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Review

Fatty liver disease is associated with the severity of acute pancreatitis:A systematic review and meta-analysis

Sen Hou[a], Xinya Tang[a], Huxiao Cui[a], Chaoxu Liu[b], Xiangyu Bai[c], Liubin Shi[b], Yong Shi[a,*]

[a] Department of General Surgery, Xuchang Central Hospital, Henan, China
[b] Department of General Surgery, Huashan Hospital, Fudan University, Shanghai, 201907, China
[c] Institute of Pharmacy, Pharmaceutical College of Henan University, 85 Minglun Street, Kaifeng, Henan, 475001, China

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ABSTRACT

Background: Fatty liver (FL) has been positively associated with the risk of acute pancreatitis (AP), but whether FL is associated with the severity of AP remains unknown. To this, a meta-analysis was conducted to assess the effect of FL on severity and outcomes of AP.

Method: We searched PubMed, EMBASE and the Cochrane library to identify all eligible studies (up to June 2017). We pooled the odds ratios (ORs) or weighted mean differences (WMD) from individual studies using a random-effects model to investigate associations between FL and the prognosis of AP.

Result: Four studies were included in the meta-analysis, including a total of 805 patients with fatty liver-related acute pancreatitis (FLAP) and 1026 patients with non fatty liver-related acute pancreatitis (NFLAP). The incidences of moderately severe AP (MSAP) (OR = 2.72, 95%CI: 1.82–4.05, $P < 0.001$) and severe AP (SAP) (OR = 3.57, 95%CI: 2.06–6.18, $P < 0.001$) were statistically significantly higher in FLAP group than those in NFLAP group. Taking obesity into consideration, a higher rate of MSAP and SAP were also found in patients with FL, no matter whether they were obese or not. Furthermore, mortality (OR = 4.16, 95%CI: 2.57–6.73, $P < 0.001$), systemic inflammatory response syndrome (SIRS) (OR = 2.82, 95%CI: 2.3–3.47, $P < 0.001$) and local complications were also statistically significantly higher in the FLAP group than in NFLAP group.

Conclusion: Fatty liver is associated with the severity of acute pancreatitis.

1. Introduction

Acute pancreatitis (AP) is an inflammatory disease of the pancreas [1]. Most episodes of acute pancreatitis are mild and self-limiting, needing only symptomatic treatment. However, 20% of patients develop a severe disease, characterized by multiple organ dysfunction syndrome and systemic inflammatory response syndrome [2,3].

Several risk factors for AP have been reported, including alcohol [4], gallstones, obesity [5], and non-alcoholic fatty liver disease (NAFLD) [6]. NAFLD is the commonest cause of liver disease in western countries. In the United States, it is estimated to affect between 3% and 40% of the population, especially among young people [7,8]. Moreover, NAFLD is predicted to become the leading cause of liver transplantation over the next 10 years [9]. Fatty liver is often seen in AP patients because both diseases share contributing factors such as diabetes mellitus type 2, hyperlipidemia, and obesity [10]. The death rate of severe acute pancreatitis has not declined significantly in the past few decades [11]. Therefore, the early diagnosis and accurate prediction of AP severity are still of great importance. Fatty liver has been positively associated with the risk of AP, but whether fatty liver is associated with the severity of AP remain unknown.

So far, no meta-analysis has investigated the influence of fatty liver on severity and outcomes of AP. Therefore, we performed the meta-analysis to examine this issue.

2. Methods

2.1. Search strategy and definitions

A comprehensive literature search of the electronic databases Pubmed, EMBASE, and Cochrane library was performed up to June 2017. Search keywords are ("Fatty liver" OR "Steatohepatitis" OR "Steatohepatitides" OR ″ Steatosis of Liver" OR ″ Visceral Steatosis" OR ″ Visceral Steatoses" OR "Liver Steatosis" OR "Liver Steatoses") AND ("Pancreatitis" OR "Pancreatitides"). Reference lists in the included studies were also searched manually to identify potential studies. AP

* Corresponding author.
E-mail address: shiyongxc3522@163.com (Y. Shi).

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Table 1
General characteristics of included studies.

