were fed western diet compared to low-fat diet. Dapagliflozin also attenuated the western diet-mediated increases in body weight, plasma glucose, plasma triglycerides, and renal fibrosis[57]. This suggests that dapagliflozin can be used for reversal of hepatic steatosis associated with NAFLD, even in humans. Indeed, the use of dapagliflozin and empagliflozin demonstrated a significant reduction in ALT levels in patients with T2DM. This change was independent of HbA1c and fasting glucose levels[58]. Dapagliflozin also showed significant improvement in BMI, AST levels, ALT levels, fasting plasma glucose and HbA1c when used for 24 wk in patients with biopsy-proven NASH and T2DM[59]. More recently, a study investigating the use of dapagliflozin for 24 wk in patients with T2DM and NASH showed a significant reduction in ALT and GGT

levels as well as significant improvement in liver stiffness measurement[60]. Dapagliflozin was also found to significantly reduce hepatic steatosis and attenuate severe liver fibrosis in patients with T2DM and NAFLD[60]. A randomized double-blind placebo-controlled trial involving 84 patients with T2DM and NAFLD demonstrated significant reduction of liver fat content with combination dapagliflozin and n-3 carboxylic acid for 12 wk. Dapagliflozin monotherapy also decreased hepatic injury biomarkers and as mentioned earlier, ALT, AST, GGT and body weight[61].

EMPAGLIFLOZIN

Empagliflozin, *vs* combination empagliflozin and linagliptin, a DPP-IV inhibitor, *vs* placebo demonstrated that empagliflozin monotherapy reduced the severity on NASH at 21 d in NASH mouse-models[62]. Furthermore, the combination of empagliflozin and linagliptin led to reduction in body weight and liver collagen deposition *i.e.*, fibrosis indicating a probable synergistic effect upon coadministration[62]. The E-LIFT trial which involved patients with T2DM and NAFLD, showed that empagliflozin in addition to standard diabetes management causes a significant reduction in liver fat content and ALT and a non-significant difference in GGT and AST levels[63]. A subgroup analysis from the EMPA-REG trial showed significant reduction in ALT independently of changes in HbA1c or body weight[64].

REMOGLIFLOZIN

Mice placed on a high fat diet for 11 wk followed by administration of remogliflozin or placebo for 4 wk resulted in significant reduction of ALT and ALT levels. Both liver weight and hepatic triglyceride content were significantly reduced. Furthermore, when compared to canagliflozin and dapagliflozin, remogliflozin had a significantly higher effect with regards to oxygen radial absorbance capacity. This study demonstrated that remogliflozin had clear significant effects on mice with NAFLD and NASH[65]. Similar studies are yet to occur in humans.

LUSEOGLIFLOZIN

Mice models receiving streptozotocin and nicotinamide to reduce insulin secretion followed by administration of luseogliflozin or placebo exhibited reductions in ALT levels along with reduction in the increase of collagen deposition in the treatment group[66]. A human-based study in which luseogliflozin was compared to metformin in patients with type 2 diabetes and NAFLD demonstrated significantly lower liver-to-spleen ratio, visceral fat, HbA1c, and BMI with luseogliflozin after 6 months of use[67]. Another prospective study showed significant reductions in ALT, AST, BMI, and GGT levels after 24 wk of therapy in patients with T2DM and NAFLD[68].

POTENTIAL ANTITUMORIGENIC EFFECTS OF SGLT2I

One of the dreadful complications of NAFLD is the development of HCC, which appears to be increasing[69], regardless of the presence cirrhosis. One *in vitro* study showed that the effects of canagliflozin on HCC showing effects that include antiproliferation, cellular arrest, and apoptosis of cancer cells[70]. Such effects were also shown to decrease HCC tumor burden in a murine xenograft model of human HCC. Interestingly, those effects were glycemic-state independent[70]. Although the data supporting the antitumorigenic effects of SGLT2 inhibitors is limited, it is potentially a promising medication in preventing HCC in patients with NAFLD. Since normal and cancer colonic tissue express SGLT2, in one case report of colon cancer with liver metastasis, treatment with dapagliflozin in combination with cetuximab showed substantial response to therapy[71]. Although such results remain in need of validation, they show the potential of SGLT2 inhibitors in the carcinogenesis that could not only be HCC-specific.

ADVERSE REACTIONS DUE TO SGLT2 INHIBITORS

There have been a few reported side effects with regards to SGLT2 inhibitors use,

namely vulvovaginal candidiasis and urinary tract infections[72], hypotension[73] through osmotic diuresis causing hypovolemia, acute kidney injury[74] likely secondary to hypoperfusion of the kidneys in the setting of hypovolemia, bone fractures[75], increased risk of amputation[76], and euglycemic diabetic ketoacidosis[77]. Although the mechanisms of SGLT2 inhibitors ketoacidosis is not fully understood, the food and drug administration (FDA) has recognized it as an important side effect to watch for, especially in patient with type-1 diabetes mellitus[78]. Monitoring of kidney function is essential during treatment particularly in those taking concomitant diuretics and other medications that predispose to hypovolemia and acute kidney injury[79]. A major potentially lethal rare consequence of SGLT2 inhibitors use is the development of Fournier's gangrene. However, it has only been reported in 12 cases, but was serious enough the FDA issued an official warning statement for clinicians to be aware of[80]. Further, it is important to acknowledge that SGLT2 inhibitors were only FDA-approved as recently as 2013[81], and as such there is ongoing research for their long-term safety profile[79] (Table 1).

CONCLUSION

Limited pharmacologic options with proven efficacy makes the treatment of NAFLD challenging. Apart from weight-loss, there are few pharmacologic treatment options. However, recent emerging evidence of the use of SGLT2-inhibitors in patients with NAFLD is promising. Those agents have shown to improve levels of serum transaminases, decrease steatosis, prevent cirrhosis and HCC, and reduce body weight. They are also gaining wide popularity due to their anti-diabetic effect and potential cardiovascular benefits. However, prior to establishing the use of those agents clinically, further studies including randomized controlled trials should be conducted.

Table 1 Sodium-glucose co-transporter inhibitors and their use in non-alcoholic fatty liver disease

SGLT2 inhibitor	ALT	AST	GGT	Bilirubin	BMI	Steatosis	Inflammation	Fibrosis	HCC	Adverse effects	Study organism	Ref.
Canagliflozin	↓	↓	↓	↑	↓	↓	↓	↓	↓	Urogenital tract fungal infections, DKA, amputations, bone fractures	Human	[44,46,76]
Ipragliflozin	↓	-	-	NR	↓	↓	↓	↓	NR	Urinary tract infections	Human/Mouse	[49,51]
Dapagliflozin	↓	↓	↓	NR	↓	↓	↓	NR	NR	Urogenital tract infections, bladder cancer, DKA, amputations	Human	[59,61,76,81]
Empagliflozin	↓	-	-	-	↓	↓	↓	↓	NR	Genital tract infections, DKA	Human/Mouse	[62-64]
Remogliflozin	↓	↓	NR	NR	↓	↓	↓	NR	NR	Urogenital tract fungal infections	Mouse	[65]
Luseogliflozin	↓ or -	↓	↓	NR	↓	↓	↓	↓ or -	NR	Vaginal itching, dehydration	Human/Mouse	[66-68]

SGLT2: Sodium-glucose co-transporter 2; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase; BMI: Body mass index; HCC: Hepatocellular carcinoma; DKA: Diabetic ketoacidosis; NR: Not reported; ↓: Decreases; ↑: Increases; -: No change.

REFERENCES

1 **Masuoka HC**, Chalasani N. Nonalcoholic fatty liver disease: an emerging threat to obese and diabetic individuals. *Ann N Y Acad Sci* 2013; **1281**: 106-122 [PMID: 23363012 DOI: 10.1111/nyas.12016]
2 **Vernon G**, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; **34**: 274-285 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]
3 **Kim HJ**, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, Lim SK, Kim KR, Lee HC, Huh KB, Cha BS. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. *Arch Intern Med* 2004; **164**: 2169-2175 [PMID: 15505132 DOI: 10.1001/archinte.164.19.2169]
4 **Chen CH**, Huang MH, Yang JC, Nien CK, Yang CC, Yeh YH, Yueh SK. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. *J Clin Gastroenterol* 2006; **40**: 745-752 [PMID: 16940890 DOI: 10.1097/00004836-200609000-00016]
5 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121 [PMID: 16012941 DOI: 10.1053/j.gastro.2005.04.014]
6 **Hashimoto E**, Taniai M, Tokushige K. Characteristics and diagnosis of NAFLD/NASH. *J Gastroenterol Hepatol* 2013; **28** Suppl 4: 64-70 [PMID: 24251707 DOI: 10.1111/jgh.12271]
7 **Rich NE**, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, Mayo H, Singal AG. Racial and Ethnic Disparities in Nonalcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 198-210.e2 [PMID: 28970148 DOI: 10.1016/j.cgh.2017.09.041]
8 **Dongiovanni P**, Anstee QM, Valenti L. Genetic predisposition in NAFLD and NASH: impact on severity of liver disease and response to treatment. *Curr Pharm Des* 2013; **19**: 5219-5238 [PMID: 23394097 DOI: 10.2174/1381612811319990381]
9 **Hickman IJ**, Jonsson JR, Prins JB, Ash S, Purdie DM, Clouston AD, Powell EE. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut* 2004; **53**: 413-419 [PMID: 14960526 DOI: 10.1136/gut.2003.027581]
10 **Petersen KF**, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 2005; **54**: 603-608 [PMID: 15734833 DOI: 10.2337/diabetes.54.3.603]

11 **Dixon JB**, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: Improvement in liver histological analysis with weight loss. *Hepatology* 2004; **39**: 1647-1654 [PMID: 15185306 DOI: 10.1002/hep.20251]

12 **Hoofnagle JH**, Van Natta ML, Kleiner DE, Clark JM, Kowdley KV, Loomba R, Neuschwander-Tetri BA, Sanyal AJ, Tonascia J; Non-alcoholic Steatohepatitis Clinical Research Network (NASH CRN). Vitamin E and changes in serum alanine aminotransferase levels in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2013; **38**: 134-143 [PMID: 23718573 DOI: 10.1111/apt.12352]

13 **Laurin J**, Lindor KD, Crippin JS, Gossard A, Gores GJ, Ludwig J, Rakela J, McGill DB. Ursodeoxycholic acid or clofibrate in the treatment of non-alcohol-induced steatohepatitis: a pilot study. *Hepatology* 1996; **23**: 1464-1467 [PMID: 8675165 DOI: 10.1002/hep.510230624]

14 **Foster T**, Budoff MJ, Saab S, Ahmadi N, Gordon C, Guerci AD. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. *Am J Gastroenterol* 2011; **106**: 71-77 [PMID: 20842109 DOI: 10.1038/ajg.2010.299]

15 **Parker HM**, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **56**: 944-951 [PMID: 22023985 DOI: 10.1016/j.jhep.2011.08.018]

16 **Shibata M**, Kihara Y, Taguchi M, Tashiro M, Otsuki M. Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2007; **30**: 2940-2944 [PMID: 17666460 DOI: 10.2337/dc07-0792]

17 **Kim CH**, Park JY, Lee KU, Kim JH, Kim HK. Fatty liver is an independent risk factor for the development of Type 2 diabetes in Korean adults. *Diabet Med* 2008; **25**: 476-481 [PMID: 18346164 DOI: 10.1111/j.1464-5491.2008.02410.x]

18 **Yamada T**, Fukatsu M, Suzuki S, Wada T, Yoshida T, Joh T. Fatty liver predicts impaired fasting glucose and type 2 diabetes mellitus in Japanese undergoing a health checkup. *J Gastroenterol Hepatol* 2010; **25**: 352-356 [PMID: 19817963 DOI: 10.1111/j.1440-1746.2009.05998.x]

19 **Sung KC**, Kim SH. Interrelationship between fatty liver and insulin resistance in the development of type 2 diabetes. *J Clin Endocrinol Metab* 2011; **96**: 1093-1097 [PMID: 21252243 DOI: 10.1210/jc.2010-2190]

20 **Bae JC**, Rhee EJ, Lee WY, Park SE, Park CY, Oh KW, Park SW, Kim SW. Combined effect of nonalcoholic fatty liver disease and impaired fasting glucose on the development of type 2 diabetes: a 4-year retrospective longitudinal study. *Diabetes Care* 2011; **34**: 727-729 [PMID: 21278140 DOI: 10.2337/dc10-1991]

21 **Sung KC**, Jeong WS, Wild SH, Byrne CD. Combined influence of insulin resistance, overweight/obesity, and fatty liver as risk factors for type 2 diabetes. *Diabetes Care* 2012; **35**: 717-722 [PMID: 22338098 DOI: 10.2337/dc11-1853]

22 **Jimba S**, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, Wasada T. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. *Diabet Med* 2005; **22**: 1141-1145 [PMID: 16108839 DOI: 10.1111/j.1464-5491.2005.01582.x]

23 **Targher G**, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* 2007; **30**: 1212-1218 [PMID: 17277038 DOI: 10.2337/dc06-2247]

24 **Williamson RM**, Price JF, Glancy S, Perry E, Nee LD, Hayes PC, Frier BM, Van Look LA, Johnston GI, Reynolds RM, Strachan MW; Edinburgh Type 2 Diabetes Study Investigators. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes Care* 2011; **34**: 1139-1144 [PMID: 21478462 DOI: 10.2337/dc10-2229]

25 **Wanless IR**, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology* 1990; **12**: 1106-1110 [PMID: 2227807 DOI: 10.1002/hep.1840120505]

26 **Silverman JF**, O'Brien KF, Long S, Leggett N, Khazanie PG, Pories WJ, Norris HT, Caro JF. Liver pathology in morbidly obese patients with and without diabetes. *Am J Gastroenterol* 1990; **85**: 1349-1355 [PMID: 2220728]

27 **Noureddin M**, Rinella ME. Nonalcoholic Fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. *Clin Liver Dis* 2015; **19**: 361-379 [PMID: 25921668 DOI: 10.1016/j.cld.2015.01.012]

28 **Fabbrini E**, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology* 2010; **51**: 679-689 [PMID: 20041406 DOI: 10.1002/hep.23280]

29 **Tilg H**, Moschen AR. Insulin resistance, inflammation, and non-alcoholic fatty liver disease. *Trends Endocrinol Metab* 2008; **19**: 371-379 [PMID: 18929493 DOI: 10.1016/j.tem.2008.08.005]

30 **Anstee QM**, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 330-344 [PMID: 23507799 DOI: 10.1038/nrgastro.2013.41]

31 **Rakoski MO**, Singal AG, Rogers MA, Conjeevaram H. Meta-analysis: insulin sensitizers for the treatment of non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2010; **32**: 1211-1221 [PMID: 20955440 DOI: 10.1111/j.1365-2036.2010.04467.x]

32 **Phielix E**, Szendroedi J, Roden M. The role of metformin and thiazolidinediones in the regulation of hepatic glucose metabolism and its clinical impact. *Trends Pharmacol Sci* 2011; **32**: 607-616 [PMID: 21824668 DOI: 10.1016/j.tips.2011.06.006]

33 **Sanyal AJ**, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR, NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; **362**: 1675-1685 [PMID: 20427778 DOI: 10.1056/NEJMoa0907929]

34 **Jespersen MJ**, Knop FK, Christensen M. GLP-1 agonists for type 2 diabetes: pharmacokinetic and toxicological considerations. *Expert Opin Drug Metab Toxicol* 2013; **9**: 17-29 [PMID: 23094590 DOI: 10.1517/17425255.2013.731394]

35 **Armstrong MJ**, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K; LEAN trial team, Abouda G, Aldersley MA, Stocken D, Gough SC, Tomlinson JW, Brown RM, Hübscher SG, Newsome PN. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016; **387**: 679-690 [PMID: 26608256 DOI: 10.1016/S0140-6736(15)00803-X]

36 **Shirakawa J**, Fujii H, Ohnuma K, Sato K, Ito Y, Kaji M, Sakamoto E, Koganei M, Sasaki H, Nagashima Y, Amo K, Aoki K, Morimoto C, Takeda E, Terauchi Y. Diet-induced adipose tissue inflammation and liver steatosis are prevented by DPP-4 inhibition in diabetic mice. *Diabetes* 2011; **60**: 1246-1257 [PMID: 21330637 DOI: 10.2337/db10-1338]

37 **Iwasaki T**, Yoneda M, Inamori M, Shirakawa J, Higurashi T, Maeda S, Terauchi Y, Nakajima A. Sitagliptin as a novel treatment agent for non-alcoholic Fatty liver disease patients with type 2 diabetes mellitus. *Hepatogastroenterology* 2011; **58**: 2103-2105 [PMID: 22024083 DOI: 10.5754/hge11263]

38 **Fukuhara T**, Hyogo H, Ochi H, Fujino H, Kan H, Naeshiro N, Honda Y, Miyaki D, Kawaoka T, Tsuge M, Hiramatsu A, Imamura M, Kawakami Y, Aikata H, Chayama K. Efficacy and safety of sitagliptin for the treatment of nonalcoholic fatty liver disease with type 2 diabetes mellitus. *Hepatogastroenterology* 2014; **61**: 323-328 [PMID: 24901133]

39 **Bonner C**, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thévenet J, Beaucamps C, Delalleau N, Popescu I, Malaisse WJ, Sener A, Deprez B, Abderrahmani A, Staels B, Pattou F. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. *Nat Med* 2015; **21**: 512-517 [PMID: 25894829 DOI: 10.1038/nm.3828]

40 **Merovci A**, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, Xiong J, Perez Z, Norton L, Abdul-Ghani MA, DeFronzo RA. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest* 2014; **124**: 509-514 [PMID: 24463448 DOI: 10.1172/JCI70704]

41 **Kabil SL**, Mahmoud NM. Canagliflozin protects against non-alcoholic steatohepatitis in type-2 diabetic rats through zinc alpha-2 glycoprotein up-regulation. *Eur J Pharmacol* 2018; **828**: 135-145 [PMID: 29608898 DOI: 10.1016/j.ejphar.2018.03.043]

42 **Seko Y**, Sumida Y, Tanaka S, Mori K, Taketani H, Ishiba H, Hara T, Okajima A, Umemura A, Nishikawa T, Yamaguchi K, Moriguchi M, Kanemasa K, Yasui K, Imai S, Shimada K, Itoh Y. Effect of sodium glucose cotransporter 2 inhibitor on liver function tests in Japanese patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus. *Hepatol Res* 2017; **47**: 1072-1078 [PMID: 27925353 DOI: 10.1111/hepr.12834]

43 **Akuta N**, Watanabe C, Kawamura Y, Arase Y, Saitoh S, Fujiyama S, Sezaki H, Hosaka T, Kobayashi M, Kobayashi M, Suzuki Y, Suzuki F, Ikeda K, Kumada H. Effects of a sodium-glucose cotransporter 2 inhibitor in nonalcoholic fatty liver disease complicated by diabetes mellitus: Preliminary prospective study based on serial liver biopsies. *Hepatol Commun* 2017; **1**: 46-52 [PMID: 29404432 DOI: 10.1002/hep4.1019]

44 **Leiter LA**, Forst T, Polidori D, Balis DA, Xie J, Sha S. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. *Diabetes Metab* 2016; **42**: 25-32 [PMID: 26575250 DOI: 10.1016/j.diabet.2015.10.003]

45 **Shiba K**, Tsuchiya K, Komiya C, Miyachi Y, Mori K, Shimazu N, Yamaguchi S, Ogasawara N, Katoh M, Itoh M, Suganami T, Ogawa Y. Canagliflozin, an SGLT2 inhibitor, attenuates the development of hepatocellular carcinoma in a mouse model of human NASH. *Sci Rep* 2018; **8**: 2362 [PMID: 29402900 DOI: 10.1038/s41598-018-19658-7]

46 **Akuta N**, Kawamura Y, Watanabe C, Nishimura A, Okubo M, Mori Y, Fujiyama S, Sezaki H, Hosaka T, Kobayashi M, Kobayashi M, Saitoh S, Suzuki F, Suzuki Y, Arase Y, Ikeda K, Kumada H. Impact of sodium glucose cotransporter 2 inhibitor on histological features and glucose metabolism of non-alcoholic fatty liver disease complicated by diabetes mellitus. *Hepatol Res* 2019; **49**: 531-539 [PMID: 30577089 DOI: 10.1111/hepr.13304]

47 **Itani T**, Ishihara T. Efficacy of canagliflozin against nonalcoholic fatty liver disease: a prospective cohort study. *Obes Sci Pract* 2018; **4**: 477-482 [PMID: 30338118 DOI: 10.1002/osp4.294]

48 **Tahara A**, Kurosaki E, Yokono M, Yamajuku D, Kihara R, Hayashizaki Y, Takasu T, Imamura M, Li Q, Tomiyama H, Kobayashi Y, Noda A, Sasamata M, Shibasaki M. Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice. *Eur J Pharmacol* 2013; **715**: 246-255 [PMID: 23707905 DOI: 10.1016/j.ejphar.2013.05.014]

49 **Honda Y**, Imajo K, Kato T, Kessoku T, Ogawa Y, Tomeno W, Kato S, Mawatari H, Fujita K, Yoneda M, Saito S, Nakajima A. The Selective SGLT2 Inhibitor Ipragliflozin Has a Therapeutic Effect on Nonalcoholic Steatohepatitis in Mice. *PLoS One* 2016; **11**: e0146337 [PMID: 26731267 DOI: 10.1371/journal.pone.0146337]

50 **Hayashizaki-Someya Y**, Kurosaki E, Takasu T, Mitori H, Yamazaki S, Koide K, Takakura S. Ipragliflozin, an SGLT2 inhibitor, exhibits a prophylactic effect on hepatic steatosis and fibrosis induced by choline-deficient l-amino acid-defined diet in rats. *Eur J Pharmacol* 2015; **754**: 19-24 [PMID: 25701721 DOI: 10.1016/j.ejphar.2015.02.009]

51 **Takase T**, Nakamura A, Miyoshi H, Yamamoto C, Atsumi T. Amelioration of fatty liver index in patients with type 2 diabetes on ipragliflozin: an association with glucose-lowering effects. *Endocr J* 2017; **64**: 363-367 [PMID: 27980239 DOI: 10.1507/endocrj.EJ16-0295]

52 **Ito D**, Shimizu S, Inoue K, Saito D, Yanagisawa M, Inukai K, Akiyama Y, Morimoto Y, Noda M, Shimada A. Comparison of Ipragliflozin and Pioglitazone Effects on Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Randomized, 24-Week, Open-Label, Active-Controlled Trial. *Diabetes Care* 2017; **40**: 1364-1372 [PMID: 28751548 DOI: 10.2337/dc17-0518]

53 **Ohki T**, Isogawa A, Toda N, Tagawa K. Effectiveness of Ipragliflozin, a Sodium-Glucose Co-transporter 2 Inhibitor, as a Second-line Treatment for Non-Alcoholic Fatty Liver Disease Patients with Type 2 Diabetes Mellitus Who Do Not Respond to Incretin-Based Therapies Including Glucagon-like Peptide-1 Analogs and Dipeptidyl Peptidase-4 Inhibitors. *Clin Drug Investig* 2016; **36**: 313-319 [PMID: 26914659 DOI: 10.1007/s40261-016-0383-1]

54 **Miyake T**, Yoshida S, Furukawa S, Sakai T, Tada F, Senba H, Yamamoto S, Koizumi Y, Yoshida O, Hirooka M, Kumagi T, Niiya T, Miyaoka H, Masanori A, Matsuura B, Hiasa Y. Ipragliflozin Ameliorates Liver Damage in Non-alcoholic Fatty Liver Disease. *Open Med (Wars)* 2018; **13**: 402-409 [PMID: 30234161 DOI: 10.1515/med-2018-0059]

55 **Kawata T**, Iizuka T, Iemitsu K, Takihata M, Takai M, Nakajima S, Minami N, Umezawa S, Kanamori A, Takeda H, Ito S, Kikuchi T, Amemiya H, Kaneshiro M, Mokubo A, Takuma T, Machimura H, Tanaka K, Asakura T, Kubota A, Aoyanagi S, Hoshino K, Ishikawa M, Matsuzawa Y, Obana M, Sasai N, Kaneshige H, Minagawa F, Saito T, Shinoda K, Miyakawa M, Tanaka Y, Terauchi Y, Matsuba I. Ipragliflozin Improves Glycemic Control and Decreases Body Fat in Patients With Type 2 Diabetes Mellitus. *J Clin Med Res* 2017; **9**: 586-595 [PMID: 28611859 DOI: 10.14740/jocmr3038w]

56 **Tang L**, Wu Y, Tian M, Sjöström CD, Johansson U, Peng XR, Smith DM, Huang Y. Dapagliflozin slows the progression of the renal and liver fibrosis associated with type 2 diabetes. *Am J Physiol Endocrinol Metab* 2017; **313**: E563-E576 [PMID: 28811292 DOI: 10.1152/ajpendo.00086.2017]

57 **Wang D**, Luo Y, Wang X, Orlicky DJ, Myakala K, Yang P, Levi M. The Sodium-Glucose Cotransporter 2

Inhibitor Dapagliflozin Prevents Renal and Liver Disease in Western Diet Induced Obesity Mice. *Int J Mol Sci* 2018; 19 [PMID: 29301371 DOI: 10.3390/ijms19010137]

58 **Lee PCH**, Gu Y, Yeung MY, Fong CHY, Woo YC, Chow WS, Tan K, Lam KSL. Dapagliflozin and Empagliflozin Ameliorate Hepatic Dysfunction Among Chinese Subjects with Diabetes in Part Through Glycemic Improvement: A Single-Center, Retrospective, Observational Study. *Diabetes Ther* 2018; **9**: 285-295 [PMID: 29322486 DOI: 10.1007/s13300-017-0355-3]

59 **Tobita H**, Sato S, Miyake T, Ishihara S, Kinoshita Y. Effects of Dapagliflozin on Body Composition and Liver Tests in Patients with Nonalcoholic Steatohepatitis Associated with Type 2 Diabetes Mellitus: A Prospective, Open-label, Uncontrolled Study. *Curr Ther Res Clin Exp* 2017; **87**: 13-19 [PMID: 28912902 DOI: 10.1016/j.curtheres.2017.07.002]

60 **Shimizu M**, Suzuki K, Kato K, Jojima T, Iijima T, Murohisa T, Iijima M, Takekawa H, Usui I, Hiraishi H, Aso Y. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. *Diabetes Obes Metab* 2019; **21**: 285-292 [PMID: 30178600 DOI: 10.1111/dom.13520]

61 **Eriksson JW**, Lundkvist P, Jansson PA, Johansson L, Kvarnström M, Moris L, Miliotis T, Forsberg GB, Risérus U, Lind L, Oscarsson J. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. *Diabetologia* 2018; **61**: 1923-1934 [PMID: 29971527 DOI: 10.1007/s00125-018-4675-2]

62 **Jojima T**, Tomotsune T, Iijima T, Akimoto K, Suzuki K, Aso Y. Empagliflozin (an SGLT2 inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes. *Diabetol Metab Syndr* 2016; **8**: 45 [PMID: 27462372 DOI: 10.1186/s13098-016-0169-x]

63 **Kuchay MS**, Krishan S, Mishra SK, Farooqui KJ, Singh MK, Wasir JS, Bansal B, Kaur P, Jevalikar G, Gill HK, Choudhary NS, Mithal A. Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial). *Diabetes Care* 2018; **41**: 1801-1808 [PMID: 29895557 DOI: 10.2337/dc18-0165]

64 **Sattar N**, Fitchett D, Hantel S, George JT, Zinman B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial. *Diabetologia* 2018; **61**: 2155-2163 [PMID: 30066148 DOI: 10.1007/s00125-018-4702-3]

65 **Nakano S**, Katsuno K, Isaji M, Nagasawa T, Buehrer B, Walker S, Wilkison WO, Cheatham B. Remogliflozin Etabonate Improves Fatty Liver Disease in Diet-Induced Obese Male Mice. *J Clin Exp Hepatol* 2015; **5**: 190-198 [PMID: 26628836 DOI: 10.1016/j.jceh.2015.02.005]

66 **Qiang S**, Nakatsu Y, Seno Y, Fujishiro M, Sakoda H, Kushiyama A, Mori K, Matsunaga Y, Yamamotoya T, Kamata H, Asano T. Treatment with the SGLT2 inhibitor luseogliflozin improves nonalcoholic steatohepatitis in a rodent model with diabetes mellitus. *Diabetol Metab Syndr* 2015; **7**: 104 [PMID: 26594248 DOI: 10.1186/s13098-015-0102-8]

67 **Shibuya T**, Fushimi N, Kawai M, Yoshida Y, Hachiya H, Ito S, Kawai H, Ohashi N, Mori A. Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: A prospective randomized controlled pilot study. *Diabetes Obes Metab* 2018; **20**: 438-442 [PMID: 28719078 DOI: 10.1111/dom.13061]

68 **Sumida Y**, Murotani K, Saito M, Tamasawa A, Osonoi Y, Yoneda M, Osonoi T. Effect of luseogliflozin on hepatic fat content in type 2 diabetes patients with non-alcoholic fatty liver disease: A prospective, single-arm trial (LEAD trial). *Hepatol Res* 2019; **49**: 64-71 [PMID: 30051943 DOI: 10.1111/hepr.13236]

69 **Charlton M**. Risk of Hepatocellular Carcinoma in Patients With Nonalcoholic Steatohepatitis. *Gastroenterol Hepatol (NY)* 2018; **14**: 247-249 [PMID: 29942224]

70 **Kaji K**, Nishimura N, Seki K, Sato S, Saikawa S, Nakanishi K, Furukawa M, Kawaratani H, Kitade M, Moriya K, Namisaki T, Yoshiji H. Sodium glucose cotransporter 2 inhibitor canagliflozin attenuates liver cancer cell growth and angiogenic activity by inhibiting glucose uptake. *Int J Cancer* 2018; **142**: 1712-1722 [PMID: 29205334 DOI: 10.1002/ijc.31193]

71 **Okada J**, Matsumoto S, Kaira K, Saito T, Yamada E, Yokoo H, Katoh R, Kusano M, Okada S, Yamada M. Sodium Glucose Cotransporter 2 Inhibition Combined With Cetuximab Significantly Reduced Tumor Size and Carcinoembryonic Antigen Level in Colon Cancer Metastatic to Liver. *Clin Colorectal Cancer* 2018; **17**: e45-e48 [PMID: 29054804 DOI: 10.1016/j.clcc.2017.09.005]

72 **Clar C**, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open* 2012; 2 [PMID: 23087012 DOI: 10.1136/bmjopen-2012-001007]

73 **Weir MR**, Januszewicz A, Gilbert RE, Vijapurkar U, Kline I, Fung A, Meininger G. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. *J Clin Hypertens (Greenwich)* 2014; **16**: 875-882 [PMID: 25329038 DOI: 10.1111/jch.12425]

74 **INVOKANA (canagliflozin)**. Tablets 48. Available from: https://www.netdoctor.co.uk/medicines/diabetic/a8900/invokana-canagliflozin

75 **Watts NB**, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, Meininger G. Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. *J Clin Endocrinol Metab* 2016; **101**: 157-166 [PMID: 26580237 DOI: 10.1210/jc.2015-3167]

76 **Ueda P**, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S, Gudbjörnsdottir S, Hveem K, Jonasson C, Pasternak B. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ* 2018; **363**: k4365 [PMID: 30429124 DOI: 10.1136/bmj.k4365]

77 **Peters AL**, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care* 2015; **38**: 1687-1693 [PMID: 26078479 DOI: 10.2337/dc15-0843]

78 Research C for DE and Drug Safety and Availability - FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections [Internet]. [cited 2019 Feb 12]; Available from: https://www.fda.gov/Drugs/DrugSafety/ucm475463.htm

79 **Filippas-Ntekouan S**, Filippatos TD, Elisaf MS. SGLT2 inhibitors: are they safe? *Postgrad Med* 2018; **130**: 72-82 [PMID: 29039237 DOI: 10.1080/00325481.2018.1394152]

80 Research C for DE and Drug Safety and Availability-FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes [Internet]. [cited 2019 Feb 12]; Available from: https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm

81 **Vasilakou D**, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, Sarigianni M, Matthews DR, Tsapas A. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013; **159**: 262-274 [PMID: 24026259 DOI: 10.7326/0003-4819-159-4-201308200-00007]

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MINIREVIEWS

Role of innovative 3D printing models in the management of hepatobiliary malignancies

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Abstract

Three-dimensional (3D) printing has recently emerged as a new technique in various liver-related surgical fields. There are currently only a few systematic reviews that summarize the evidence of its impact. In order to construct a systematic literature review of the applications and effects of 3D printing in liver surgery, we searched the PubMed, Embase and ScienceDirect databases for relevant titles, according to the PRISMA statement guidelines. We retrieved 162 titles, of which 32 met the inclusion criteria and are reported. The leading application of 3D printing in liver surgery is for preoperative planning. 3D printing techniques seem to be beneficial for preoperative planning and educational tools, despite their cost and time requirements, but this conclusion must be confirmed by additional randomized controlled trials.

Key words: Three-dimensional printing; Three-dimensional models; Liver; Surgery; Hepatic phantom models

Core tip: Three-dimensional printing is an emerging technology that seems to have useful applications in various medical fields. The most thoroughly studied applications are in medical education and preoperative planning. However, the financial and time requirements for its use remain issues to be resolved. In this Minireview, we analyze the uses of three-dimensional printing models which are reported in the literature, with special emphasis on their role in surgical education in hepatic surgery.

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INTRODUCTION

Three-dimensional (3D) printing is a rapid prototyping additive manufacturing technology that offers the opportunity to create numerous artificial parts and objects, made of different materials with various mechanical and physical properties[1,2]. The first 3D printed object was reported by Hideo Kodama in 1982. Since then, the technological aspects of 3D printing procedures have achieved an exponential development rate and, nowadays, big specialized companies, as well as individuals with their personal printers, can construct a variety of 3D objects, ranging in cost and quality depending on their intended use. 3D printing is an emerging technological achievement that could be deployed for a variety of applications in many medical fields, such as preoperative planning and medical education. This state-of-the-art technology displays certain advantages against older techniques, and seems to overcome some existing limitations, although there are still some drawbacks to be resolved[3-5]. 3D printed models seem to be capable of satisfying the needs for tactile and spatial perception of human anatomical structures[6,7]. Thus, they can be used to create 3D organ models for spatial and anatomical understanding, so that surgeons can achieve a better preoperative plan and prepare their surgical manipulations on 3D, graspable models[4,6]. 3D printing also provides optimized strategies for device testing[6] and serves educational purposes[8-10]. One of the most prominent medical applications of 3D printing is the development of medical devices and instrumentation[4,9]. 3D printing appears to be a significantly useful and cost-effective technique compared to traditional cadaveric models. Surgeons can have an accurate optical and tactile sense of the structures, and perform complex operations on them[6,11,12]. Moreover, the use of additive manufacturing technologies in tissue engineering has been recently explored with revolutionary results. Many materials are used to fabricate a scaffold and then print functional cells onto it in order to mimic human tissue, which is a process called bioprinting[13,14].

Liver diseases, and especially those requiring surgical interventions, have led the way for the implementation of 3D printing techniques for many applications. Liver resection is the "gold standard" procedure in liver cancer that guarantees successful treatment. Despite technological improvements, liver resections remain a challenging area, especially for young surgeons. Although the knowledge of liver anatomy is essential for safe surgical resections, there are many anatomical variations. To perform an accurate hepatic resection, knowledge of the anatomical relationships among the branches of Glisson's sheath, the hepatic veins and the tumor is crucial[15]. Magnetic resonance imaging (MRI) and computed tomography (CT) are conventional diagnostic methods that estimate the location of the lesions and their relationship with neighboring structures, and also provide 2-dimensional images. Virtual and Augmented Reality tools can possibly offer a more comprehensive alternative for 3D visualization, but still lack the ability to provide tactile feedback. Advanced navigation systems during liver resections can provide us with some help, but they demonstrate numerous limitations while maintaining a relatively high cost[16]. 3D printing techniques provide an effective solution for preoperative planning, by creating precise, patient-specific, graspable, 3D printed models of organs and lesions based on imaging data. While liver surgery can be challenging, and requires technical excellence and experience, implementation of a 3D printed pre-operative model seems to be very promising[13]. The implementation of 3D objects in medical education and surgical training also seems promising, as it provides live models that the trainees can handle and better comprehend[17,18]. In the present study, we analyze the studies that report the applications and the outcomes of 3D printing technologies in liver surgery, with special emphasis on preoperative planning and surgical education.

BASIC PRINCIPLES OF 3D PRINTING

3D printing is similar to conventional inkjet printing. It is a process of layering a material that initially has polymeric properties (or reaches a fluid state through heat),

horizontally deposited and solidified, either by cooling or by ultraviolet light irradiation, to eventually create a complete 3D model. Every horizontal section of the final printed product closely resembles the way images of an axial or magnetic tomography are acquired. In 3D printing, instead of having a detection level that records the different densities corresponding to the different web structures between the irradiation head and its recorder, the print head composes an artefact in three dimensions.

The resemblance of how a printed item is created by the process of reconstituting a CT scan helps physicians' understanding of both the printing process and its necessity in both medicine and surgery. CT and MRI scans are the most frequent preoperative examinations performed during the investigation of many pathological conditions, and guide the treating physician in finding the optimal therapeutic approach. However, the nature of CT is completely different from the 3D reality, and the physician's perception is constrained by the two-dimensional representation of sequential tomography images, which often result in the erroneous assessment of an existing disease state. CT and MRI data files (Digital Imaging and Communications in Medicine, DICOM format) were usually stored in CAD software (©Google sketchup). After isolating the relevant structures in each image set, 3-D volume reconstruction was performed. The final model was saved in the STL format. This extension STL supported the visualization of the model as a fully rotated virtual 3-D representation (360° on the x, y and z axes). A physical model of the processed 3-D digital model was created by a 3-D printer using commercially available polymeric filament materials. In all studies, "Digital Imaging and Communications in Medicine" (DICOM) files from MRI or CT tomography are reconstructed using computer-aided design (CAD) drawings software. Digital 3-D objects are sent to a 3-D printer, and 3-D models are then ready for use[3] (Figure 1).

LITERATURE REVIEW

We performed a thorough review of the literature in accordance with PRISMA statement guidelines, using the PubMed, Embase and ScienceDirect indexing databases[19]. "3D printing", "three-dimensional printing" and "rapid prototyping", in combination with "liver", "hepatic" or "surgical", were used as search terms to identify relevant titles. We included only original papers written in English and published between January 2008 and August 2018. Moreover, we excluded the semantically irrelevant studies that did not refer to the use of 3D printing in liver surgery, based on the content of the abstract and the full text. The studies involving non-human subjects, as well as those referring to 3D bioprinting, were also excluded (Figure 2).

CURRENT STATUS AND CHALLENGES OF 3D PRINTING IN HEPATIC SURGERY

Data extraction and appraisal

The initial search retrieved 162 titles. Two expert reviewers screened the papers independently, and after the removal of studies not meeting the inclusion criteria, 32 full-text papers were included (Figure 2). All included papers refer to 3D printing applications strictly related to liver surgery. Characteristics, such as the study type, the field of application, the study setting, the clinical or practical outcome and the time and cost required, were extracted and are presented (Table 1).

Preoperative planning is the leading application of 3D printing technology. Fifteen of the 32 studies refer to the utilization of 3D printed organs, based on the patients' CT and MRI imaging data, to establish a better understanding of the lesions and the surrounding structures pre-operatively[16,20-33]. Ten studies refer to the use of 3D printed objects for educational uses[28,32,34-41], while seven studies describe and evaluate the technical properties of 3D printed models[34-36,42-45]. Other uses of 3D printing techniques account for six of the included studies[32,46-50]. Additionally, 20 of the studies were case reports, reporting the use or the properties of one 3D printed model, while seven were case series, involving more than one object. There were a limited number of cohort studies and randomized controlled trials (RCT), constituting only seven and four of the included studies, respectively. Cohort studies quantitatively explore the characteristics of a group of 3D printed models or of a cohort of patients/trainees where a 3D printing method is employed. RCTs compare the outcome (clinical or educational) of a 3D printing method to another conventional one. Some of the studies described more than one application field using different study designs, and

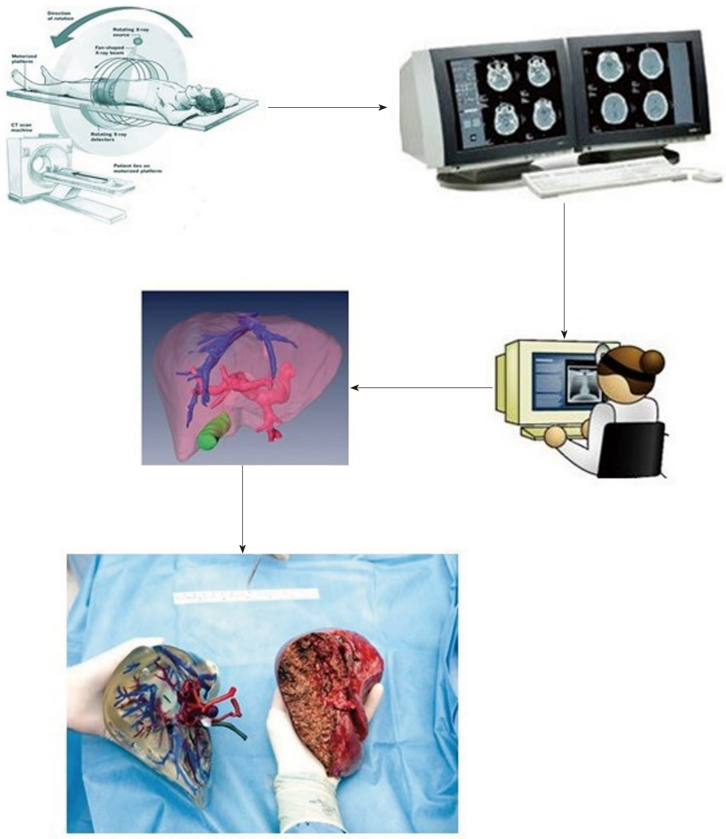

Figure 1 Long way from bedside to three-dimensional printed objects.

thus are included in more than one category. The results are summarized (Table 2).