Study	Study type	Country	Study population	Year	Cases (n) FLAP/ NFLAP	Sex (M/F)	APACHE-II Score FLAP /NFLAP	Patient inclusion time	NOS score
Yoon et al.	Re	Korea	M&W	2017	67/133	119/81	NR	July 2009 and June 2016	7
Xu et al.	Re	China	M&W	2015	480/2091	1590/ 1081	7.0 (4.0–12.5)/4.5 (2.0–7.5)	January 2000 and June 2014	6
Mikolasevic et al.	Re	Croatia	M&W	2016	198/624	402/420	8.4 ± 4.1/7.2 ± 4	January 1st, 2008 and June 30th, 2015	6
Wang et al.	Re	China	M&W	2015	60/60	60/60	NR	August 2012 and August 2014	6

Abbreviations: Re, retrospective; NR, not reported; M&W, male and female; FLAP, fatty liver related acute pancreatitis; NFLAP, non-fatty liver related acute pancreatitis; M, male; F, female; AP, acute pancreatitis; APACHE-II: acute physiology and chronic health evaluation; NOS, Newcastle-Ottawa Scale.

was defined as the following three points: 1) abdominal pain characteristic of AP; 2) serum amylase and/or lipase values of more than three times the upper limit of normal; 3) characteristic findings of AP on the CT scan. According to the 2012 revision of the Atlanta classification and definitions by international consensus, the severity of AP was defined as the following three degrees: mild AP (MAP), moderately severe AP (MSAP), and severe AP (SAP) [12]. The MAP was defined as a diagnosed AP without organ failure and local or systemic complications. Patients were diagnosed as MSAP if remote organ failure was relieved within 48 h and/or local or systemic complications without persistent organ failure. Patients were classified as SAP if persistent organ failure (single or multiple) was present for more than 48 h [12]. According to etiology, fatty liver disease can be classified as alcoholic fatty liver disease (ALFLD) and nonalcoholic fatty disease (NAFLD). ALFLD is a type of alcoholic liver disease, which is caused by long-term heavy drinking. Patients have a long history of drinking, usually more than 5 years. Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome characterized by excessive fat deposition in hepatocytes. The etiology should be excluded from alcohol and other definite liver-damaging factors. NAFLD include simple fatty liver (SFL), nonalcoholic steatohepatitis (NASH) and related cirrhosis. Fatty liver (FL) was defined as a liver/spleen ratio < 1.0 and classified into mild FL (liver/spleen ratio > 0.7 and < 1.0), moderate FL (liver/spleen ratio > 0.5 and 0.7), and severe FL (liver/spleen ratio 0.5) [13]. SIRS was defined by presence of the following two or more criteria: 1) heart rate > 90 beats/min; 2) core temperature < 36 °C or > 38 °C; 3) white blood count < 4000 or > 12000/mm3; 4) Respirations > 20/min or $PCO_2 < 32$ mm Hg [12]. The local complications of acute pancreatitis include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis. A systemic complication is defined as the exacerbation of pre-existing co-morbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis. Organ failure is defined as a score of 2 or more for one of the three organ systems (respiratory, cardiovascular and renal) using the modified Marshall scoring system [14]. According to the World Health Organization (WHO) Western Pacific Region, patients were categorized as obese state when BMI ≥ 25 kg/m^2 [15]. The work has been reported in line with PRISMA and AMSTAR guidelines.

2.2. Selection criteria

(一) Inclusive criteria

The selection criteria were defined according to the population, intervention, comparison, outcome and study design (PICOS) framework.

(1) population: participants with fatty liver-related acute pancreatitis and patients with non fatty liver-related acute pancreatitis.
(2) intervention: patients with fatty liver-related acute pancreatitis.
(3) comparison: patients with non fatty liver-related acute pancreatitis were considered (control).
(4) outcomes: endpoints included at least one of the following: moderately severe AP, severe AP, SIRS, local complications, systemic complications, and organ failure.
(5) study design: any comparative studies, such as case-control studies or cohort studies were included. The most recent studies, the most samples, and the quality studies that included reports with the same patients were included.