Principles of function, and requirements of 3D printing

In the majority of the cases, 3D printers are "fed" with real patients' data obtained from CT and MRI imaging files. In particular, 26 of the 32 studies used CT-derived images as the pool of data for the printer. In four of the 26 cases, the use of MRI imaging was included. One study did not clarify the source of the 3D model's data, while the remaining five studies used alternative sources of data. The segmentation of the images, and the conversion of the data to a "3D-printer-friendly" format, is a time-consuming procedure, lasting from a few hours to a few days, and can be performed by a variety of different software systems[18]. An .STL file, which is compatible with the majority of 3D printers, is produced. The printer uses the .STL file to construct a 3D artificial object, which simulates the shape of the individual's structures with precision. There is a variety of different 3D printers, each one compatible with specific fabrication materials, selected according to the desired application. Both conventional, personal 3D printers and professional, sophisticated 3D printing systems from big companies were used. Printing time can also be time-consuming. Different structures, such as the biliary tract, gallbladder, vessels, parenchyma and tumor, are manufactured with different materials and colored in different colors, a procedure often performed manually. In most cases, the parenchyma is transparent to allow visibility of the inner structures, while in some cases it is not printed at all. Depending on the system employed, the materials used, the size and the complexity of the printed object, the time necessary for segmentation, conversion and printing, as well as the economic cost can vary substantially[13,17,18]. Eighteen studies do not provide clues about the time required, and 14 studies do not refer to the cost of printing. Neither the cost, nor the time requirements are included in 11 of the studies. The economic data and time information from the rest of the studies are inhomogeneous and of poor quality. We can roughly say that the whole procedure time ranges from 1-3 d, although there are many factors that determine this variable, and significant deviations are observed[28,38]. The cost also displays a wide range, depending on the method used and the size of the object. Seven studies use more economical settings at a cost of around $100, four studies reach a cost of approximately $400-$600, and four studies use high accuracy materials and techniques that exceed the cost of $1000

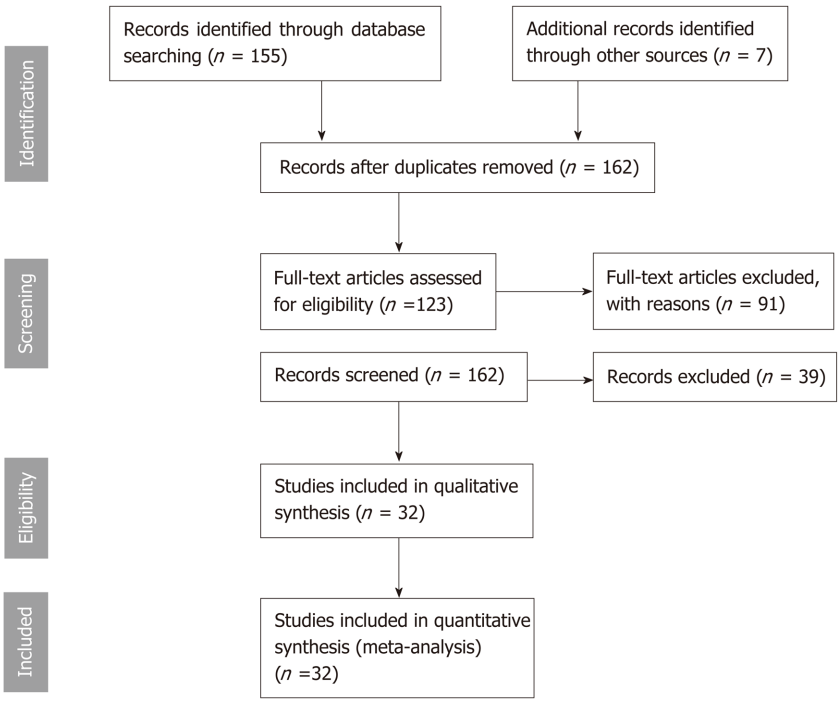

Figure 2 PRISMA statement chart.

(Table 1). However, there are also numerous factors, such as the cost of the dyes, the materials and the handmade work cost, that can drastically affect the cost and are vaguely explained in most of the studies.

Preoperative planning

Preoperative planning is the most popular application of 3D printing in liver surgery, and is referred to in 15 (47%) of the studies. The authors describe the potent use of 3D printed models of the patients' organs in helping them better understand the lesions and the surrounding structures, as well as plan a more efficient surgical strategy. The individualized, artificially manufactured liver replicates hold many advantages, such as the tactile feedback, the ability to distinctly demonstrate the different structures by using different colors, and the ability to reveal small lesions that could be invisible intraoperatively[22]. However, there are also drawbacks regarding the cost and the time they require[13,18]. Eleven of the studies describe its use in tumor resection and partial hepatectomy, while in one of them it is mentioned that the surgery was abandoned, as the 3D printed model revealed that the tumor was unresectable[32]. One study describes the use of 3D printing for reducing the radiation dose and detecting small tumors[27], while three studies exhibit the usefulness of 3D printing in liver transplantations[20,23,26]. The majority of the studies referring to preoperative planning with 3D printing are case reports (13 of the 15 studies, 87%)[21-33], while there are also two (13%) case series, one with six subjects (three organ donors and three LDLT recipients), and the other with two[16,20].

Most of the studies report good results regarding the usefulness of 3D printing in preoperative planning, although there is no objective evidence for any significantly beneficial clinical outcome, as there are no RCTs that could compare the outcome of these applications with the more traditional ones. Zein *et al*[19] was the first to describe the application of 3D printing in liver surgery and the crucial field of transplantation. This study employed 3D printed models to visualize the donors' and recipients' livers, and used them to both identify better anatomical landmarks and optimize preoperative planning. It is mentioned that the mean errors of the measurements are < 4 mm for the whole liver and < 1.3 mm for the diameter of the vessels. In 2014 and 2015, the number of publications concerning the use of 3D printing in preoperative planning for liver surgery began to rise. There were three studies advocating the beneficial role of 3D printing in partial hepatectomy for tumor removal[21,22,24], one study testing these methods in pediatric patients with malignant tumors[25], and also one study concerning transplantation[23]. Soejima *et al*[25] tried to use a 3D printed model to simulate the liver of a 11-mo-old female receiving LDLT for biliary atresia after a failed Kasai procedure, as well as the liver of the donor father. The results were

Table 1 Report of studies referring to 3D printing applications in liver diseases

Authors[REF], year	Study type	Field of application	Imaging tools	Outcome
Zein *et al*[19], 2013	Case series	PP	CT and MRI	Accurate in providing liver volume and size measurement
Takagi *et al*[20], 2014	Case report	PP, TP	CT	Reported reproducibility of the model and possible future aid to surgical procedures
Igami *et al*[21], 2014	Case report	PP	CT	Helpful in preoperative planning. Detects small tumors invisible with intraoperative US
Watson[36], 2014	Case series	ET	CT and MRI	Ability of creating patient-simulated 3D printed liver models at low cost
Baimakhanov *et al*[22], 2015	Case report	PP (transplantation)	CT	Helpful in preoperative planning and surgical training
Xiang *et al*[23], 2015	Case report	PP (hepatectomy for tumor)	CT	Helpful in preoperative planning
Dhir *et al*[33], 2015	Cohort study	ET, TP	MRCP	Accurate understanding liver anatomy
Souzaki *et al*[24], 2015	Case report	PP	CT	Assists surgical planning understanding of the anatomy
Soejima *et al*[25], 2016	Case report	PP	CT	Useful for small infants or neonates Realistic liver graft that is helpful in optimizing the procedure
Leng *et al*[26], 2016	Case report	PP	CT	Could be useful in reducing radiation dose and detecting small liver lesions
Kong *et al*[35], 2016	RCT, Cohort study	ET, TP	CT	Anatomy teaching and significantly improved knowledge
Kong *et al*[34], 2016	RCT, Cohort study	ET, TP	CT	Teaching of hepatic segments
Burdall *et al*[41], 2016	Cohort study	TP	CR, MRI	Scored 5.6/10 for fidelity, 6.2/10 for complexity and 7.36/10 for usefulness. All would suggest it and think it is reproducible
Takao *et al*[42], 2016	Case series	TP	CT	High accuracy of 3D
Koganemaru *et al*[45], 2016	Case report	PP	CT	Successful embolization and follow-up markers
Javan *et al*[37], 2016	Case series	ET	CT	Useful in comprehending difficult anatomical structures
Witowski *et al*[12,27], 2017	Case report	PP, ET	CT	Useful for planning procedures like hepatic resection and for educational purposes.
Kuroda *et al*[15], 2017	Case series	PP	CT	Successful resection
Madurska *et al*[28], 2017	Case report	PP	CT, MRI	Anatomical structures and lesions were clearly demonstrated
Oshiro *et al*[29], 2017	Case report	PP	CT	The surgical procedure was easier, and the visibility of small tumors was improved
Perica *et al*[17,30], 2017	Case report	PP	CT	Possible benefit in preoperative planning and intraoperative guidance
Andolfi *et al*[31], 2017	Case report	PP ET, PE	VR	Clearer observations of the relationship between the mass and blood vessels
Trout *et al*[46], 2017	Case series	PP	CT, MRI	A new technique to standardize hepatic sectioning was used

Weng *et al*[47], 2017	Case report	PP, TP	CT, MRI	Positive comments from relatives and experts
Choi *et al*[43], 2017	Cohort study	TP	CT, US	No significant difference in tumor size was found between the CT images and 3D model measured with US
Bücking *et al*[44], 2017	Case series	TP	CT	High accuracy in fidelity
Igami *et al*[32], 2017	Case report	PP	CT	The 3D printed model was useful in determining the resection line
Yang *et al*[48], 2018	Cohort study	PE	CT	Parental understanding of basic liver anatomy
Li *et al*[38], 2018	RCT	ET	CT	The 1st group, trained with the 3D printed model
Yang *et al*[39], 2018	RCT	ET	CT	Better understanding liver anatomy
Javan *et al*[40], 2018	Case report	ET	CT, MRI	Abscess drainage, artery embolization, and catheter placement procedures were well-exhibited
Tang *et al*[49], 2018	Case report	VR	CT	Navigation was effective, although stability in tracking was not satisfactory

3D: Three-dimensional; PP: Preoperative planning; ET: Education and training; PE: Patient education; TP: Evaluation of technical properties; RCT: Randomized controlled trial; CT: Computed tomography; MRI: Magnetic resonance imaging; LDLT: Living donor liver transplantation; MRCP: Magnetic resonance cholangiopancreatography; VR: Virtual reality; AR: Augmented reality; 2D: Two-dimensional; US: Ultrasound.

reported as encouraging. Leng *et al*[26] developed a method, involving 3D printed liver models, to reduce radiation dose and detect small liver lesions. In 2017, there were six original papers that described the beneficial effects of 3D printing in the preoperative planning of liver surgeries[16,28-32], while no similar studies were published in 2018. Although these studies clearly explain the concept of involving 3D printing in hepatic surgery, and the opinions are expressed by prominent professionals, they have been designed as case reports or case series, so it is therefore impossible to objectively compare their results to another preoperative planning method. Moreover, there is insufficient information in most of the studies concerning the time and cost requirements that would allow for the accurate evaluation of their overall efficiency in the context of these two critical factors.

Education and training

Both student education in liver anatomy and resident training in liver surgical techniques with the use of 3D printed models are the second most widely studied application. Ten studies refer to this field, five of which were designed as case reports or case series[28,32,37,38,41], one was an observational cohort study[34] and four were RCTs[35,36,39,40]. The case reports and case series state that 3D printed models could help in both the understanding of liver anatomy and surgical training, but fail to provide objective evidence. Dhir *et al*[33] was the first to use 3D printed liver models to train a cohort of 15 individuals in EUS-guided biliary drainage (EUS-BD) and, moreover, to measure the educational outcomes. The success rates were: 100% for needle puncture, 82.35% for wire manipulation and 80% for stent placement. However, the more experienced trainees were found to score lower in stent placement. This may be attributed to the small sample size that may not have supported safe comparison tests. Two RCTs were published in 2016[35,36], and two in 2018[39,40], comparing the educational impact of 3D printing to more conventional strategies. Kong *et al*[34] randomized 61 medical students into three cohorts: the 1st was trained in 3D printed models, the 2nd in 3D virtual models on computers and the 3rd in traditional anatomy atlases. The results favored both 3D printed and virtual models against the traditional atlases. However, the sample was small, and there was no cost analysis to the use of 3D printing against 3D virtual methods. In another study that same year, Kong *et al*[35] randomized 92 students into four groups, and trained them in different settings: The 1st was trained on a 3D printed model with hepatic segments without parenchyma, the 2nd on a 3D printed model with hepatic segments with transparent parenchyma, the 3rd on a biliary tract model with segmental partitions and the 4th on traditional anatomic atlases. In general, the 3rd group was found to have better results, although the samples in the randomized groups may also lack enough statistical power. Li *et al*[38] tried to use 3D printed models against virtual, computer-based 3D models in order to

Table 2 Cross-tabulation of the study characteristics

Field of application	Type of study				Sum
	Case report	Case series	Cohort studies	RCT	
Preoperative planning	13	2	0	0	15
ET	3	2	1	4	10
TP	0	2	5	0	7
Other	4	1	1	0	6
Sum	20	7	7	4	

ET: Education and training; TP: Evaluation of technical properties; RCT: Randomized controlled trial. Five of the studies belong to more than one application group, and they display different study types for each application, thus belonging to more than one cell.

train 20 individuals in choledochoscopy. Although the randomized sample was also small, the design was sophisticated, and the results showed 3D printed models to be superior. Yang *et al*[39] evaluated the educational impact of 3D printed models against 3D virtual models and CT-based tools, and found them to be superior. These studies provide significant evidence that 3D printing could be applied in education and training in liver surgery, although they may have some methodological weaknesses.

Evaluation of technical properties

There are also a number of studies that aim to evaluate the technical properties of 3D printed models, such as their accuracy in simulating the real organ. There are seven published studies, two of which are case series[43,45] and five of which are observational cohort studies[34,36,36,42,44]. The case series mention high accuracy and fidelity of the 3D printed models when compared with the CT-derived models. Choi *et al*[43] printed 20 CT-based 3D livers with tumors, and measured the sizes of the anatomical structures with US. The results were not significantly different from those derived from CT, indicating high accuracy. Burdall *et al*[41] constructed a liver-like base with a cuboid slot in which a sponge with a green balloon, simulating the gallbladder, was placed. This setting was evaluated by ten trainees for its possible educational effect, and scored high for fidelity, complexity, usefulness and reproducibility. Dhir *et al*[33], Kong *et al*[34] and Kong *et al*[35], except for measuring the differences in the educational impact between the different cohorts of trainees, also employed independent teams of experts to quantitatively evaluate the settings. The results showed 3D printed models to be equal to or more satisfactory than computer-based virtual 3D models, and better than older, traditional strategies.

Additional applications

Additional uses of 3D printing in liver surgery are described in six studies. Andolfi *et al*[31] and Yang *et al*[48] describe the effect 3D printed liver models can have on patient education. They can enlighten the patients about their condition, and contribute to the facilitation of a better understanding and patient-physician collaboration. Tang *et al*[49] proposes the use of 3D printed models when training in AR-assisted endoscopy. Although the setting and equipment were described thoroughly, there were no quantitative variables in the study that could measure the benefit of this method. Weng *et al*[47] describes an alternative use of 3D printing. 3D printed objects were used to replace the heart, the kidneys and the liver of a brain-dead patient whose organs were removed for transplantation. In this study, the motives and the relevant ethical issues are explained, as well as the cost and the procedure. Koganemaru *et al*[45] reported the use of a CT-based, 3D printed copy of a portacaval shunt following transplantation, to better understand the complication and decide the embolization technique and material. Additionally, Trout *et al*[46] described a 3D printing-based technique for applying better sectioning to explants, resulting in better pathology results.

Impact of 3D printing technology in the era of hepatobiliary surgery

In this systematic review, we analyzed and reported the findings of 32 original studies concerning the role of 3D printing models in liver surgery. As indicated from the literature, 3D printing has already been applied to a variety of relevant fields, with preoperative planning as the one most commonly reported. The second most encountered application is for educational and training purposes. The remaining studies evaluate the technical aspects of 3D printed models, or refer to some less

frequent uses. 3D printed models of patients' livers have been found to be useful in preoperative planning, as they provide a more realistic view of the lesion and the surrounding anatomical structures, a conclusion shared by other reviews as well[13,15,18]. These models can also offer the ability to interact with a graspable object, so that surgical manipulations can be tested, in contrast with 3D visualizations based on a computer setting. Although virtual and augmented reality techniques can also provide tactile feedback, they lack fidelity with the current equipment available[50]. The most common type of surgery was partial hepatectomy for the resection of malignant tumors, while three studies applied 3D printing methods in LDLT[20,23,26]. The application in transplantation seems to be extremely helpful, as it can provide models for both donor and recipient livers, thus enabling the surgeon to better understand the crucial landmarks and structures, as well as better prepare for the procedure and avoid the large-for-size syndrome[26]. Education offers a great field for 3D printing applications, as the innovative technology can address the need for high quality visualization of the interior, tactile feedback and reproducible models. 3D printed copies are used both in anatomy teaching and for providing tools for training in advanced interventions, such as choledochoscopy. Some studies have evaluated the accuracy and reproducibility of 3D printed models in a positive manner. Remarkably interesting are some rarely encountered uses of 3D printing in liver surgery, such as its use in filling the hollow cavities of brain-dead patients after the removal of their organs, or its involvement in a novel technique for better sectioning of explants for pathology purposes[47,48]. These are examples of the numerous yet unknown uses of such techniques and technologies, and can lead the way for further exploration.

Although 3D printing exhibits significant advantages, there are certain drawbacks that may undermine its wide use. The large eco nomic cost and the extended time required for printing are often referred as such in the literature[13,31]. Unfortunately, these types of information are inadequately reported in the included studies, and when they do, there are numerous factors that can significantly affect these parameters, which are rarely explained. As far as the cost is concerned, the price for printing one model starts at around $100 and can exceed $1000. However, the printing technique and the printer, the fabrication materials used, and the size of the model can drastically change the cost. Moreover, in some studies, the printing is assigned to third specialized companies, which may include extra costs in the final price (branding, shipping costs) or make marketing discounts. In some studies, the lesions, biliary tract and vascular structures are printed, but not the parenchyma, not only for educational/clinical reasons (touching the structures), but also to reduce the cost. In terms of time, it seems that not only the printing procedure itself is a time-consuming process, but so are the preliminary stages of image segmentation and data conversion to a printer-compatible format. The size of the model, the desired quality and the software used determine the needed time.

Our findings are in agreement with the conclusions of other relevant reviews. According to our search, there have been four reviews analyzing the use of 3D printing in liver pathology[13,17,18,51,52]. Three of the reviews include less than or equal to 19 studies[17,18,51,52], while Witowski *et al*[12] also includes articles referring to 3D tissue bioprinting. One review was published in 2016, two in 2017 and two in 2018. In the current review, 32 original papers were included, which makes it the most comprehensive review in this rapidly developing field. One of the limitations of this review is that the majority of the studies included were case reports or case series, while there were only few observational cohort studies and RCTs. The observational cohort design was mainly used in studies that evaluated the technical properties of the models. In most cases, a group of experts evaluated specific variables of the models, such as their accuracy, their potential usefulness (according to the evaluators' subjective judgement) or their reproducibility. In these studies, the scores of the various models were not compared to other standardized, gold-standard techniques[34-36,42,44]. On the contrary, the included RCTs evaluated the effect of 3D printed models against other conventional methods, such as 3D visualizations on computers or CT imaging, mostly in the field of educational applications[35,36,39,40]. However, even these papers, which constitute the most robustly designed studies, contain small sample sizes that fail to add statistical power to the tests used. All of the studies referring to preoperative planning are case reports or case series, reporting the subjective evaluation of the experts using these models in single cases. This can at least partly be explained by the fact that an RCT would require many different, individualized 3D printed models of the livers of the intervention cohort, which would be discouragingly costly. Moreover, even if an RCT with sufficiently large samples could show the clinical benefit of 3D printing, we would also have to assess the cost of the intervention in order to conclude, not only if it is an effective method, but also if it constitutes a cost-efficient and massively applicable one. More RCTs are needed that will show the possible superiority of 3D printing methods against more

conventional ones, and will extensively report the time and cost aspects. This thorough evaluation of 3D printing technology, and its medical and surgical applications, is critical, as the key question remains whether this impressive, innovative technology will actually benefit our patients and their families. As we are at the dawn of this new technology, we expect to continue seeing new evidence and expanding our knowledge.

CONCLUSION

3D printing is a novel technique that has applications in several liver surgical conditions. Most published studies refer to its use in preoperative planning and education. Although the advantages it offers seem numerous, the cost and time required for the whole process is currently an important issue. As this technology has emerged recently, we can speculate that these drawbacks will be resolved in the future so that these methods will be widely accessible and better explored.

REFERENCES

1 **Takagishi K**, Umezu S. Development of the Improving Process for the 3D Printed Structure. *Sci Rep* 2017; **7**: 39852 [PMID: 28054558 DOI: 10.1038/srep39852]
2 **Chua CK**, Yeong WY, An J. Special Issue: 3D Printing for Biomedical Engineering. *Materials (Basel)* 2017; 10 [PMID: 28772604 DOI: 10.3390/ma10030243]
3 **Bangeas P**, Voulalas G, Ktenidis K. Rapid prototyping in aortic surgery. *Interact Cardiovasc Thorac Surg* 2016; **22**: 513-514 [PMID: 26803324 DOI: 10.1093/icvts/ivv395]
4 **Shaheen E**, Alhelwani A, Van De Casteele E, Politis C, Jacobs R. Evaluation of Dimensional Changes of 3D Printed Models After Sterilization: A Pilot Study. *Open Dent J* 2018; **12**: 72-79 [PMID: 29492172 DOI: 10.2174/1874210601812010072]
5 **Sodian R**, Schmauss D, Markert M, Weber S, Nikolaou K, Haeberle S, Vogt F, Vicol C, Lueth T, Reichart B, Schmitz C. Three-dimensional printing creates models for surgical planning of aortic valve replacement after previous coronary bypass grafting. *Ann Thorac Surg* 2008; **85**: 2105-2108 [PMID: 18498831 DOI: 10.1016/j.athoracsur.2007.12.033]
6 **Lioufas PA**, Quayle MR, Leong JC, McMenamin PG. 3D Printed Models of Cleft Palate Pathology for Surgical Education. *Plast Reconstr Surg Glob Open* 2016; **4**: e1029 [PMID: 27757345 DOI: 10.1097/GOX.0000000000001029]
7 **Schmauss D**, Haeberle S, Hagl C, Sodian R. Three-dimensional printing in cardiac surgery and interventional cardiology: a single-centre experience. *Eur J Cardiothorac Surg* 2015; **47**: 1044-1052 [PMID: 25161184 DOI: 10.1093/ejcts/ezu310]
8 **Kurenov SN**, Ionita C, Sammons D, Demmy TL. Three-dimensional printing to facilitate anatomic study, device development, simulation, and planning in thoracic surgery. *J Thorac Cardiovasc Surg* 2015; **149**: 973-9.e1 [PMID: 25659851 DOI: 10.1016/j.jtcvs.2014.12.059]
9 **Rankin TM**, Giovinco NA, Cucher DJ, Watts G, Hurwitz B, Armstrong DG. Three-dimensional printing surgical instruments: are we there yet? *J Surg Res* 2014; **189**: 193-197 [PMID: 24721602 DOI: 10.1016/j.jss.2014.02.020]
10 **Kolyva C**, Biglino G, Pepper JR, Khir AW. A mock circulatory system with physiological distribution of terminal resistance and compliance: application for testing the intra-aortic balloon pump. *Artif Organs* 2012; **36**: E62-E70 [PMID: 21039645 DOI: 10.1111/j.1525-1594.2010.01071.x]
11 **Biglino G**, Capelli C, Binazzi A, Reggiani R, Cosentino D, Migliavacca F, Bonhoeffer P, Taylor AM, Schievano S. Virtual and real bench testing of a new percutaneous valve device: a case study. *EuroIntervention* 2012; **8**: 120-128 [PMID: 22580256 DOI: 10.4244/EIJV8I1A19]
12 **Witowski JS**, Coles-Black J, Zuzak TZ, Pędziwiatr M, Chuen J, Major P, Budzyński A. 3D Printing in Liver Surgery: A Systematic Review. *Telemed J E Health* 2017; **23**: 943-947 [PMID: 28530492 DOI: 10.1089/tmj.2017.0049]
13 **Michael S**, Sorg H, Peck CT, Koch L, Deiwick A, Chichkov B, Vogt PM, Reimers K. Tissue engineered skin substitutes created by laser-assisted bioprinting form skin-like structures in the dorsal skin fold chamber in mice. *PLoS One* 2013; **8**: e57741 [PMID: 23469227 DOI: 10.1371/journal.pone.0057741]
14 **Oshiro Y**, Ohkohchi N. Three-Dimensional Liver Surgery Simulation: Computer-Assisted Surgical Planning with Three-Dimensional Simulation Software and Three-Dimensional Printing. *Tissue Eng Part A* 2017; **23**: 474-480 [PMID: 28343411 DOI: 10.1089/ten.tea.2016.0528]
15 **Kuroda S**, Kobayashi T, Ohdan H. 3D printing model of the intrahepatic vessels for navigation during anatomical resection of hepatocellular carcinoma. *Int J Surg Case Rep* 2017; **41**: 219-222 [PMID: 29096348 DOI: 10.1016/j.ijscr.2017.10.015]
16 **Wang JZ**, Xiong NY, Zhao LZ, Hu JT, Kong DC, Yuan JY. Review fantastic medical implications of 3D-printing in liver surgeries, liver regeneration, liver transplantation and drug hepatotoxicity testing: A review. *Int J Surg* 2018; **56**: 1-6 [PMID: 29886280 DOI: 10.1016/j.ijsu.2018.06.004]
17 **Perica ER**, Sun Z. A Systematic Review of Three-Dimensional Printing in Liver Disease. *J Digit Imaging* 2018; **31**: 692-701 [PMID: 29633052 DOI: 10.1007/s10278-018-0067-x]
18 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535 [PMID: 19622551 DOI: 10.1136/bmj.b2535]
19 **Zein NN**, Hanouneh IA, Bishop PD, Samaan M, Eghtesad B, Quintini C, Miller C, Yerian L, Klatte R. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. *Liver Transpl* 2013; **19**: 1304-1310 [PMID: 23959637 DOI: 10.1002/lt.23729]
20 **Takagi K**, Nanashima A, Abo T, Arai J, Matsuo N, Fukuda T, Nagayasu T. Three-dimensional printing model of liver for operative simulation in perihilar cholangiocarcinoma. *Hepatogastroenterology* 2014; **61**:

2315-2316 [PMID: 25699373]
21 **Igami T**, Nakamura Y, Hirose T, Ebata T, Yokoyama Y, Sugawara G, Mizuno T, Mori K, Nagino M. Application of a three-dimensional print of a liver in hepatectomy for small tumors invisible by intraoperative ultrasonography: preliminary experience. *World J Surg* 2014; **38**: 3163-3166 [PMID: 25145821 DOI: 10.1007/s00268-014-2740-7]
22 **Baimakhanov Z**, Soyama A, Takatsuki M, Hidaka M, Hirayama T, Kinoshita A, Natsuda K, Kuroki T, Eguchi S. Preoperative simulation with a 3-dimensional printed solid model for one-step reconstruction of multiple hepatic veins during living donor liver transplantation. *Liver Transpl* 2015; **21**: 266-268 [PMID: 25302632 DOI: 10.1002/lt.24019]
23 **Xiang N**, Fang C, Fan Y, Yang J, Zeng N, Liu J, Zhu W. Application of liver three-dimensional printing in hepatectomy for complex massive hepatocarcinoma with rare variations of portal vein: preliminary experience. *Int J Clin Exp Med* 2015; **8**: 18873-18878 [PMID: 26770510]
24 **Souzaki R**, Kinoshita Y, Ieiri S, Hayashida M, Koga Y, Shirabe K, Hara T, Maehara Y, Hashizume M, Taguchi T. Three-dimensional liver model based on preoperative CT images as a tool to assist in surgical planning for hepatoblastoma in a child. *Pediatr Surg Int* 2015; **31**: 593-596 [PMID: 25895074 DOI: 10.1007/s00383-015-3709-9]
25 **Soejima Y**, Taguchi T, Sugimoto M, Hayashida M, Yoshizumi T, Ikegami T, Uchiyama H, Shirabe K, Maehara Y. Three-dimensional printing and biotexture modeling for preoperative simulation in living donor liver transplantation for small infants. *Liver Transpl* 2016; **22**: 1610-1614 [PMID: 27434755 DOI: 10.1002/lt.24516]
26 **Leng S**, Chen B, Vrieze T, Kuhlmann J, Yu L, Alexander A, Matsumoto J, Morris J, McCollough CH. Construction of realistic phantoms from patient images and a commercial three-dimensional printer. *J Med Imaging (Bellingham)* 2016; **3**: 033501 [PMID: 27429998 DOI: 10.1117/1.JMI.3.3.033501]
27 **Witowski JS**, Pędziwiatr M, Major P, Budzyński A. Cost-effective, personalized, 3D-printed liver model for preoperative planning before laparoscopic liver hemihepatectomy for colorectal cancer metastases. *Int J Comput Assist Radiol Surg* 2017; **12**: 2047-2054 [PMID: 28144830 DOI: 10.1007/s11548-017-1527-3]
28 **Madurska MJ**, Poyade M, Eason D, Rea P, Watson AJ. Development of a Patient-Specific 3D-Printed Liver Model for Preoperative Planning. *Surg Innov* 2017; **24**: 145-150 [PMID: 28134003 DOI: 10.1177/1553350616689414]
29 **Oshiro Y**, Mitani J, Okada T, Ohkohchi N. A novel three-dimensional print of liver vessels and tumors in hepatectomy. *Surg Today* 2017; **47**: 521-524 [PMID: 27456277 DOI: 10.1007/s00595-016-1383-8]
30 **Perica E**, Sun Z. Patient-specific three-dimensional printing for pre-surgical planning in hepatocellular carcinoma treatment. *Quant Imaging Med Surg* 2017; **7**: 668-677 [PMID: 29312871 DOI: 10.21037/qims.2017.11.02]
31 **Andolfi C**, Plana A, Kania P, Banerjee PP, Small S. Usefulness of Three-Dimensional Modeling in Surgical Planning, Resident Training, and Patient Education. *J Laparoendosc Adv Surg Tech A* 2017; **27**: 512-515 [PMID: 27813710 DOI: 10.1089/lap.2016.0421]
32 **Igami T**, Nakamura Y, Oda M, Tanaka H, Nojiri M, Ebata T, Yokoyama Y, Sugawara G, Mizuno T, Yamaguchi J, Mori K, Nagino M. Application of three-dimensional print in minor hepatectomy following liver partition between anterior and posterior sectors. *ANZ J Surg* 2018; **88**: 882-885 [PMID: 29266603 DOI: 10.1111/ans.14331]
33 **Dhir V**, Itoi T, Fockens P, Perez-Miranda M, Khashab MA, Seo DW, Yang AM, Lawrence KY, Maydeo A. Novel ex vivo model for hands-on teaching of and training in EUS-guided biliary drainage: creation of "Mumbai EUS" stereolithography/3D printing bile duct prototype (with videos). *Gastrointest Endosc* 2015; **81**: 440-446 [PMID: 25475900 DOI: 10.1016/j.gie.2014.09.011]
34 **Kong X**, Nie L, Zhang H, Wang Z, Ye Q, Tang L, Li J, Huang W. Do Three-dimensional Visualization and Three-dimensional Printing Improve Hepatic Segment Anatomy Teaching? A Randomized Controlled Study. *J Surg Educ* 2016; **73**: 264-269 [PMID: 26868314 DOI: 10.1016/j.jsurg.2015.10.002]
35 **Kong X**, Nie L, Zhang H, Wang Z, Ye Q, Tang L, Huang W, Li J. Do 3D Printing Models Improve Anatomical Teaching About Hepatic Segments to Medical Students? A Randomized Controlled Study. *World J Surg* 2016; **40**: 1969-1976 [PMID: 27172803 DOI: 10.1007/s00268-016-3541-y]
36 **Watson RA**. A low-cost surgical application of additive fabrication. *J Surg Educ* 2014; **71**: 14-17 [PMID: 24411417 DOI: 10.1016/j.jsurg.2013.10.012]
37 **Javan R**, Herrin D, Tangestanipoor A. Understanding Spatially Complex Segmental and Branch Anatomy Using 3D Printing: Liver, Lung, Prostate, Coronary Arteries, and Circle of Willis. *Acad Radiol* 2016; **23**: 1183-1189 [PMID: 27283072 DOI: 10.1016/j.acra.2016.04.010]
38 **Li A**, Tang R, Rong Z, Zeng J, Xiang C, Yu L, Zhao W, Dong J. The Use of Three-Dimensional Printing Model in the Training of Choledochoscopy Techniques. *World J Surg* 2018; **42**: 4033-4038 [PMID: 30066020 DOI: 10.1007/s00268-018-4731-6]
39 **Yang T**, Lin S, Xie Q, Ouyang W, Tan T, Li J, Chen Z, Yang J, Wu H, Pan J, Hu C, Zou Y. Impact of 3D printing technology on the comprehension of surgical liver anatomy. *Surg Endosc* 2019; **33**: 411-417 [PMID: 29943060 DOI: 10.1007/s00464-018-6308-8]
40 **Javan R**, Zeman MN. A Prototype Educational Model for Hepatobiliary Interventions: Unveiling the Role of Graphic Designers in Medical 3D Printing. *J Digit Imaging* 2018; **31**: 133-143 [PMID: 28808803 DOI: 10.1007/s10278-017-0012-4]
41 **Burdall OC**, Makin E, Davenport M, Ade-Ajayi N. 3D printing to simulate laparoscopic choledochal surgery. *J Pediatr Surg* 2016; **51**: 828-831 [PMID: 27085850 DOI: 10.1016/j.jpedsurg.2016.02.093]
42 **Takao H**, Amemiya S, Shibata E, Ohtomo K. Three-Dimensional Printing of Hollow Portal Vein Stenosis Models: A Feasibility Study. *J Vasc Interv Radiol* 2016; **27**: 1755-1758 [PMID: 27926413 DOI: 10.1016/j.jvir.2016.05.022]
43 **Choi YR**, Kim JH, Park SJ, Hur BY, Han JK. Therapeutic response assessment using 3D ultrasound for hepatic metastasis from colorectal cancer: Application of a personalized, 3D-printed tumor model using CT images. *PLoS One* 2017; **12**: e0182596 [PMID: 28797089 DOI: 10.1371/journal.pone.0182596]
44 **Bücking TM**, Hill ER, Robertson JL, Maneas E, Plumb AA, Nikitichev DI. From medical imaging data to 3D printed anatomical models. *PLoS One* 2017; **12**: e0178540 [PMID: 28562693 DOI: 10.1371/journal.pone.0178540]
45 **Koganemaru M**, Horiuchi H, Abe T. Treatment of Hypohepatia After Transplantation of Liver From a Living Donor Liver by Transcatheter Embolization, Using a Simulated 3-Dimensional Printing Vascular Model. *Gastroenterology* 2016; **151**: e11-e13 [PMID: 27256862 DOI: 10.1053/j.gastro.2016.02.020]
46 **Trout AT**, Batie MR, Gupta A, Sheridan RM, Tiao GM, Towbin AJ. 3D printed pathological sectioning boxes to facilitate radiological-pathological correlation in hepatectomy cases. *J Clin Pathol* 2017; **70**:

984–987 [DOI: 10.1136/jclinpath-2016-204293]
47 **Weng JY**, Wang CC, Chen PJ, Lim SW, Kuo JR. The Application of a Three-Dimensional Printed Product to Fill the Space After Organ Removal. *World Neurosurg* 2017; **107**: 1045.e17-1045.e19 [PMID: 28826704 DOI: 10.1016/j.wneu.2017.07.149]
48 **Yang T**, Tan T, Yang J, Pan J, Hu C, Li J, Zou Y. The impact of using three-dimensional printed liver models for patient education. *J Int Med Res* 2018; **46**: 1570-1578 [PMID: 29436243 DOI: 10.1177/0300060518755267]
49 **Tang R**, Ma L, Li A, Yu L, Rong Z, Zhang X, Xiang C, Liao H, Dong J. Choledochoscopic Examination of a 3-Dimensional Printing Model Using Augmented Reality Techniques: A Preliminary Proof of Concept Study. *Surg Innov* 2018; **25**: 492-498 [PMID: 29909727 DOI: 10.1177/1553350618781622]
50 **Pantelidis P**, Chorti A, Papagiouvanni I, Paparoidamis G, Drosos C, Panagiotakopoulos T, Lales G, Sideris M, Tsoulfas G. Virtual and Augmented Reality in Medical Education. Tsoulfas G. *Medical and Surgical Education-Past, Present and Future*. Rijeka: InTech 2018; 77-99
51 **Ikegami T**, Maehara Y. Transplantation: 3D printing of the liver in living donor liver transplantation. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 697–698 [DOI: 10.1038/nrgastro.2013.195]
52 **Soon DS**, Chae MP, Pilgrim CH, Rozen WM, Spychal RT, Hunter-Smith DJ. 3D haptic modelling for preoperative planning of hepatic resection: A systematic review. *Ann Med Surg (Lond)* 2016; **10**: 1-7 [PMID: 27489617 DOI: 10.1016/j.amsu.2016.07.002]

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ORIGINAL ARTICLE

Retrospective Study

Epidemiology and outcomes of acute liver failure in Australia

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Abstract

BACKGROUND

Acute liver failure (ALF) is a life-threatening syndrome with varying aetiologies requiring complex care and multidisciplinary management. Its changing incidence, aetiology and outcomes over the last 16 years in the Australian context remain uncertain.

AIM

To describe the changing incidence, aetiology and outcomes of ALF in South Eastern Australia.

METHODS

The database of the Victorian Liver Transplant Unit was interrogated to identify all cases of ALF in adults (> 16 years) in adults hospitalised between January 2002 and December 2017. Overall, 169 patients meeting criteria for ALF were identified. Demographics, aetiology of ALF, rates of transplantation and outcomes were collected for all patients. Transplant free survival and overall survival (OS) were assessed based on survival to discharge from hospital. Results were compared to data from a historical cohort from the same unit from 1988-2001.

RESULTS

Paracetamol was the most common aetiology of acute liver failure, accounting for

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data collected as a clinical Audit.

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50% of cases, with an increased incidence compared with the historical cohort (P = 0.046). Viral hepatitis and non-paracetamol drug or toxin induced liver injury accounted for 15% and 10% of cases respectively. Transplant free survival (TFS) improved significantly compared to the historical cohort (52% *vs* 38%, P = 0.032). TFS was highest in paracetamol toxicity with spontaneous recovery in 72% of cases compared to 31% of non-paracetamol ALF (P < 0.001). Fifty-nine patients were waitlisted for emergency liver transplantation. Nine of these died while waiting for an organ to become available. Forty-two patients (25%) underwent emergency liver transplantation with a 1, 3 and 5 year survival of 81%, 78% and 72% respectively.

CONCLUSION
Paracetamol toxicity is the most common aetiology of ALF in South-Eastern Australia with a rising incidence over 30 years. TFS has improved, however it remains low in non-paracetamol ALF.

Key words: Liver failure; Acute; Paracetamol; Australia; Victoria; Liver transplant

Core tip: Acute liver failure (ALF) is a life-threatening syndrome with varying aetiologies based on geographic location. Paracetamol is the most common cause of ALF in South Eastern Australia with a rising incidence over 30 years. Despite this, transplantation for paracetamol induced ALF is lower than other large centres at 4% with a comparable overall survival. Non-paracetamol ALF however portends a poor prognosis with less than one third surviving without emergency liver transplantation.

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INTRODUCTION

Acute liver failure (ALF) is a clinical syndrome characterised by severe liver injury associated with the development of coagulopathy and hepatic encephalopathy in the absence of known pre-existing liver disease[1]. The causes of ALF differ markedly based on geographic location[2]. In developing countries viral hepatitis is the most common aetiology, whereas in the developed world, the majority of ALF cases are due to paracetamol poisoning and / or other drug reactions[3-5].

Historically, ALF was associated with low rates of spontaneous survival and in regions with transplant programs, the majority of eligible patients underwent emergency liver transplantation (ELT)[6]. However, more recently, transplant-free survival (TFS) has improved[3,7,8]. In the United States, rates of liver transplantation for ALF have been reported to be as low as 20% with an overall survival to hospital discharge of 75%[8]. For non-paracetamol aetiologies, however, TFS is less than 30%, and ELT has an established survival benefit[9]. In contrast, for paracetamol induced ALF, TFS is much higher and the survival advantage of transplantation is less clear [10].

The Victorian Liver Transplant Unit (VLTU) provides liver transplantation and quaternary hepatology services for a population of 6.7 million in South-East Australia, representing 27% of the total Australian population[11]. Essentially all cases of ALF are referred to the VLTU, with only very few patients either not referred or dying prior to transfer. King's College Criteria is used to determine suitability for liver transplantation.

The primary aim of this study was to report the aetiology, incidence and outcomes of all adult cases of ALF presenting to the VLTU over the last 16 years. Our secondary aim was to compare current data to historical data by the same unit[12]. We hypothesised that the incidence and underlying causes of ALF across the population would be unchanged, but that outcomes would be improved despite relatively low utilization of ELT.

MATERIALS AND METHODS

All adult patients with ALF aged greater than 16 years managed at the VLTU between January 01, 2002 and December 31, 2017 were included in this study. ALF was defined as acute liver injury with the development of coagulopathy and hepatic encephalopathy within 26 wk of onset of symptoms, in the absence of known chronic liver disease[13]. Data were extracted from the VLTU database for comparison with a previously published historical cohort[12]. Patients with previous liver transplantation and primary non-function of the graft were excluded.

Information was collected from the unit database and crosschecked against medical records. The aetiology of ALF was determined by the treating team based on clinical history, paracetamol levels, viral and autoimmune serology, metabolic testing and, if available, histology from liver biopsy or explant specimens. Indeterminate ALF, also known as non-A non-B hepatitis or seronegative hepatitis, was diagnosed when all other aetiologies had been excluded.

Demographics, aetiology of ALF, rates of transplantation and outcomes were collected for all patients. Transplant free survival and overall survival (OS) were assessed based on survival to discharge from hospital. Patients who recovered without the need for liver transplantation were typically discharged back to the care of the referring health service and therefore, long-term outcomes are unknown. Medical records of patients who undergo liver transplantation, however, are regularly updated and were used to calculate post-transplant survival.

This study was approved through the Austin Health Human Research Ethics Committee.

Statistical analysis

The incidence of ALF was calculated based on annual local population data available from the Australian Bureau of Statistics. Where data was normally distributed (by Shapiro-Wilk analysis), two-tailed student *t*-tests were used to compare for significance. Data not meeting normality criteria were reported as median (IQR) and compared using the Mann-Whitney *U* test. To assess differences in endpoints and changes in aetiology over time, data were first analysed by comparison of the two cohorts, and then as a continuous set. For categorical data, comparison was made using chi-square test. Time-series analysis was completed using linear regression.

RESULTS

Records of 221 patients who had a diagnosis of acute liver injury on the liver transplant database were reviewed. Twenty-one patients were excluded due to the absence of hepatic encephalopathy. Twenty-two cases were excluded as they had underlying cirrhosis with acute decompensation and four cases because they had been transplanted at other centres. Five patients were excluded because they suffered ALF secondary to primary graft non-function after liver transplantation for non-ALF indications.

One hundred and sixty-nine patients met the inclusion criteria. One hundred and thirty-two cases (78%) were female and 37 (22%) were male. The median age at presentation was 41 years[31;52] for females and 37 years[27;49] for males. The median rate of referral over the study period was 9 cases per year, or 1.6 cases per million population per year. Twenty-two patients (13%) presented directly to our centre, 118 cases (70%) were referred from other metropolitan hospitals and 29 (17%) from regional and rural hospitals. One hundred and fifty-seven patients (92.9%) required support in the intensive care unit during their admission.

Aetiology

Paracetamol toxicity was the most common cause of ALF accounting for a total of 84 cases (50%) (Table 1). The median rate of paracetamol induced ALF referred to the centre over the 16-year study period was 0.7 cases per million population per year[11]. Non-paracetamol drug or toxin induced liver injury was the cause of ALF in 17 patients (10%). Viral hepatitis was the cause of ALF in 26 cases (15%). This included 20 cases of fulminant hepatitis B virus (HBV) infection and two from reactivated chronic HBV following systemic chemotherapy. Hepatitis A virus (HAV) was identified in four cases. Other viral aetiologies included herpes simplex virus-2 (HSV) and varicella zoster virus both in isolated cases.