(二) Exclusive criteria

(1) Studies irrelevant to our topics were excluded.
(2) Non-English and non-human studies were excluded.
(3) Studies with data that were incomplete or could not be combined were excluded.
(4) Narrative reviews, systematic reviews and meta-analysis were excluded.
(5) Studies not in accordance with the revised Atlanta diagnostic criteria of the severity of AP were excluded.

2.3. Data extraction

A data extraction table was set up to enter data from each study, including author, year, country, patient number, APACHE-II score, clinical outcomes, Newcastle-Ottawa Scale (NOS) score, etc. (Table 1). The NOS score was used to assess the quality of the included studies. Two authors (Q.W and G.W) independently assessed the quality of the studies, extracted data carefully and compared the results to avoid bias. A consensus decision was made regarding any discrepancies by the third investigator (X.H).

2.4. Quality assessment

We used the NOS score to assess the study quality [16]. The included studies will be judged from the following three aspects: the selection of the study groups; the comparability of the groups and the ascertainment of outcome of interest. The range of NOS is 0–9 points. In this study, we defined a high-quality study achieving 6 or more points. Two authors (Q.W and C.L) independently assessed the quality of the studies.

2.5. Statistical analysis

We conducted the meta-analysis using STATA version 12.1 (STATA Corporation, College Station, TX). Heterogeneity was detected using the I^2 statistic (25%, 50% and 75% indicated low, moderate and high heterogeneity, respectively) [17]. In this analysis, $I^2 < 50\%$ indicated low heterogeneity, and $I^2 > 50\%$ indicated substantial heterogeneity. Egger's regression plot and Begg's test were used to evaluate the risk of publication bias [18]. Subgroup analyses were carried out according to obesity and cause of pancreatitis. Weighted mean differences (WMD, for continuous data) and odds ratios (OR, for event-related data) were