Fulminant autoimmune hepatitis was diagnosed in nine patients (5%). The diagnosis was made based on a combination of positive auto-antibody testing, elevated IgG levels and histology results either during the episode of ALF or after recovery. ALF secondary to malignancy was identified in four patients. Veno-

Table 1 Drugs and toxins implicated in cases of acute liver failure managed at the Victorian Liver Transplant Unit from 2002-2017

Drug/Toxins	Cases of ALF	Waitlisted for ELT	ELT
	(*n* = 101)	(*n* = 21)	(*n* = 13)
Paracetamol	84	11	3
Antibiotics	4	2	2
Amoxicillin/clavulanate (2), clarithromycin, isoniazid			
Infliximab	2	2	2
Illicit drugs	4	1	1
LSD, injected buprenorphine, amphetamines, MDMA			
NSAIDs	1	1	1
Amanita phalloides	1	1	1
Herbal medicines			
Black cohosh herb, kava kava	2	2	2
Other			
Moxonidine, fenofibrate, chlorambucil	3	1	1

ALF: Acute liver failure; ELT: Emergency liver transplantation; NSAIDs: Non-steroid anti-inflammatory drugs; LSD: Lysergic acid diethylamide; MDMA: Methylenedioxymethamphetamine; NSAIDs: Non-steroidal anti-inflammatory drugs

occlusive disease caused ALF in one case following allogeneic stem cell transplantation. Wilson's disease was the cause of ALF in two cases. Severe ischemic hepatitis due to hepatic artery injury and extensive portal vein thrombosis resulted in ALF in four patients.

ALF occurred in five patients during pregnancy. Aetiologies included acute fatty liver disease of pregnancy, HSV hepatitis and pregnancy-precipitated liver failure from a urea-cycle disorder[14]. Unintentional paracetamol poisoning causing ALF occurred in two cases in the context of hyperemesis and malnutrition. One of these cases presented with foetal death in utero in the third trimester of pregnancy, however in all other pregnancies, the infants survived. Twenty-one cases (12%) were classified as indeterminate ALF after exclusion of other aetiologies.

Survival

Over the study period the TFS was 52% and OS to discharge from hospital was 72%. TFS was significantly higher in patients with paracetamol induced ALF at 74% compared to non-paracetamol aetiologies at 31% ($P < 0.0001$). OS however did not differ significantly at 77% and 67% for paracetamol and non-paracetamol aetiologies respectively ($P = 0.13$). ALF caused by indeterminate hepatitis had the lowest TFS at 10%.

Transplantation

Fifty-nine patients (35%) were waitlisted for transplantation (Figure 1). Eight patients improved and were delisted, however one subsequently died of sepsis. One patient was delisted following an intraoperative finding of ischemic gut and eight patients died while waiting for a donor liver (14%). 42 patients (25%) underwent liver transplantation for ALF. Rates of liver transplantation were highest in patients with indeterminate hepatitis at 67%. Only three patients with paracetamol induced ALF were transplanted (4%).

After medical and psychosocial assessment, liver transplantation was contraindicated in 24 patients. Of these, fifteen cases were deemed medically unsuitable for transplantation. Medical contraindications included uncontrolled sepsis, ischemic bowel, intracranial events, active malignancy and known severe coronary artery disease. Only three (20%) of these patients recovered and survived to discharge. Six patients had psychiatric or psychosocial contraindications and three patients had concurrent heavy alcohol intake rendering them unsuitable for transplantation. Paracetamol was the cause of ALF in eight of these patients (89%). Four (44%) recovered and were discharged from hospital.

For patients undergoing liver transplantation for ALF, 1, 3 and 5-year survival was 81%, 78% and 72% respectively. Seven patients (17%) died within 30 d of transplantation. The aetiology of ALF for such patients included indeterminate hepatitis (2), AIH (2), drug and toxins (2) and hepatic arterial injury leading to

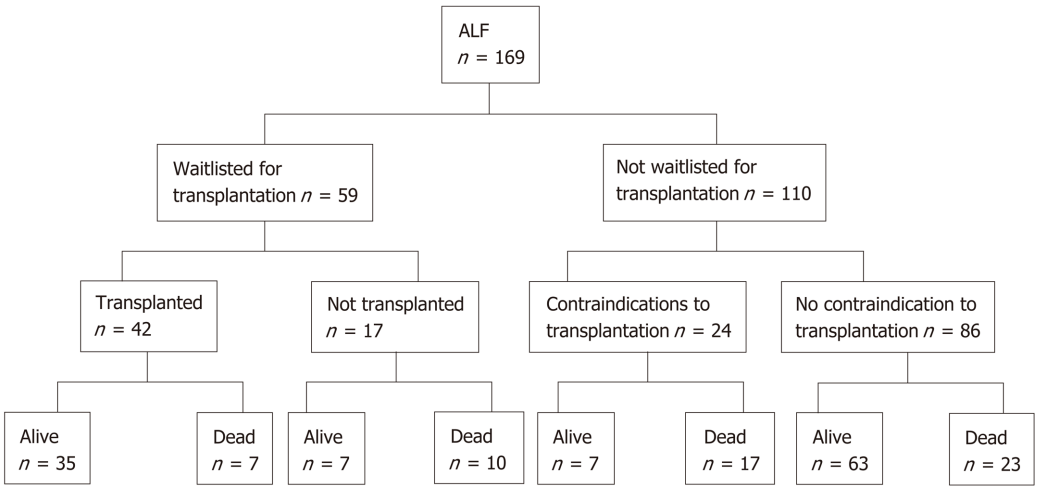

Figure 1 Flowchart of outcomes of patients meeting criteria for acute liver failure.

ischamic heptitis (1). Causes of death post operatively included sepsis in three cases, cardiovascular or cerebral events in three patients and hepatic artery thrombosis in one case.

Comparison over time

Compared to historical data published by the unit from 1988-2001[12]. there was no difference in age at presentation or gender distribution (Table 2). Paracetamol poisoning remained the most common aetiology over the two time periods. There was a significant increase in the rate of paracetamol-induced ALF in this current data set compared to the historical cohort (36% *vs* 50%, P = 0.046). When presented as continuous data, linear regression analysis also identified a significant increase in paracetamol-induced ALF per capita across the 30 years (R^2 = 0.275; F(1,28) = 10.643, P = 0.003) (Figure 2). Overall ALF referrals to the unit also increased significantly over the time period (R^2 = 0.178; F(1,28) = 6.074, P = 0.020). Comparing this dataset to historical data (1988-2001) also identified no differences in rates of viral hepatitis.

TFS to discharge from hospital improved in the present study compared to the historical cohort from 38% to 52% (P = 0.032). An improvement in TFS was observed in both paracetamol toxicity (69% *vs* 74%, P = 0.614) and non-paracetamol aetiologies (20% *vs* 31%, P = 0.160) although neither met significance (Table 3). Overall, there was no statistically significant difference in hospital survival (63% to 72%, P = 0.122) or transplantation rates for ALF (33% to 25%, P = 0.206).

DISCUSSION

This cohort study represents the largest modern series of patients presenting with ALF in Australia. As the sole liver transplant unit responsible for a population of 6.7 million, the VLTU captured both the incidence and outcomes of this rare but life-threatening syndrome. We identified paracetamol toxicity as the commonest cause of ALF, responsible for 50% of presentations. We also found an increasing rate of paracetamol induced ALF referrals to our centre over a 30-year period. Finally, we found that transplant-free survival for both paracetamol toxicity and non-paracetamol aetiologies has improved, but that spontaneous survival for non-paracetamol ALF remains low. This is particularly the case for indeterminate hepatitis and non-paracetamol drug-induced liver injury, highlighting the need for early referral to a transplant centre.

Our reported prevalence of paracetamol-induced ALF is similar to series from the United Kingdom and United States with rates ranging from 37%-79%[3,4,15]. However, of concern, this is the only cohort to show an overall steady increase in its incidence. These results differ from local Victorian data demonstrating a decrease in hospital admissions for non-ALF paracetamol poisoning from 2000 to 2007[16]. In the United States, rates of ALF due to paracetamol poisoning have also fallen following the introduction of paracetamol sales restrictions in 1998[3,17]. These regulations limited pharmacy sales to a maximum of 32 tablets per pack. While restrictions in non-pharmacy sales of paracetamol have been in place in Australia since 2013, packets of

Table 2 Demographics and aetiology of acute liver failure managed at the Victorian Liver Transplant Unit in a historical cohort[1] compared to current series

	1988-2001[1] (*n* = 80)		2002-2017 (*n* = 169)		*P* value
	n	%	*n*	%	
Referral rate[2], median [IQR]	1.2 [0.6;1.6]		1.6 [1.3;1.7]		0.020
Age, yr, median [IQR]	36 [27.0;48.0]		40 [30.0;52.0]		0.168
Gender					
Male	16	20.0	37	21.9	
Female	64	80.0	132	78.1	0.733
Aetiology					
Paracetamol	29	36.3	84	49.7	0.046
Viral hepatitis	11	13.8	26	15.3	0.734
Hepatitis B	8	10.0	20	11.8	0.669
Hepatitis A	3	3.8	4	2.4	0.538
Varicella zoster	0	0.0	1	0.1	0.491
Herpes simplex	0	0.0	1	0.1	0.491
Non-paracetamol drug/toxin	5	6.3	17	10.1	0.323
Indeterminate	27	33.8	21	12.4	<0.001
Autoimmune hepatitis	0	0.0	9	5.3	0.036
Other	8	10.0	12	7.1	0.432
Waitlisted for transplantation	35	43.8	59	33.5	0.179
Waitlist mortality	9	25.7	8	13.6	0.139
Liver transplantation	26	32.5	42	24.9	0.206
Transplant-free survival	30	37.5	88	52.1	0.032
Overall hospital survival	50	62.5	122	72.2	0.122

[1]Gow *et al*[12], 2001;
[2]Referral rate per million population per year. IQR: Interquartile range.

up to 100 tablets are still readily available in pharmacies. Risk factors for ALF from paracetamol include prolonged fasting and malnutrition often resulting in inadvertent toxicity[18] and combination pain relief products can also result in accidental overdose[16]. Improved awareness and public health strategies to address these factors may curtail this trend in life-threatening paracetamol toxicity.

Viral hepatitis was the second most common cause of ALF in this series. HBV accounted for 12% of all cases of ALF with no change compared to the historical cohort. This is in contrast to the declining incidence of HBV-induced ALF in other developed countries[3,19,20]. This may in part reflect the fact that many older Australians are still not vaccinated against the virus[21]. Also, Australia has high rates of immigration from countries in Asia where HBV remains endemic. Fulminant flares of HBV in the setting of inappropriately ceasing anti-viral therapy was a common background scenario in this patient group. Additionally, two patients in this cohort developed ALF from HBV infection during treatment of haematological malignancies with systemic chemotherapy. In both cases, reactivation of HBV was fatal. This emphasises the importance of early identification of patients at risk, monitoring and prophylaxis with nucleoside analogues where appropriate[22].

Hepatitis A was the cause of ALF in just four (2%) of our cases. HAV vaccination is not routine in Australia and is recommended only in high-risk populations including men who have sex with men and travellers to endemic areas. However, outbreaks do occur in a predominantly non-immune population[23]. Of note, three of the HAV induced ALF cases occurred in the same year, coinciding with a large food-born outbreak of HAV in Victoria [24]. While HAV and HBV were uncommon causes of ALF, mortality and morbidity were high with less than 40% of this patient population surviving without transplantation.

In this series we demonstrated that patients with paracetamol induced ALF have high rates of spontaneous survival and are unlikely to require transplantation. Indeed, rates of transplantation for paracetamol poisoning in this cohort are lower than reported by other large centres at 8%-25% but with comparable overall survival[3,15,18].

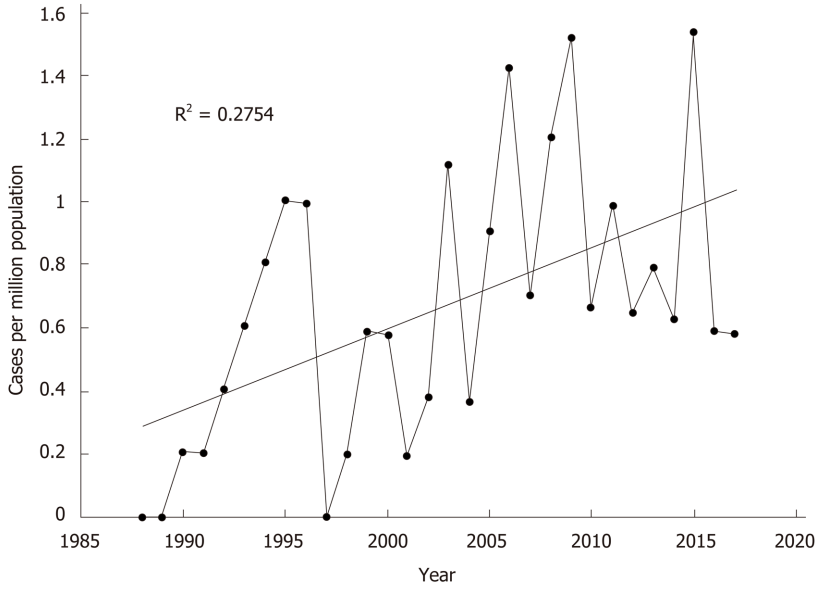

Figure 2 Rate of paracetamol induced acute liver failure per capita.

The role of ELT in paracetamol induced ALF has been questioned for more than 25 years[25]. King's College Hospital have been the world leaders in defining patients with paracetamol induced ALF who will die without transplantation and these criteria have been debated and refined over the last 30 years[1,10,26-28]. More recently the King's group have questioned whether transplantation plays any role in paracetamol induced ALF[28]. Our own policy is to consider transplantation only for the small subgroup of patients who have progressive coagulopathy and hyperlactatemia despite 48-72 hours of supportive treatment.

Over the 30-year period under review, TFS for ALF improved significantly. This finding has been observed in other large cohorts[3,4,8,15]. Early recognition of ALF and referral to specialised transplant centres may be one factor that has improved TFS. Supportive care for ALF within intensive care units has also evolved. This is particularly the case in the monitoring and management of cerebral oedema. For the last decade, we have had a protocolised approach to the management of this patient group with the aim of minimizing deaths from cerebral oedema. This combination approach, termed "quadruple-H therapy" comprises hyperventilation, hypernatremia, hypothermia and hemodiafiltration[29]. This multimodal approach has minimised the use of invasive intracranial pressure monitoring devices. Death attributed to cerebral oedema occurred in just one patient (0.6%) in this series.

Despite improvements in supportive care, transplantation still plays a pivotal role in this condition. Organ allocation in Australia is typically State based. However, patients with ALF who are ventilated in intensive care are classified as a category 1 and are allocated the next suitable organ within Australia or New Zealand[30]. Despite this approach, waitlist mortality remained high. There is often a brief window period where patients with ALF can be transplanted before they develop refractory multiple organ failure. Therefore, timely availability of a suitable donor organ for waitlisted patients remains critical.

This is the largest Australian cohort to report on the changing incidence and aetiology of ALF. We identified a concerning rise in paracetamol toxicity causing ALF. However, despite the high incidence of paracetamol induced ALF, we report on our very low use of ELT in this group of patients despite a comparable overall survival to other large international centres.

This study has several limitations. Firstly, this is a retrospective study, which interrogated prospectively recorded data. The diagnosis of ALF requires the presence of hepatic encephalopathy, which relied on the adequate documentation of this clinical finding in medical records. Additionally, these data did not include patients who were treated at other centres. It is possible that death prior to transfer, suicidal intent, substance abuse or significant comorbidities deemed unsuitable for transplantation may have prevented some patients being referred to the VLTU.

In conclusion, paracetamol toxicity remains the most common aetiology of ALF, with increasing rates over time, highlighting the need for public health measures to reduce this preventable cause. TFS has improved which may reflect advances in

Table 3 Outcomes of acute liver failure managed at the Victorian Liver Transplant Unit in a historical cohort[†] compared to the current series

Aetiology	TFS (%)					OS (%)				
	1988-2001[1]		2002-2017		*P* value	1988-2001[1]		2002-2017		*P* value
	n	%	*n*	%		*n*	%	*n*	%	
Paracetamol	20	69.0	62	73.8	0.614	21	72.4	65	77.4	0.589
Non-paracetamol	10	19.6	26	30.6	0.160	29	56.9	57	67.1	0.230
Viral hepatitis	2	18.2	10	38.4	0.228	5	45.5	18	69.2	0.173
HBV	2	25.0	7	35.0	0.609	4	50.0	14	70.0	0.318
HAV	0	0.0	3	75.0	0.047	1	0.33	3	75.0	0.270
Drug/toxin induced	3	60.0	5	29.4	0.211	4	80.0	12	70.6	0.678
Autoimmune hepatitis	0	0.0	3	33.3	-	0	0.0	6	66.7	-
Indeterminate hepatitis	5	18.5	2	9.5	0.381	15	55.5	14	66.7	0.435
Other	0	0.0	6	50.0	0.017	5	62.5	7	58.3	0.852

[1]Gow *et al*[12], 2001. TFS: Transplant-free survival; OS: Overall hospital survival; HBV: Hepatitis B virus; HAV: Hepatitis A virus.

supportive care measures. Regardless, the majority of cases of non-paracetamol ALF still require transplantation and therefore early referral to a specialised transplant centre remains imperative.

ARTICLE HIGHLIGHTS

Research background

Acute liver failure (ALF) is a rare clinical syndrome with varying aetiologies based on geographic location. This condition is associated with high morbidity and mortality, and emergency liver transplantation is often life-saving.

Research motivation

In Australia, published data from 1988-2001 demonstrated that paracetamol toxicity was the major cause of ALF, followed by non-A non-B hepatitis. An updated analysis of aetiologies and outcomes in an Australian context is therefore required.

Research objections

This study aimed to provide a description of the aetiologies and outcomes of acute liver failure presenting to a large Australian liver transplant centre. We also aimed to describe changes over the past thirty years since the availability of liver transplantation for this condition.

Research methods

This is a retrospective cohort study of all patients admitted to the Victorian Liver Transplant Unit from 2001-2017. Data were compared to previous published series from the unit from 1988-2001, and as continuous data, to assess changes in aetiologies and outcomes over the past 30 years.

Research results

Paracetamol toxicity accounted for half of all cases of ALF, with a rise in the incidence of this condition over the past 30 years. Despite this observation, rates of liver transplantation for this condition are low at 4%, with an excellent overall survival. Rates of emergency liver transplantation were highest in indeterminate hepatitis and non-paracetamol drug induced liver injury. Transplant-free survival improved in this cohort compared to the historical cohort, however there was no significant change in overall survival.

Research conclusions

Paracetamol represents the major cause of ALF in South-Eastern Australia with a concerning rise in its incidence over the past 30 years. Transplant-free survival has improved but remains low for ALF due to non-paracetamol causes.

Research perspectives

This study shows a concerning rise in the incidence of paracetamol induced ALF in Australia, raising important questions regarding awareness and public health strategies to curb this rise. Larger multi-centre studies are required to confirm this observation. Transplant-free survival

improved in this population similar to reports from other large international series, highlighting advances in supportive care.

REFERENCES

1 **O'Grady JG**, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439-445 [PMID: 2490426]
2 **Ichai P**, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. *Liver Transpl* 2008; **14** Suppl 2: S67-S79 [PMID: 18825677 DOI: 10.1002/lt.21612]
3 **Bernal W**, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O'Grady JG, Wendon J, Williams R. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol* 2013; **59**: 74-80 [PMID: 23439263 DOI: 10.1016/j.jhep.2013.02.010]
4 **Ostapowicz G**, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM; U. S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; **137**: 947-954 [PMID: 12484709]
5 **Khuroo MS**, Kamili S. Aetiology and prognostic factors in acute liver failure in India. *J Viral Hepat* 2003; **10**: 224-231 [PMID: 12753342]
6 **Schiodt FV**, Atillasoy E, Shakil AO, Schiff ER, Caldwell C, Kowdley KV, Stribling R, Crippin JS, Flamm S, Somberg KA, Rosen H, McCashland TM, Hay JE, Lee WM. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transpl Surg* 1999; **5**: 29-34 [PMID: 9873089]
7 **Koch DG**, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a Model to Predict Transplant-free Survival of Patients With Acute Liver Failure. *Clin Gastroenterol Hepatol* 2016; **14**: 1199-1206.e2 [PMID: 27085756 DOI: 10.1016/j.cgh.2016.03.046]
8 **Reuben A**, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT, Durkalski V, Larson AM, Liou I, Fix O, Schilsky M, McCashland T, Hay JE, Murray N, Shaikh OS, Ganger D, Zaman A, Han SB, Chung RT, Smith A, Brown R, Crippin J, Harrison ME, Koch D, Munoz S, Reddy KR, Rossaro L, Satyanarayana R, Hassanein T, Hanje AJ, Olson J, Subramanian R, Karvellas C, Hameed B, Sherker AH, Robuck P, Lee WM. Outcomes in Adults With Acute Liver Failure Between 1998 and 2013: An Observational Cohort Study. *Ann Intern Med* 2016; **164**: 724-732 [PMID: 27043883 DOI: 10.7326/m15-2211]
9 **Kremers WK**, van IJperen M, Kim WR, Freeman RB, Harper AM, Kamath PS, Wiesner RH. MELD score as a predictor of pretransplant and posttransplant survival in OPTN/UNOS status 1 patients. *Hepatology* 2004; **39**: 764-769 [PMID: 14999695]
10 **O'Grady J**. Timing and benefit of liver transplantation in acute liver failure. *J Hepatol* 2014; **60**: 663-670 [PMID: 24211740 DOI: 10.1016/j.jhep.2013.10.024]
11 **Australian Bureau of Statistics**. 3101.0 - Australian Demographic Statistics, Dec 2017. [Cited 2018 Mar. 3] Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Dec%202017
12 **Gow PJ**, Jones RM, Dobson JL, Angus PW. Etiology and outcome of fulminant hepatic failure managed at an Australian liver transplant unit. *J Gastroenterol Hepatol* 2004; **19**: 154-159 [PMID: 14731124]
13 **Lee WM**, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology* 2012; **55**: 965-967 [PMID: 22213561 DOI: 10.1002/hep.25551]
14 **Sinclair M**, Ket S, Testro A, Gow PJ, Angus PW. Acute hepatic decompensation precipitated by pregnancy-related catabolic stress: a rare mimic of acute liver failure. *Obstet Gynecol* 2014; **123**: 480-483 [PMID: 24413235]
15 **Donnelly MC**, Davidson JS, Martin K, Baird A, Hayes PC, Simpson KJ. Acute liver failure in Scotland: changes in aetiology and outcomes over time (the Scottish Look-Back Study). *Aliment Pharmacol Ther* 2017; **45**: 833-843 [PMID: 28097670 DOI: 10.1111/apt.13943]
16 **Sood S**, Howell J, Sundararajan V, Angus PW, Gow PJ. Paracetamol overdose in Victoria remains a significant health-care burden. *J Gastroenterol Hepatol* 2013; **28**: 1356-1360 [PMID: 23489151 DOI: 10.1111/jgh.12196]
17 **Hawton K**, Simkin S, Deeks J, Cooper J, Johnston A, Waters K, Arundel M, Bernal W, Gunson B, Hudson M, Suri D, Simpson K. UK legislation on analgesic packs: before and after study of long term effect on poisonings. *BMJ* 2004; **329**: 1076 [PMID: 15516343 DOI: 10.1136/bmj.38253.572581.7C]
18 **Larson AM**, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, Reisch JS, Schiødt FV, Ostapowicz G, Shakil AO, Lee WM; Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* 2005; **42**: 1364-1372 [PMID: 16317692 DOI: 10.1002/hep.20948]
19 **Manka P**, Verheyen J, Gerken G, Canbay A. Liver Failure due to Acute Viral Hepatitis (A-E). *Visc Med* 2016; **32**: 80-85 [PMID: 27413724 DOI: 10.1159/000444915]
20 **Daniels D**, Grytdal S, Wasley A; Centers for Disease Control and Prevention (CDC). Surveillance for acute viral hepatitis - United States, 2007. *MMWR Surveill Summ* 2009; **58**: 1-27 [PMID: 19478727]
21 **The Kirby Institute**. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2017. Sydney: Kirby Institute, UNSW Sydney. Available from: https://kirby.unsw.edu.au/report/annual-surveillance-report-hiv-viral-hepatitis-and-stis-australia-2017
22 **European Association For The Study Of The Liver**. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; **57**: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]
23 **Wasley A**, Fiore A, Bell BP. Hepatitis A in the era of vaccination. *Epidemiol Rev* 2006; **28**: 101-111 [PMID: 16775039 DOI: 10.1093/epirev/mxj012]
24 **Donnan EJ**, Fielding JE, Gregory JE, Lalor K, Rowe S, Goldsmith P, Antoniou M, Fullerton KE, Knope K, Copland JG, Bowden DS, Tracy SL, Hogg GG, Tan A, Adamopoulos J, Gaston J, Vally H. A multistate outbreak of hepatitis A associated with semidried tomatoes in Australia, 2009. *Clin Infect Dis* 2012; **54**: 775-781 [PMID: 22238166 DOI: 10.1093/cid/cir949]
25 **Gow PJ**, Angus PW, Smallwood RA. Transplantation in patients with paracetamol-induced fulminant hepatic failure. *Lancet* 1997; **349**: 651-652 [PMID: 9057756 DOI: 10.1016/S0140-6736(05)61600-5]
26 **Craig DG**, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. *Aliment Pharmacol Ther* 2010; **31**: 1064-1076 [PMID: 20180786 DOI:

10.1111/j.1365-2036.2010.04279.x]
27 **Bailey B**, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. *Crit Care Med* 2003; **31**: 299-305 [PMID: 12545033 DOI: 10.1097/01.ccm.0000034674.51554.4c]
28 **O'Grady JG**. Transplant in haste, repent at your leisure? *Liver Transpl* 2015; **21**: 570-571 [PMID: 25824853 DOI: 10.1002/lt.24124]
29 **Warrillow SJ**, Bellomo R. Preventing cerebral oedema in acute liver failure: the case for quadruple-H therapy. *Anaesth Intensive Care* 2014; **42**: 78-88 [PMID: 24471667 DOI: 10.1177/0310057X1404200114]
30 The Transplantation Society of Australia and New Zealand: Clinical Guidelines for Organ Transplantation from Deceased Donors May 2017. Available from: https://www.tsanz.com.au/organallocationguidelines/documents/ClinicalGuidelinesV1.1May2017.pdf

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SYSTEMATIC REVIEW

Spontaneous fungal peritonitis: Micro-organisms, management and mortality in liver cirrhosis-A systematic review

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Abstract

BACKGROUND

Spontaneous peritonitis is an infection of ascitic fluid without a known intra-abdominal source of infection. spontaneous fungal peritonitis (SFP) is a potentially fatal complication of decompensated cirrhosis, defined as fungal infection of ascitic fluid in the presence of ascitic neutrophil count of greater than 250 cells/mL.

AIM

To determine the prevalence of fungal pathogens, management and outcomes (mortality) of SFP in critically ill cirrhotic patients.

METHODS

Studies were identified using PubMed, EMBASE, Cochrane Central Register of Controlled Trials and Scopus databases until February 2019. Inclusion criteria included intervention trials and observation studies describing the association between SFP and cirrhosis. The primary outcome was in-hospital, 1-mo, and 6-mo mortality rates of SFP in cirrhotic patients. Secondary outcomes were fungal microorganisms identified and in hospital management by anti-fungal medications. The National Heart, Lung and Blood Institute quality assessment tools were used to assess internal validity and risk of bias for each included study.

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RESULTS

Six observational studies were included in this systematic review. The overall quality of included studies was good. A meta-analysis of results could not be performed because of differences in reporting of outcomes and heterogeneity of the included studies. There were 82 patients with SFP described across all the included studies. Candida species, predominantly *Candida albicans* was the fungal pathogen in majority of the cases (48%-81.8%) followed by *Candida krusei* (15%-25%) and *Candida glabrata* (6.66%-20%). *Cryptococcus neoformans* (53.3%) was the other major fungal pathogen. Antifungal therapy in SFP patients was utilized in 33.3% to 81.8% cases. The prevalence of in hospital mortality ranged from 33.3% to 100%, whereas 1-mo mortality ranged between 50% to 73.3%.

CONCLUSION

This systematic review suggests that SFP in end stage liver disease patient is associated with high mortality both in the hospital and at 1-mo, and that antifungal therapy is currently underutilized.

Key words: Spontaneous fungal peritonitis; Bacterial peritonitis; Liver; Cirrhosis; Critical

Core tip: Spontaneous fungal peritonitis (SFP) in patients with cirrhosis is associated with high in-hospital mortality rate of 33.3% to 100% and 1-mo mortality rate of 50% to 73.3%. In our systematic review of the literature, despite such high mortality rates, the condition is under diagnosed and antifungal therapy is underutilized; 33.3% to 81.8% SFP patients received anti-fungal therapy. High clinical suspicion, new methods of early diagnosis and empiric treatment in critically ill patients with peritonitis may improve outcomes.

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INTRODUCTION

Spontaneous peritonitis (SP), defined as an infection of the ascitic fluid without any apparent intra-abdominal source of infection, is a potentially fatal complication of decompensated cirrhosis and occurs in approximately 12% of patients with end stage liver disease (ESLD) with mortality rates up to 40%[1,2]. It has a culture positive and a culture negative variant, also known as culture negative neutrocytic ascites (CNNA)[3]. SP is further classified into spontaneous bacterial peritonitis (SBP) and spontaneous fungal peritonitis (SFP) on the basis of microbiological cultures performed on ascitic fluid[4]. Another classification of SP includes nosocomial SP which is defined as SP which is diagnosed 48-72 h after hospital admission and community acquired (CA) SP if it is diagnosed on admission or within 2 d of presentation to the hospital[5].

SFP, a catastrophic and underestimated complication of ESLD is defined as fungal infection of the ascitic fluid and the presence of ascitic neutrophil count of > 250 cells/mL[6]. It is distinct from fungi ascites which has a neutrophil count of < 250 cells/mL in the ascitic fluid[4]. Cirrhosis with concomitant critical illness is a relevant combination that causes acquired immunodeficiency leading to increased risk of developing SFP[2]. Scarce data exists regarding clinical course, risk factors, management and outcomes of SFP particularly in critically ill patients. The aim of this systematic review was to determine the prevalence of fungal micro-organisms, management and mortality rates of critically ill cirrhotic patients with SFP.

MATERIALS AND METHODS

Data selection

The study was conducted in accordance with PRISMA guidelines[7]. PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus were searched up to February 5, 2019. The search strategy for PubMed, EMBASE, Cochrane and Scopus included search terms for all databases along with Medical Subject Headings (MeSH) terms for PubMed/Medline, and Emtree terms for EMBASE. No language restrictions were applied. The search strategy was the following for the various databases: (1) MEDLINE (PubMed); ("SFP") AND ("cirrhosis"[Mesh] OR "cirrhotic"[Mesh] OR "Liver Cirrhosis"[Mesh]); (2) EMBASE; ("Spontaneous" NEAR/2 "fungal peritonitis" OR "fungal peritonitis"/exp) AND ("cirrhosis" OR "cirrhotic" OR "liver cirrhosis"/exp); (3) CENTRAL; ("SFP" OR "fungal peritonitis") AND (""liver cirrhosis"); (4) Scopus; "SFP".

Intervention trials and observational studies (cross-sectional, case-control and cohort study-designs) describing the association between SFP and cirrhosis in adults (> 18 years) were included. In addition, studies with bacterial and other fungal infections in the presence of concomitant SFP were included. References of review articles and included studies were hand searched to identify any additional studies.

Exclusion criteria were studies involving children (age < 18 years) or those lacking data on outcomes listed below. In addition, review articles, case reports, letter to the editor, comments, perspectives, and animal studies were excluded. The primary outcome was in-hospital, 1-mo, and 6-momortality rates of cirrhotic patients with SFP (in percentage). The secondary outcomes were fungal micro-organisms implicated in SFP cirrhotic patients and in-hospital management by anti-fungal medications (in percentage).

Risk of bias assessment

The National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools were used to assess internal validity and risk of bias for each included study[8]. The following data elements were extracted from included studies: First author, publication year, journal, study design and setting, study population, controls, definition of SFP and its method of diagnosis. Quantitative estimates extracted included: In-hospital, 1-mo and 6-mo mortality rates of cirrhotic patients with SFP; fungal pathogens isolated; and in-hospital management by anti-fungal medications.

Statistical analysis

Two authors (Irfan FB and Farishta M) independently assessed the eligible studies for inclusion, and quality, and performed data extraction. In cases of discrepancy between the two authors, a third author (Tariq T) was consulted to reach consensus. The statistical methods of this study were reviewed by Patrick Karabon, William Beaumont School of Medicine, Oakland University.

RESULTS

Characteristics of included studies

The PRISMA flowchart of included studies selection is shown in Figure 1. There were 6 studies included that evaluated mortality rates of cirrhotic patients with SFP. Of the included 6 studies, 5 studies determined the secondary outcome measure of in-hospital management of SFP patients by anti-fungal medications (Table 1). There was 1 study from South Korea; 1 study from Egypt; 2 studies from Portugal and Germany; 1 study from the United States; and 1 multi-center database study from 28 health centers in United States, Canada and Saudi Arabia. There were 3 cross-sectional studies, 1 case-control study, 1 prospective cohort study, and 1 nested-cohort study. The differences in reporting of outcomes (mortality, micro-organisms and management) and heterogeneity of included studies did not allow a pooled analysis of results.

There was a total of 82 cirrhotic patients with SFP in all the included 6 studies. Of the total 82 SFP patients, 27 patients had polymicrobial SFP. Candida spp. was the fungal pathogen in the majority of cases: *Candida albicans* (48%-81.8%); *Candida krusei* (15%-25%); *Candida glabrata* (6.66%-20%); *Candida parapsilosis* (5%-16%); *Candida tropicalis* (6.66%-12%); *Candida kefyr* (10%); *Candida lusitaniae* (12.5%); and *Candida zeylanoides* (4%). Besides candida spp., other significant fungal pathogens included Cryptococcus neoformans (53.3%). Antifungal therapy utilization ranged from 33.3% to 81.8%. The prevalence of in-hospital mortality ranged from 33.3%-100%, 1-mo mortality had a range of 50%-73.3%. Only 1 study described 6-mo mortality of 20% in their study.

Table 1 Management, prognosis and mortality in cirrhotic patients with spontaneous fungal peritonitis

Study	Country, setting	Study design	Study population	Management	Mortality
				n (%)	*n* (%)
Hwang *et al*[10], 2014	South Korea, University Hospital	Retrospective, Cross-sectional	*n* = 416 patients	3rd generation cephalosporin (*n* = 15)	In-hospital: -
			SBP (*n* = 401)	Antifungal: *n* = 5 (33.3%)	1-mo: 11/15 (73.3%)
			SFP (*n* = 4)	Amphotericin B: *n* = 2	6-mo: 3/15 (20%)
			Polymicrobial SFP (*n* = 11)	Liposomal Amphotericin B: *n* = 1	
				Fluconazole: *n* = 2	
Hassan *et al*[9], 2014	Egypt, University Hospital	Prospective cohort study	*n* = 46 patients	Not described	In-hospital: 1/3 (33.33%)
			Control patients with no infection (*n* = 18)		
			SFP (*n* = 4; only 3 patients described with ascitic fluid polymorphs > 250 cells/mm^3)		
Karvellas *et al*[11], 2015	(CATSS Database) from 28 medical centers in United States, Canada, Saudi Arabia	Retrospective cohort study	*n* = 126 patients	Anti-fungal: *n* = 9 (81.8%)	In-hospital: 11/11 (100%)
			SBP (*n* = 126)		
			SFP and SBP (*n* = 11)		
Bremmer *et al*[1], 2015[1]	University of Pittsburgh, United States	Retrospective, cross-sectional study	*n* = 25	Antifungal: *n* = 15 (60%)	In hospital: 15/25 (60%)
			SFP (*n* = 25)		One mo: 14/25 (56%)
Lahmer, *et al*[2], 2016	University Hospital, Germany	Retrospective, cross-sectional study	*n* = 208 SFP (*n* = 20)	Antibiotic pretreatment: SFP *n* = 17 Antifungal: *n* = 6 (30% of SFP)	In-hospital: 18/20 (90%)
			SBP (*n* = 28)		
Gravito-Soares *et al*[6], 2017	University of Coimbra, Coimbra, Portugal	Retrospective, case–control study	*n* = 231	Cefotaxime *n* = 231	1 -mo: 4/8
			SFP (*n* = 3)	Antifungal: *n* = 5/8 (62.5%)	(50%)
			Polymicrobial SFP (*n* = 5)	Fluconazole: *n* = 3	
			SBP (*n* = 119)	Caspofungin: *n* = 1	
				Amphotericin B: *n* = 1	

[1]The study was described as a retrospective cohort study design but in the absence of a comparative non-exposure/control group we decided it more appropriately fitted the description of a cross—sectional study. SBP: Spontaneous bacterial peritonitis; SFP: Spontaneous fungal peritonitis.

Micro-organisms, management and mortality in cirrhotic patients with SFP

Bremmer *et al*[1], conducted a retrospective study and identified patients with fungal ascitic fluid cultures through microbiology records. Exclusion criteria included patients without a history of cirrhosis or if an alternative reason for peritonitis was found. There were 25 SFP cirrhotic patients with the following fungal infections: 48% (12/25) patients had *Candida albicans*; 20% (5/25) patients had *C. glabrata*; 16% (4/25) patients had *C. parapsilosis*; 12% (3/25) patients had *C. tropicalis*; and 4% (1/25) patient had *C zeylanoides*. Antifungal therapy was given to 60% (15/25) patients. There were 15 patients that were treated with antifungal medications, 3 patients had persistent or recurrent peritonitis. The 1 mo and in-hospital mortality were 56% (14/25) and 60% (15/25), respectively. There was no statistically significant difference in mortality between patients managed with caspofungin (38%), fluconazole (57%) or patients from whom antifungals were withheld electively (25%). The median time to death was 6 d (IQR: 3-7)[1].

Gravito-Soares *et al*[6], carried out a case-control study, with 8 cirrhotic SFP patients compared with 119 cirrhotic SBP (control) patients. Of 8 cirrhotic SFP patients, 62.5% (5/8) patients had co-infection by bacteria and fungi. Antifungal therapy was utilized in 7 (87.5%) patients. Appropriate antifungal therapy was given to 62.5% (5/8) patients: *Candida albicans* infection was treated with Fluconazole (2/3); *Candida lusitaniae* infection treated with Fluconazole (1/1); Candida tropicalis managed with *Caspofungin* (1/1); and *Geotrichum capitatus* treated with Amphotericin B (1/1). There were 2 patients (25%) with *Candida krusei* that had resistance to initial antifungal therapy with Fluconazole; and 1 patient died due to late diagnosis of SFP. The 30-d (1 mo) mortality was 50% (4/8) and overall mortality was 62.5% (5/8) of cirrhotic SFP

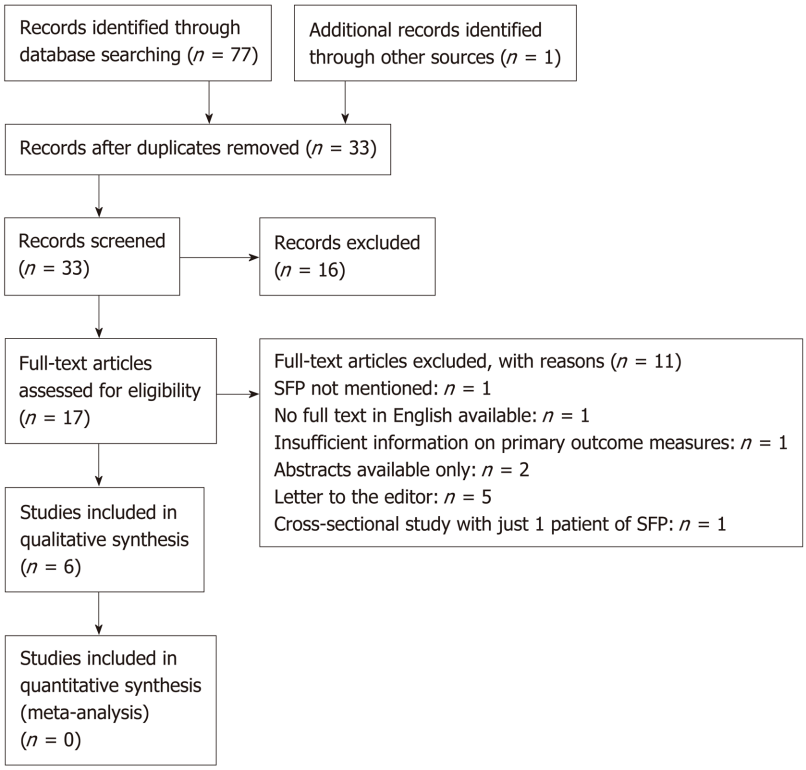

Figure 1 PRISMA flow diagram[27].

patients in the study. The mean time duration between SFP diagnosis and death was 17.6 d ± 11.5 d.

Hassan *et al*[9] carried out a prospective cohort study including 46 ESLD patients; 18 control patients with no infection and 28 patients with invasive fungal infection. Of 28 cases, 4 (16%) patients had SFP. Although 4 patients were described as having SFP, ascitic fluid polymorphs > 250 cells/mm^3 were only described in three patients, and only 2 patients had fungal micro-organisms (Aspergillus niger and *Candida albicans*) isolated from ascitic fluid. Management of SFP patients was not described. Of the three SFP patients with ascitic fluid polymorphs > 250 cells/mm^3, in-hospital mortality occurred in only one patient[9].

Hwang *et al*[10] conducted a retrospective cross-sectional study and compared SFP patients with SBP patients. During the study period of 5 years, 416 patients with SP were included of which 15 (3.6%) had SFP and 410 (96.4%) had SBP. Eleven out of 15 SFP patients had concomitant bacterial infection. The fungal isolates identified in SFP patients were the following: *Candida albicans* (*n* = 8), Candida tropicalis (*n* = 1), Candida glabrata (*n* = 1) and Cryptococcus neoformans (*n* = 8). However, only 5 patients, among 15 SFP patients received anti-fungal therapy. All patients received third-generation cephalosporin (cefotaxime/ceftriaxone). The SFP patients had a 1-mo mortality rate of 73.3% (11/15). The median time to death was 2 d (range, 0-20 d)[10].

Karvellas *et al*[11] utilized the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) database and carried out a nested cohort study to determine the appropriate antimicrobial management in cirrhotic patients with SBP-associated septic shock. The Cooperative Antimicrobial Therapy of Septic Shock (CATSS) database collected data on septic shock patient from 28 medical centers in Canada, the United States, and Saudi Arabia. There were 126 cirrhotic SBP associated-septic shock patients included in the study from CATSS database. Of these, 11 patients had concomitant SFP; *Candida albicans* (9/11) and Candida tropicalis (1/11) and Candida glabrata (1/11). Nine patients (81.8%) were treated with antifungal therapy. All SFP patients died during the course of their hospital stay[11].

Lahmer *et al*[2] performed a retrospective cross-sectional study by reviewing medical records of cirrhotic critically ill patients with SBP. Of 205 patients included in the study, 20 (10%) patients were identified with SFP. Majority of the patients had Candida spp.: *C. albicans* (*n* = 12), *C. glabrata* (*n* = 3), *C. krusei* (*n* = 3), *C. Kefyr* (*n* = 2), *C. parapsilosis* (*n* = 1), *C. tropicalis* (*n* = 1). Antifungal therapy was given to 30% (*n* = 6) patients. Mortality rate was 90% (*n* = 18) patients[2].

Quality assessment

Quality assessment of the included studies was performed according to NHLBI quality assessment tools (Tables 2 and 3)[8]. All the cross-sectional and cohort studies were of high-quality while the case-control study was of fair quality[1,2,6,9-11]. None of the studies described sample size or power estimates. Low sample size was the major limitation in all studies (n ≤ 25). Only 2 studies did not define SFP. Four studies; Hwang *et al*[10], Gravito-Soares *et al*[6], Lahmer *et al*[2], and Bremmer *et al*[1], had primary outcomes of SFP in patients with cirrhosis. The other two studies had the following primary outcomes in cirrhotic patients: Karvellas *et al*[11] had a primary outcome of SBP; and Hassan *et al*[9], had a primary outcome of invasive fungal infection. All the studies included patient baseline characteristics and risk factors, fungal pathogens, management with anti-fungal therapy (except Hassan *et al*[9]) and mortality.

DISCUSSION

Based on our review, the prevalence of SFP anywhere from 2%-10% (Table 1). This is in keeping with a prior meta-analysis which documented a 4.28% prevalence[12]. The reasons for this low prevalence are several most important of which are low index of suspicion leading to a delay in carrying out appropriate diagnostic work up, and longer period of time required for fungal growth. Despite a lower prevalence than SBP, this systematic review confirms that SFP patients with cirrhosis have a high in-hospital mortality (33.3%-100%) and 1-mo mortality (50%-73.3%).

Our systematic review suggests several reasons for the high mortality rates in cirrhotic patients with SFP. Patients with SFP had 3.6 times higher risk of admissions to ICU with severe sepsis/septic shock as compared to SBP patients[6]. Higher mortality rates were observed in patients with high Charlson Comorbidity Index, Model for ESLD and APACHE II scores. Another unique observation was a significantly higher 1-mo mortality in patients who did not undergo liver transplantation compared to patients who underwent liver transplantation. Hence, antifungal therapy in SFP patients could be utilized as a bridging therapy to liver transplantation[1]. Furthermore, a high rate of mortality was noted in patients with SFP who were treated empirically for suspected SBP. After empirical treatment for suspected SBP was initiated, the condition of most of the SFP patients deteriorated resulting in death, even when treated with antifungal agents[10]. In a systemic review suggested that lack of improvement within 48 h after admission is linked to an increased risk of SFP. Hence, fungi should be sought as potential pathogens in cases of ceftriaxone or cefotaxime-resistant SP[13] which occurs in approximately 7%-17% of cirrhotic patients[6].

Understanding the microbiology, diagnosis, and treatment of SFP may lower the associated mortality. Our systematic review provides insight into the microbiology of SFP. Fungi are saprophytes that are common commensal organisms of the skin and mucous membranes[14]. Significant fungal colonization occurs when antibiotics are used for the prevention of SBP in patients with ascites as a result of reduction in the intestinal bacterial flora. This subsequently leads to translocation across the damaged gastrointestinal tract mucosa into the peritoneal activity, causing peritonitis[4]. This effect is enhanced in the setting of immunosuppression and malnutrition which is common in ESLD[5]. Fungi are much larger in size (Candida spp. 10-12 μm) than bacteria including *E. coli* (0.3-1 μm and *K. pneumoniae* (0.6-6 μm) hence a higher gut permeability is required for fungal translocation[1,10]. This explains why SFP is likely limited to those individuals who experience the greatest hit to their innate immunity and those with advanced cirrhosis.

In keeping with the literature, this systematic review shows that *Candida albicans* is the most frequent fungal infectious agent isolated from ascitic fluid cultures, followed by *candida glabrata, candida parapsilosis, candida krusei*, and *candida tropicalis*. A recent study described a shift towards increasing prevalence of candida glabrata and candida parapsilosis infections in cirrhotic patients[15]. Cryptococcus neoformans, Aspergillus spp. and Fusarium have also been isolated though less commonly than candidal spp[2,5]. One of the possible explanations as to why candida is more common in patients with SFP as compared to other fungi such as cryptococcus is probably related to the size difference between these pathogenic organisms[10]. Cryptococcal spp. have diameters up to 20 μm which limit their migration across the intestinal wall[16]. Fungal infections are often polymicrobial with bacterial colonization occurring in 32%-74% of SFP cases[13].

This systematic review also provides data on risk factors for SFP. The findings of our review reveal that SFP is more commonly seen in patients with Child Pugh Class C liver cirrhosis and those with MELD score beyond 30 points[13]. Higher bilirubin

Table 2 Quality assessment of included observational cohort and cross-sectional studies according to NHBLI Quality Assessment Tool

	Hwang *et al*[10], 2014	Hassan *et al*[9], 2014	Karvellas *et al*[11], 2015	Bremmer *et al*[1], 2015	Lahmer *et al*[2], 2016
1 Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes
2 Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes
3 Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes
4 Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes
5 Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No
6 For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes
7 Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes
8 For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?	NA	NA	Yes	NA	NA
9 Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes
10 Was the exposure(s) assessed more than once over time?	No	No	No	No	No
11 Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes

12 Were the outcome assessors blinded to the exposure status of participants?	No	No	No	No	No
13 Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes
14 Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	Yes	Yes	Yes	Yes
Rating	Good	Good	Good	Good	Good

levels, blood urea nitrogen levels, low ascitic fluid protein (< 1 g/dL), antibiotic prophylaxis against SBP and hepatorenal syndrome (HRS) are other potential risk factors that have been described in literature[6,11]. It has been speculated that prophylactic antibiotics alter the normal intestinal flora and cause an excessive growth of fungi and is considered one of the pathophysiological mechanisms for the development of fungal peritonitis and dissemination[17]. Furthermore, patients with corticosteroid use, prolonged antimicrobial use, central venous catheter, total parenteral nutrition, high APACHE score, renal replacement therapy, or malnutrition are more susceptible to opportunistic fungal infections[18-20]. Renal failure is associated with impaired cell mediated immunity and defective granulocyte-macrophage function, which are the dominant host defenses against fungal pathogens[9]. Nosocomial development of SP was also found to be a risk factor for SFP[10,12,13]. As a result of commensal colonization of mucocutaneous membranes, percutaneous inoculation of fungi can commonly occur in patients with refractory ascites who undergo routine paracentesis[9]. Other invasive procedures such as colonoscopy, urinary catheterization and nasogastric intubation have also been identified as risk factors for SFP[6].

This systematic review also sheds light on the risk factors associated with increased mortality from SFP. These factors include severity of liver disease as measured by higher MELD or Child-Pugh score C, recent antibacterial prophylaxis, presence of HRS, low ascitic protein concentration, high acute physiology, and Chronic Health Evaluation II (APACHE II) score and presence of septic shock[12]. In a retrospective cohort study of 241 cirrhotic patients with invasive candidiasis, multivariate analysis demonstrated septic shock (odds ratio 3.2, CI: 1.7-6, $P < 0.001$) as the most significant predictor of mortality[15].

Given the high mortality related to SFP, early diagnosis and treatment are essential to improving outcomes for patients with SFP. Newer diagnostic tests like pan-fungal PCR assay and 1,3 beta-D-Glucan are not only more sensitive in detecting fungi in peritoneal fluid but also help in early identification of SFP by shortening the time to diagnosis[21,22]. In patients with risk factors for SFP, our systematic review supports early testing of peritoneal fluid with these assays. In addition, laboratorial parameters such as leukocyte count, procalcitonin or C-reactive are too non-specific for SFP and hence are not very useful in SFP diagnosis[2]. It is important to note that ascitic lactate dehydrogenase, blood WBC count, blood urea nitrogen and predominance of lymphocytes in ascitic fluid were significantly higher in SFP compared with patients with SBP and might provide a clue to diagnosis[6,9,23].

Despite its high mortality, the results from this systematic review show suboptimal utilization of antifungal therapy utilization in cirrhotic SFP patients, ranging from 33.3% to 81.8%. In addition, we note that only a small percent was treated using appropriate systemic antifungal therapy. Based on the contemporary microbiology of SFP, our review supports the use of echinocandins as initial therapy with tailoring after culture results are available. Echinocandins are preferred over fluconazole in septic shock due to their lower overall toxicity and high tolerability. They are associated with lower hepatoxicity compared to fluconazole. Once patients become clinically stable, antimicrobial therapy is de-escalated from echinocandins to fluconazole[15,24-27]. Furthermore, empiric treatment is essential for reducing risk of mortality in SFP as fungal recovery using routine culture methods is associated with significant delays. Our review shows that 73% of patients receiving antifungal therapy experienced a median lag in treatment of 3 d until yeast was isolated from ascitic fluid cultures with the average time from SFP diagnosis to death was 2 d[1,10].

Table 3 Quality assessment of included case-control studies according to NHBLI Quality Assessment Tool

Gravito-Soares *et al*[6], 2017	
1 Was the research question or objective in this paper clearly stated?	Yes
2 Was the study population clearly specified and defined?	Yes
3 Did the authors include a sample size justification?	No
4 Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Yes
5 Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	No
6 Were the cases clearly defined and differentiated from controls?	Yes
7 If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	NA
8 Was there use of concurrent controls?	No
9 Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	Yes
10 Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Yes
11 Were the assessors of exposure/risk blinded to the case or control status of participants?	No
12 Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	Yes
Rating	Fair

This further supports the use of empiric broad-spectrum antifungals while awaiting culture results in those who are most at risk. Limited and low-quality data exists regarding the appropriate time for initiation of empiric antifungal treatment. Based on this systematic review and current literature, it is reasonable to use antifungal therapy in critically ill cirrhotics with ascites who fail to recover within 48 h of receiving broad spectrum antibiotics, in those patients who are at increased risk of developing infections. For instance, patients on immunosuppressants or antibiotics for a long time, those with invasive vascular access devices, patients on total parenteral nutrition or renal replacement therapy or those who have high APACHE scores and are malnourished. These patients are at higher risk of mortality from SFP if mis-diagnosed[4,18]. However, given the low overall incidence of SFP, empiric antifungal therapy is generally not recommended in patients with CA SP.

In conclusion, SFP is not an uncommon complication in cirrhotic patients and associated with high mortality both in the hospital and at 1 mo. High clinical suspicion is required particularly in those with higher MELD and Child Pugh scores who fail to improve despite appropriate antibiotic treatment. Antifungal therapy is inappropriately used and currently underutilized. Our review suggests rapid initiation of antifungal therapy in the presence of septic shock and failure to respond to broad spectrum antibiotic regimen. It also highlights the need for further studies that will inform the timing and choice of anti-fungal use in patients at high-risk for SFP. Finally, our review also shows that liver transplantation is a possible outcome for those with SFP with low risk for short-term recurrence and acceptable 1-mo mortality rates.

ARTICLE HIGHLIGHTS

Research background

Spontaneous fungal peritonitis (SFP) is a devastating and underestimated complication of end stage liver disease (ESLD) which is defined as fungal infection of the ascitic fluid and the presence of ascitic neutrophil count of > 250 cells/mL. The combination of cirrhosis and critical illness causes acquired immunodeficiency leading to increased risk of developing SFP. There is limited literature regarding clinical course, risk factors, management and outcomes of SFP particularly in critically ill patients. With this study, we have compiled a systematic review of available data on SFP.

Research motivation
When compared to spontaneous bacterial peritonitis, SFP is less well recognized and is associated with higher mortality rates. In many cases, the clinical importance of isolating Candida from abdominal cultures is unknown and therapeutic approaches are largely undefined. Furthermore, the epidemiology and outcomes of patients with SFP have only been reported sporadically in literature. Hence, by performing a systematic review we aimed to increase the available knowledge regarding SFP.

Research objectives
The main objective of the study was to determine the prevalence of fungal micro-organisms and describe the risk factors, management and mortality rates of SFP in critically ill patients with cirrhosis.

Research methods
This is a systematic review of available studies identified using PubMed, EMBASE, Cochrane Central Register of Controlled Trials and Scopus databases. Inclusion criteria were intervention trials and observation studies describing the association between SFP and cirrhosis. The primary outcome was in-hospital, 1-mo, and 6-mo mortality rates of SFP in cirrhotic patients. Secondary outcomes were fungal microorganisms identified and anti-fungal medications utilized for the management of SFP. The National Heart, Lung and Blood Institute quality assessment tools were used to assess internal validity and risk of bias for each included study.

Research results
Six observational studies were included in this systematic review. A total of 82 patients with SFP were identified in these studies. *Candida albicans* was the predominant fungal pathogen in majority of the cases (48-81.8%) followed by *Candida krusei* (15%-25%) and *Candida glabrata* (6.66%-20%). Antifungal therapy in SFP patients was utilized in 33.3% to 81.8% cases. The in-hospital mortality ranged from 33.3% to 100%, whereas 1-mo mortality ranged between 50% and 73.3%.

Research conclusions
SFP is not an uncommon complication associated with a worse prognosis in cirrhotic patients, particularly those with higher MELD and Child Pugh scores who fail to improve despite appropriate antibiotic treatment. Our study also showed that antifungal therapy is currently underutilized. Rapid initiation of antifungal therapy in the presence of septic shock and failure to respond to broad spectrum antibiotic regimen is crucial in the management of SFP.

Research perspectives
Future large-scale, prospective studies aimed at identifying the ideal timing and choice of anti-fungal therapy in patients at high-risk for developing SFP are needed. Also, research efforts should aim at determining appropriate non-cultural tests for SFP in order to improve the rapidity of diagnosis.

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REFERENCES

1 **Bremmer DN**, Garavaglia JM, Shields RK. Spontaneous fungal peritonitis: a devastating complication of cirrhosis. *Mycoses* 2015; **58**: 387-393 [PMID: 25851525 DOI: 10.1111/myc.12321]
2 **Lahmer T**, Brandl A, Rasch S, Schmid RM, Huber W. Fungal Peritonitis: Underestimated Disease in Critically Ill Patients with Liver Cirrhosis and Spontaneous Peritonitis. *PLoS One* 2016; **11**: e0158389 [PMID: 27390856 DOI: 10.1371/journal.pone.0158389]
3 **Sheer TA**, Runyon BA. Spontaneous bacterial peritonitis. *Dig Dis* 2005; **23**: 39-46 [PMID: 15920324 DOI: 10.1159/000084724]
4 **Maraolo AE**, Buonomo AR, Zappulo E, Scotto R, Pinchera B, Gentile I. Unsolved Issues in the Treatment of Spontaneous Peritonitis in Patients with Cirrhosis: Nosocomial Versus Community-acquired Infections and the Role of Fungi. *Rev Recent Clin Trials* 2019; **14**: 129-135 [PMID: 30514194 DOI: 10.2174/1574887114666181204102516]
5 **Fiore M**, Leone S. Spontaneous fungal peritonitis: Epidemiology, current evidence and future prospective. *World J Gastroenterol* 2016; **22**: 7742-7747 [PMID: 27678356 DOI: 10.3748/wjg.v22.i34.7742]
6 **Gravito-Soares M**, Gravito-Soares E, Lopes S, Ribeiro G, Figueiredo P. Spontaneous fungal peritonitis: a rare but severe complication of liver cirrhosis. *Eur J Gastroenterol Hepatol* 2017; **29**: 1010-1016 [PMID: 28614081 DOI: 10.1097/MEG.0000000000000927]
7 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; **151**: W65-W94 [PMID: 19622512]
8 **National Heart, Lung, and Blood Institute**. Development and use of quality assessment tools. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

9 **Hassan EA**, Abd El-Rehim AS, Hassany SM, Ahmed AO, Elsherbiny NM, Mohammed MH. Fungal infection in patients with end-stage liver disease: low frequency or low index of suspicion. *Int J Infect Dis* 2014; **23**: 69-74 [PMID: 24726663 DOI: 10.1016/j.ijid.2013.12.014]

10 **Hwang SY**, Yu SJ, Lee JH, Kim JS, Yoon JW, Kim YJ, Yoon JH, Kim EC, Lee HS. Spontaneous fungal peritonitis: a severe complication in patients with advanced liver cirrhosis. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 259-264 [PMID: 23996048 DOI: 10.1007/s10096-013-1953-2]

11 **Karvellas CJ**, Abraldes JG, Arabi YM, Kumar A; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Appropriate and timely antimicrobial therapy in cirrhotic patients with spontaneous bacterial peritonitis-associated septic shock: a retrospective cohort study. *Aliment Pharmacol Ther* 2015; **41**: 747-757 [PMID: 25703246 DOI: 10.1111/apt.13135]

12 **Fiore M**, Chiodini P, Pota V, Sansone P, Passavanti MB, Leone S, Aurilio C, Pace MC. Risk of spontaneous fungal peritonitis in hospitalized cirrhotic patients with ascites: a systematic review of observational studies and meta-analysis. *Minerva Anestesiol* 2017; **83**: 1309-1316 [PMID: 28726361 DOI: 10.23736/S0375-9393.17.12034-1]

13 **Shizuma T**. Spontaneous bacterial and fungal peritonitis in patients with liver cirrhosis: A literature review. *World J Hepatol* 2018; **10**: 254-266 [PMID: 29527261 DOI: 10.4254/wjh.v10.i2.254]

14 **Gould D**. Diagnosis, prevention and treatment of fungal infections. *Nurs Stand* 2011; **25**: 38-47; quiz 48 [PMID: 21661530 DOI: 10.7748/ns2011.04.25.33.38.c8464]

15 **Bassetti M**, Peghin M, Carnelutti A, Righi E, Merelli M, Ansaldi F, Trucchi C, Alicino C, Sartor A, Toniutto P, Wauters J, Laleman W, Tascini C, Menichetti F, Luzzati R, Brugnaro P, Mesini A, Raviolo S, De Rosa FG, Lagunes L, Rello J, Dimopoulos G, Colombo AL, Nucci M, Vena A, Bouza E, Muñoz P, Tumbarello M, Losito R, Martin-Loeches I, Viscoli C. Clinical characteristics and predictors of mortality in cirrhotic patients with candidemia and intra-abdominal candidiasis: a multicenter study. *Intensive Care Med* 2017; **43**: 509-518 [PMID: 28271321 DOI: 10.1007/s00134-017-4717-0]

16 **Gazzoni AF**, Oliveira Fde M, Salles EF, Mayayo E, Guarro J, Capilla J, Severo LC. Unusual morphologies of Cryptococcus spp. in tissue specimens: report of 10 cases. *Rev Inst Med Trop Sao Paulo* 2010; **52**: 145-149 [PMID: 20602024 DOI: 10.1590/S0036-46652010000300006]

17 **Choi SH**, Soo Kim Y, Chung JW, Choo EJ, Kwak YG, Lee YS, Kim MN, Woo JH, Ryu J, Kim NJ. Clinical significance of untreated Candida species isolated from ascites in cirrhotic patients. *Scand J Infect Dis* 2004; **36**: 649-655 [PMID: 15370651 DOI: 10.1080/00365540410020866]

18 **Nadim MK**, Durand F, Kellum JA, Levitsky J, O'Leary JG, Karvellas CJ, Bajaj JS, Davenport A, Jalan R, Angeli P, Caldwell SH, Fernández J, Francoz C, Garcia-Tsao G, Ginès P, Ison MG, Kramer DJ, Mehta RL, Moreau R, Mulligan D, Olson JC, Pomfret EA, Senzolo M, Steadman RH, Subramanian RM, Vincent JL, Genyk YS. Management of the critically ill patient with cirrhosis: A multidisciplinary perspective. *J Hepatol* 2016; **64**: 717-735 [PMID: 26519602 DOI: 10.1016/j.jhep.2015.10.019]

19 **Righi E**. Management of bacterial and fungal infections in end stage liver disease and liver transplantation: Current options and future directions. *World J Gastroenterol* 2018; **24**: 4311-4329 [PMID: 30344417 DOI: 10.3748/wjg.v24.i38.4311]

20 **Kojic EM**, Darouiche RO. Candida infections of medical devices. *Clin Microbiol Rev* 2004; **17**: 255-267 [PMID: 15084500 DOI: 10.1128/cmr.17.2.255-267.2004]

21 **Runyon BA**; AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009; **49**: 2087-2107 [PMID: 19475696 DOI: 10.1002/hep.22853]

22 **Nguyen MH**, Wissel MC, Shields RK, Salomoni MA, Hao B, Press EG, Shields RM, Cheng S, Mitsani D, Vadnerkar A, Silveira FP, Kleiboeker SB, Clancy CJ. Performance of Candida real-time polymerase chain reaction, β-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. *Clin Infect Dis* 2012; **54**: 1240-1248 [PMID: 22431804 DOI: 10.1093/cid/cis200]

23 **Bal CK**, Bhatia V, Khillan V, Rathor N, Saini D, Daman R, Sarin SK. Spontaneous cryptococcal peritonitis with fungemia in patients with decompensated cirrhosis: Report of two cases. *Indian J Crit Care Med* 2014; **18**: 536-539 [PMID: 25136195 DOI: 10.4103/0972-5229.138161]

24 **Wang JL**, Chang CH, Young-Xu Y, Chan KA. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. *Antimicrob Agents Chemother* 2010; **54**: 2409-2419 [PMID: 20308378 DOI: 10.1128/AAC.01657-09]

25 **Pappas PG**, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Executive Summary: Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; **62**: 409-417 [PMID: 26810419 DOI: 10.1093/cid/civ1194]

26 **Fiore M**, Andreana L, Leone S. Preemptive therapy of spontaneous fungal peritonitis. *Hepatology* 2016; **64**: 997-998 [PMID: 26754934 DOI: 10.1002/hep.28448]

27 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed1000097]

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CASE REPORT

Wilson disease developing osteoarthritic pain in severe acute liver failure: A case report

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Abstract

BACKGROUND

Wilson disease (WD) is a rare copper metabolism disorder with symptoms including hepatic disorders, neuropsychiatric abnormalities, Kayser-Fleischer rings, and hemolysis in association with acute liver failure (ALF). Osteoarthritis is a rare manifestation of WD. We experienced a case of WD with arthritic pain in the knee and liver cirrhosis. Here, we report the clinical course in a WD patient with arthritic pain and liver cirrhosis receiving combination therapy with Zn and a chelator and discuss the cause of arthritic pain.

CASE SUMMARY

We present an 11-year-old boy who developed osteoarthritis symptoms and ALF, with a New Wilson Index Score (NWIS) of 12. He was diagnosed with WD with decreased serum ceruloplasmin and copper levels, increased urinary copper excretion, and *ATP7B* gene mutations detected on gene analysis. There was improvement in the liver cirrhosis, leading to almost normal liver function and liver imaging, one year after receiving combination therapy with Zn and a chelator. Moreover, his arthritic pain transiently deteriorated but eventually improved with a decrease in the blood alkaline phosphatase levels following treatment.

CONCLUSION

Patients with WD who develop ALF with an NWIS > 11 may survive after treatment with Zn and chelators, without liver transplantation, when they present with mild hyperbilirubinemia and stage ≤ II hepatic encephalopathy. Osteoarthritis symptoms may improve with long-term Zn and chelator therapy without correlation of liver function in WD.

Key words: Acute liver failure; New Wilson Index; Osteoarthritis; Wilson disease; Case report

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Core tip: We present an 11-year-old boy with Wilson disease (WD) who developed osteoarthritis symptoms and acute liver failure, with a New Wilson Index Score (NWIS) of 12. His liver cirrhosis improved, leading to almost normal liver function and liver imaging results, one year after receiving combination therapy with Zn and a chelator. Patients with WD with a NWIS > 11 may be able to survive with treatment with Zn and chelators, without liver transplantation, in cases wherein they present with mild hyperbilirubinemia and stage ≤ II hepatic encephalopathy. Symptoms of associated osteoarthritis may also improve with long-term Zn and chelator therapy.

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INTRODUCTION

Wilson disease (WD) is a rare copper metabolism disorder caused by a mutation in the *ATP7B* gene, with a prevalence of 1 in 30000 to 1 in 100000 individuals. The clinical manifestations are secondary to accumulation of copper in various organs, with typical symptoms of hepatic disorders, neuropsychiatric abnormalities, Kayser-Fleischer (K-F) rings, and hemolysis in association with acute liver failure (ALF). WD may rarely present with extrahepatic conditions, such as skeletal abnormalities, including premature osteoporosis and arthritis[1], cardiomyopathy, pancreatitis, hypoparathyroidism, and infertility or repeated miscarriages.

Most symptoms in WD first appear in the second and third decades of life; thus, the diagnosis is sometimes difficult and delayed. Most WD patients with hepatic encephalopathy and ALF would have already developed decompensated liver cirrhosis. Therefore, the disease is usually severe and may often be fatal without liver transplantation (LT).

The New Wilson Index Score (NWIS) is an important indication criterion for LT in cases of severe ALF in WD[2]. Although Dhawan *et al*[2] reported that patients with WD who present with ALF with an NWIS > 11 cannot survive without undergoing LT, we have previously demonstrated that even a WD patient with NWIS >11 could recover from ALF with treatment consisting of Zn, chelator and plasma exchange (PE)[3]. Here, we report a new case of WD with arthritic pain in the knee and liver cirrhosis. The patient developed ALF with NWIS >11 and stage I hepatic encephalopathy but survived with Zn and chelator treatment, without the need for continuous hemodiafiltration (CHDF) or PE. His arthritic pain was also alleviated with improved liver function; however, his knee pain deteriorated with increased blood alkaline phosphatase (ALP) levels, and he could not walk by himself.

CASE PRESENTATION

Chief Complaints

A 11-year-old boy complained of pain in both knees and sought an orthopedic consultation. The orthopedic surgeon did not detect any problem in his knees. He consulted his general physician for persistent pain in both knees. The physician noticed his pale complexion and edema of both the eyelids and lower limbs, and based on abdominal ultrasonography, diagnosed him with liver cirrhosis; he was subsequently referred to our institution.

History of present illness

The patient had experienced knee pain for 2 mo.

History of past illness

His neonatal history was unremarkable. He was born at 38 wk and 4 d of gestation with a birthweight of 2.66 kg and had no postnatal medical problems. He had been

diagnosed with genu valgum several years prior.

Physical examination

The patient showed jaundice and splenohepatomegaly with tenderness in both hypochondrial regions. His vital signs were normal.

Laboratory examinations

Laboratory data and abdominal computed tomography (CT) revealed liver cirrhosis (Child-Pugh grade C) with ascites and liver atrophy. Multiple high-density mottled nodular shadows scattered in the liver were observed (Figure 1).

Imaging examinations

The diagnosis of WD was suspected due to his presentation with severe ALF (Table 1), and he immediately received treatment with Zn (3 mg/kg/d), concentrated human anti-thrombin III, and fresh-frozen plasma (FFP). His consciousness and physical lethargy gradually improved. The diagnosis of WD was confirmed based on low copper (27 mg/dL) and serum ceruloplasmin (7.0 mg/dL) levels, elevated urinary copper excretion (720 μg/d), and the presence of Coombs-negative hemolytic anemia [hemoglobin (Hb) level, 9.5 g/dL] without definite K-F rings. Moreover, gene analysis revealed compound heterozygous mutations (*p.Arg778Leu/c.2333G>T* and *p.Asn958ThrfsX9/c.2871delC*). The Leipzig's score[4] for WD diagnosis was 9.

He received combination therapy with Zn and trientine following the diagnosis of WD, and his physical condition gradually improved. However, he complained of pain in both knees and had difficulty walking by himself. Magnetic resonance imaging (MRI) of the knee did not show significant abnormal findings (Figure 2).

Follow-up and outcomes

The patient was discharged after prolonged hospitalization for 70 d because of the time required for the recovery of the coagulation parameters [prothrombin time (PT): 24%, prothrombin time-international normalized ratio (PT-INR): 2.5]. A liver CT scan performed 2 mo after hospitalization revealed fewer hyperdense mottled nodular shadows compared to those observed in the CT scans recorded at the time of hospitalization. Following his discharge, the coagulation parameters and liver CT findings became almost normal by one year after the initiation of therapy.

Although his knee pain was alleviated and blood ALP levels were decreased at the time of discharge, his knee pain persisted for some months after discharge and markedly improved with a further decrease in blood ALP levels (Figure 3), and he could walk by himself with little pain and could continue his schooling following treatment with Zn (1 mg/kg/d) and trientine (10 mg/kg/d). The coagulation parameters and liver CT findings also became almost normal by one year after the start of therapy.

DISCUSSION

Our patient with WD and severe ALF presented initially with arthritic pain in both knees. Here we report that a patient with ALF with WD could recover normal liver function by one year after initiation of combination therapy with Zn and trientine (Table 1). The mutations of *p.Arg778Leu/c.2333G>T* and *p.Asn958ThrfsX9/c.2871delC* present in this patient have been commonly detected in Japanese patients with WD[5]. Previously, WD patients presenting with ALF with an NWIS >11 were considered to require LT for successful treatment[2]. However, in recent years, certain institutions have reported that some WD patients developing severe ALF with an NWIS > 11, even when presenting with stage II hepatic encephalopathy, can be rescued following conservative therapy with Zn, chelators, CHDF and/or plasma exchange without LT[3,6-8]. We administered Zn to our patient immediately on suspecting WD based on his abdominal CT findings. Moreover, we monitored his clinical course, administering FFP and transfusing glucose and electrolytes without CHDF, as he had developed ALF with mild hyperbilirubinemia and significant coagulopathy without definite encephalopathy. CHDF was not performed because there was mild improvement in his physical condition without any deterioration of liver function and consciousness in the first 3 d following treatment with Zn and the aforementioned conservative therapies. A combination of Zn and trientine therapy was initiated after confirming the diagnosis of WD.

Santos *et al*[9] reported that even patients with decompensated WD could recover in one year following either chelator treatment alone or combination therapy with Zn and chelators, even though they qualified as candidates for LT. In our patient, the combination therapy of Zn and trientine for 14 months contributed to the recovery of

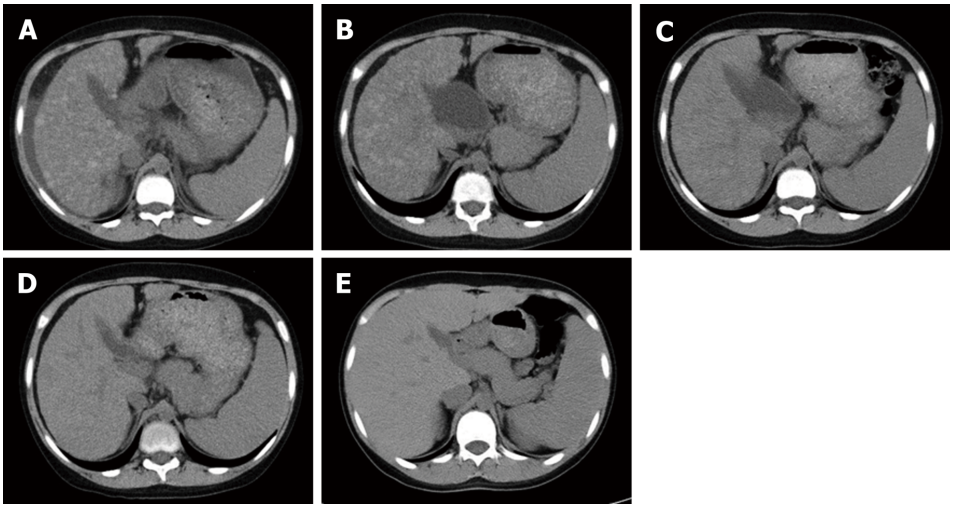

Figure 1 Hepatic computed tomography image obtained while receiving Zn and trientine treatment. The mottled nodular shadows with a high density in the liver improved over time. However, splenomegaly did not improve. A: On admission; B: 1 mo after treatment; C: 2 mo after treatment; D: 4 mo after treatment; E: 14 mo after treatment.

the liver function and liver CT findings to almost normal levels. Therefore, teenagers with WD and decompensated liver cirrhosis are likely to recover normal liver functions following treatment with combination therapy involving Zn and trientine.

Devarbhavi *et al*[7] reported that children aged less than 18 years with WD who developed ALF leading to impaired consciousness were evaluated for LT, and that children with WD with hepatic encephalopathy and a Devarbhavi's score ≥10.4 could not be rescued without LT. Devarbhavi's score in our case was 8.1. The children with WD discussed in Devarbhavi *et al*[7] report had only stage I or II hepatic encephalopathy. Therefore, we considered that patients with decompensated WD, with mildly impaired consciousness, mildly elevated blood total bilirubin (T-Bil) levels, and an NWIS > 11, could be rescued without receiving LT.

Although MRI of the knee did not reveal significant abnormal findings, osteoarthritis has been reported as a rare complication of WD, and Golding *et al*[1] reported on the clinical and radiological features of arthropathy of WD. Nazer *et al*[10] reported some evidence of bony abnormality ranging from mild demineralization to chondromalacia and osteoarthritis. The cause of these bone abnormalities is not known and is not likely to be related to copper toxicity alone, because copper loading in experimental animals does not lead to bone abnormalities. Moreover, patients with severe hepatic WD who were diagnosed and treated in our hospital did not present with knee pain[3]. The knee pain in the present case deteriorated after the patient's liver function improved.

Moreover, Golding *et al*[1] suggested that these bone changes in patients with WD resulted from the loss of calcium and phosphorus in the urine; therefore, the bone changes could be related to chelator therapy, also because of unusual bone mineral metabolism in the resorption and remodeling of the new bone during chelator therapy[1]. Our patient presented with knee pain before receiving treatment, and the knee pain deteriorated following trientine treatment; the pain improved after he had received trientine treatment for one year. The patient had genu valgum, which might have been a complication of longstanding WD. The blood ALP levels significantly increased on trientine treatment. The blood ALP levels correlated with the knee pain, and when the increased ALP level deceased to less than 2500 (IU/L) on Day 287, the patient experienced a definite improvement in knee pain and could walk by himself. It is not the increased blood ALP levels *per se*, but a ratio of ALP to T-Bil < 2.0 that is referred to in the diagnosis of severe WD. However, in cases of severe WD with bone symptoms, these referral values may not be relevant.

CONCLUSION

Even patients with WD who develop ALF with an NWIS >11 may be able to survive without LT if they present with mild hyperbilirubinemia and stage ≤ II hepatic encephalopathy. Moreover, the arthritic pain is not associated with the severity of WD. The pain temporarily deteriorates, but eventually improves following Zn and chelator therapy because bone mineral metabolism itself leads to a stable state.

Table 1 Clinical data during hospitalization and follow-up

	Day 0	Day 1	Day 3	Day 5	Day 7	Day 14	Day 21	Day 31	Day 42	Day 61	Day 98	Day 118	Day 180	Day 287	Day 371	Day 441
WBC (×103/μL)	9.6	7.5	6.6	4.7	5	3.5	3.9	4.1	4.1	5.6	5.9	3.9	5.3	4.9	5.8	5.7
Hb (g/dL)	9.5	9.8	10.7	10.9	10.8	10.7	9.6	9.3	8.9	8.3	8.9	8.9	9.4	9.8	10.5	11.6
Plt (103/μL)	126	144	145	130	124	43	46	51	58	69	91	80	132	187	166	160
PT (%)	18	18	23	24	22	21	19	20	22	24	31	31	43	57	60	79
PT-INR	3.1	3	2.5	2.3	2.7	2.6	2.8	2.7	2.6	2.5	2.1	2.1	1.7	1.4	1.3	1.1
APTT (%)	27	26	30	29	24	28	22	23	22	24	35	38	50	66	78	78
ATIII (%)	NA	20	22	45	46	51	53	33	25	26	35	32	64	90	115	136
Factor V(%)	NA	NA	NA	NA	13	16	15	19	15	25	33	27	46	81	84	80
BUN (mg/dL)	9.9	7	8.3	7.1	7.7	9.8	8.4	9.8	9.2	8.6	8	8.1	8.7	10.7	8.5	9.6
Cr (mg/dL)	0.49	0.5	0.52	0.47	0.48	0.44	0.43	0.38	0.34	0.35	0.29	0.32	0.33	0.29	0.31	0.36
AST (IU/L)	156	79	53	48	47	76	51	60	55	55	69	75	64	43	38	31
ALT (IU/L)	67	26	30	29	33	69	49	50	42	39	54	68	53	46	45	39
LDH (IU/L)	450	386	290	272	258	247	222	219	217	218	256	286	263	196	179	188
T-Bil (mg/dL)	4.9	2.6	2	1.7	1.4	1.8	2	2.4	3.2	2.9	1.3	1.1	0.5	0.4	0.4	0.3
D-Bil (mg/dL)	1.5	0.8	0.5	0.4	0.2	0.3	0.4	0.6	0.9	0.8	0.2	0.1	0.1	0.1	0.1	0.1
TP (g/dL)	4.8	5.8	6.2	6.3	6.1	6.4	6.4	6.7	7	6.9	6.5	6.1	6.8	7.6	7.3	7.6
ALB (g/dL)	1.4	1.6	2.4	2.5	2.4	2.7	2.9	3.1	3.1	3.2	2.8	2.6	3.3	4.3	4.3	4.7
[1]PELD score	26	22	14	12	14	14	15	15	16	14	8	8	2	-4	-5	-9
NWIS	12	9	7	5	7	6	6	6	6	6	5	5	4	2	2	0
The Devarbhavi's score	8.11	5.65	2.14	1.82	1.50	1.93	2.14	2.57	3.42	3.10	1.39	1.18	0.54	0.43	0.43	0.32
Hepatic encephalopathy	I	I	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[1]PELD score: All the scores were described in the PELD score, though the patient's age was 12 years at Day 287; Day 371; and Day 441. WBC: White blood cell count; Hb: Hemoglobin; Plt: Platelets; PT: Prothrombin time; PT-INR: Prothrombin time international normalized ratio; APTT: Activated partial thromboplastin time; AT III: Antithrombin III; BUN: Blood urea nitrogen; Cre: Creatinine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; T-Bil: Total bilirubin; D-Bil: Direct bilirubin; TP: Total protein; Alb: Albumin; NA: Not available.

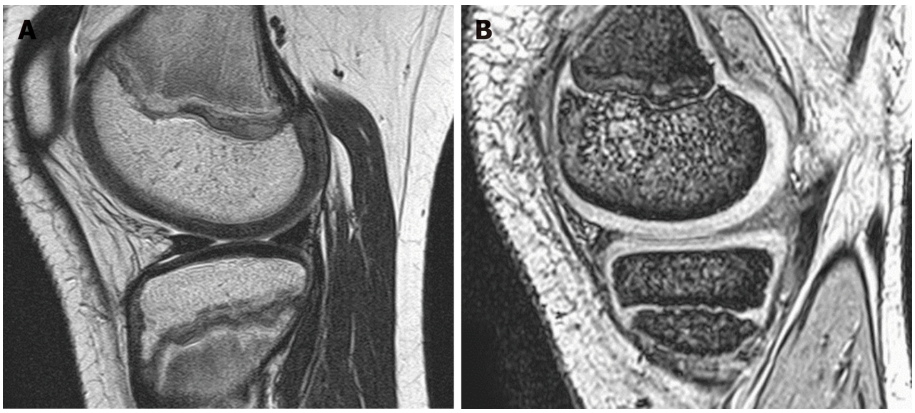

Figure 2 Magnetic resonance imaging scan of the knee during the hospitalization. T2-weighted image. A: Mildly increased signal intensity in the medial meniscus of right knee; B: No abnormal signal intensity.

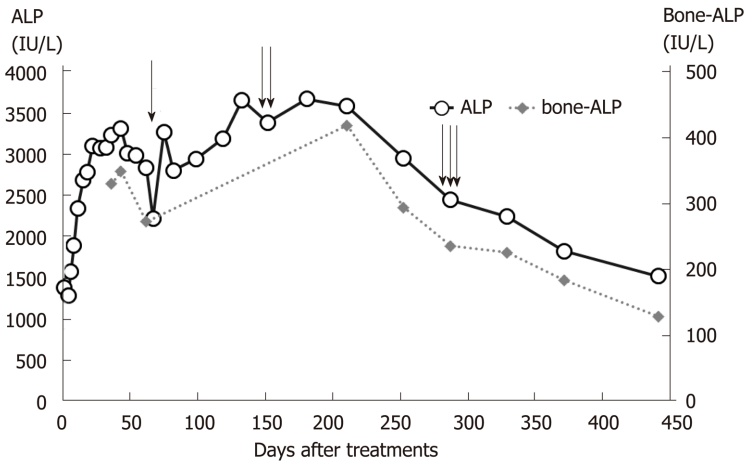

Figure 3 Blood alkaline phosphatase and bone type alkaline phosphatase levels while receiving Zn and trientine treatment. The blood alkaline phosphatase (ALP) and bone type ALP levels increased with deterioration in knee pain owing to trientine treatment. However, the blood ALP and bone type ALP levels gradually decreased with improvement in the clinical status of Wilson disease, and pain was attenuated in both knees. Zn and trientine (15 mg/kg/d) were administered on Day 5, and trientine was increased to 30 mg/kg/d on Day 8 and 40 mg/kg/d on Day 40. Trientine was then decreased to 30 mg/kg/d on Day 70 (one black arrow), 20 mg/kg/d on D 152 (two black arrows), and 10 mg/kg/d on Day 288 (three black arrows).

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REFERENCES

1 **Golding DN**, Walshe JM. Arthropathy of Wilson's disease. Study of clinical and radiological features in 32 patients. *Ann Rheum Dis* 1977; **36**: 99-111 [PMID: 857745 DOI: 10.1136/ard.36.2.99]
2 **Dhawan A**, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. *Liver Transpl* 2005; **11**: 441-448 [PMID: 15776453 DOI: 10.1002/lt.20352]
3 **Kido J**, Matsumoto S, Momosaki K, Sakamoto R, Mitsubuchi H, Inomata Y, Endo F, Nakamura K. Plasma exchange and chelator therapy rescues acute liver failure in Wilson disease without liver transplantation. *Hepatol Res* 2017; **47**: 359-363 [PMID: 27007780 DOI: 10.1111/hepr.12711]
4 **Ferenci P**, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, Schilsky M, Cox D, Berr F. Diagnosis and phenotypic classification of Wilson disease. *Liver Int* 2003; **23**: 139-142 [PMID: 12955875]
5 **Tatsumi Y**, Hattori A, Hayashi H, Ikoma J, Kaito M, Imoto M, Wakusawa S, Yano M, Hayashi K, Katano Y, Goto H, Okada T, Kaneko S. Current state of Wilson disease patients in central Japan. *Intern Med* 2010; **49**: 809-815 [PMID: 20453399]
6 **Eisenbach C**, Sieg O, Stremmel W, Encke J, Merle U. Diagnostic criteria for acute liver failure due to Wilson disease. *World J Gastroenterol* 2007; **13**: 1711-1714 [PMID: 17461475 DOI: 10.3748/wjg.v13.i11.1711]
7 **Devarbhavi H**, Singh R, Adarsh CK, Sheth K, Kiran R, Patil M. Factors that predict mortality in children with Wilson disease associated acute liver failure and comparison of Wilson disease specific prognostic indices. *J Gastroenterol Hepatol* 2014; **29**: 380-386 [PMID: 24033813 DOI: 10.1111/jgh.12356]
8 **Tian Y**, Gong GZ, Yang X, Peng F. Diagnosis and management of fulminant Wilson's disease: a single center's experience. *World J Pediatr* 2016; **12**: 209-214 [PMID: 26041495 DOI: 10.1007/s12519-015-0026-2]
9 **Santos Silva EE**, Sarles J, Buts JP, Sokal EM. Successful medical treatment of severely decompensated Wilson disease. *J Pediatr* 1996; **128**: 285-287 [PMID: 8636833]
10 **Nazer H**, Ede RJ, Mowat AP, Williams R. Wilson's disease: clinical presentation and use of prognostic index. *Gut* 1986; **27**: 1377-1381 [PMID: 3792921 DOI: 10.1136/gut.27.11.1377]

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