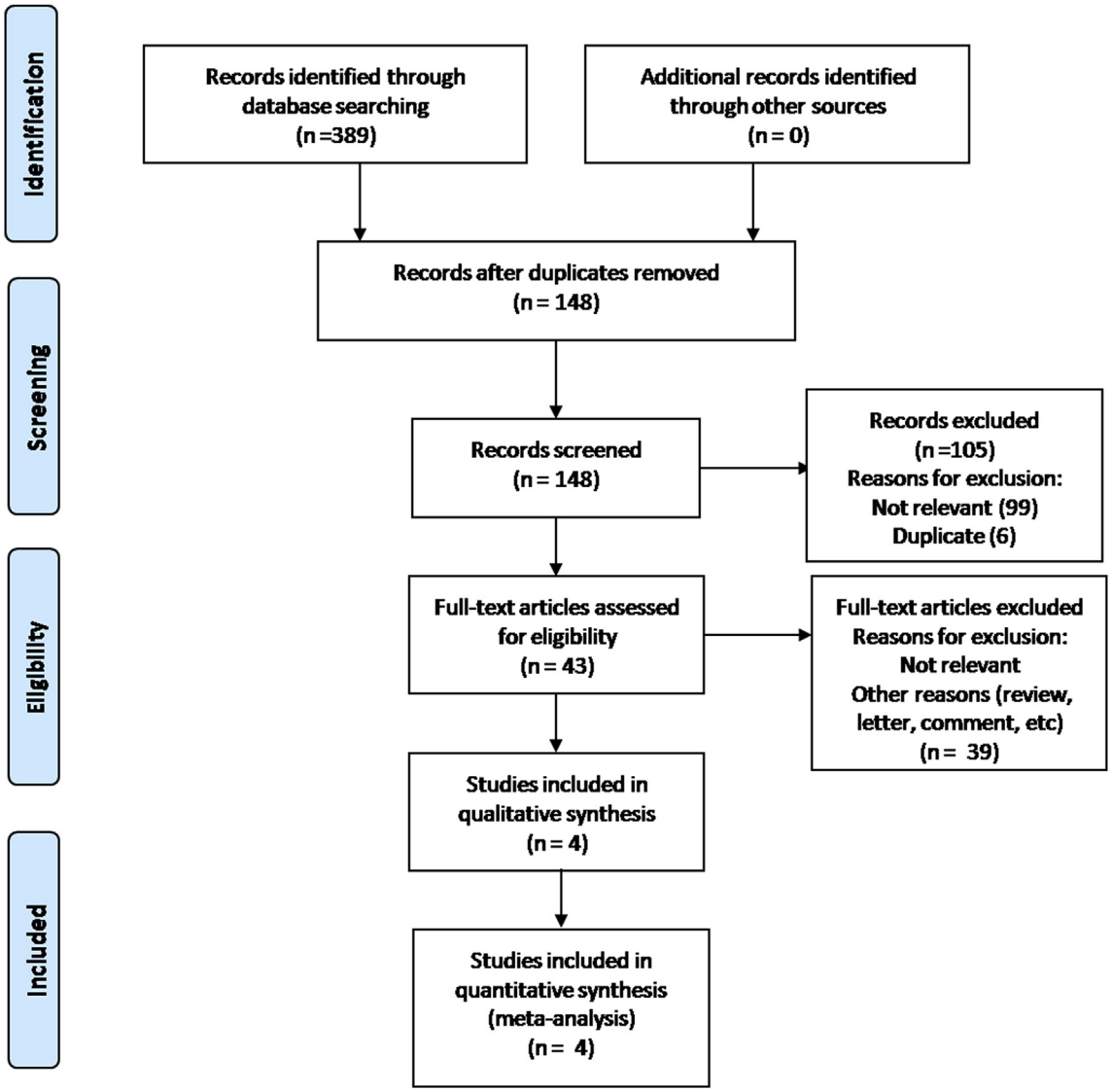

Fig. 1. Flowchart of the process of identifying relevant studies.

used to express the estimates in this study. A random-effect model was used if there was marked heterogeneity between studies.

3. Results

3.1. Literature selection

Fig. 1 shows the process of identifying eligible studies. A total of 389 studies was initially identified for the meta-analysis. Two hundred and forty-one studies were excluded for duplication and 148 were selected for the further consideration. Among them, 105 studies were excluded after reviewing the titles and abstracts, and 39 studies were excluded after reviewing the full-text articles. After the final screening, 4 published studies met the predetermined inclusion criteria [10,13,19,20]. The characteristics of the included studies are listed in Table 1.

3.2. Quality assessment of included studies

The NOS tool was used to assess the quality of the included studies and the study with NOS score of 6 or higher was defined as a high-quality study, while the study with 5 or less score was considered as low-quality study. According to the results of the quality assessment, the score of individual studies ranged from 6 to 7, indicating all the included studies were of acceptable quality (Supplementary Table 1).

3.3. Comparison of characteristics in AP patients with and without fatty liver

A total of 4 studies assessed the effect of fatty liver on the prognosis of AP. The results of the different outcomes variables of FLAP and NFLAP groups, including APACHE II score, systemic complications, local complications, persistent organ failure, overall length of hospital stay and mortality, are shown in Table 2. The incidences of persistent organ failure (OR = 2.32, 95% CI: 1.36–3.96) and systemic complications (OR = 3.60, 95% CI: 2.91–4.44) were higher in the FL group than those in non-FL group, as well as the incidence of SIRS (OR = 2.82, 95% CI: 2.3–3.47) and metabolic disturbance (OR = 3.90, 95% CI: 3.09–4.91). Moreover, higher levels of C reactive protein at day three (WMD = 0.65, 95% CI: 0.083–1.22) and higher mortality (OR = 4.16, 95% CI: 2.57–6.73) were found in FL group than in non-FL group. According to the 2012 revision of the Atlanta classification, local complications were comprised of acute peripancreatic fluid collection, pancreatic pseudocyst and acute necrotic collection. The pooled analysis showed the incidences of local complications were still higher in the FL group than in non-FL group. However, there were no differences between FLAP and NFLAP groups in age (WMD = -0.16, 95% CI:

Table 2
Meta-analysis of different outcomes variables.

Variable	Included studies	Patients (n) FLAP/NFLAP	OR/WMD	95% CI	*P* value	P_h	I^2(%)
Age (year)	4	805/3008	−0.16[a]	−0.36,0.23	0.127	0.007	75.5%
Sex (male)	4	805/3008	0.99[b]	0.59, 1.68	0.981	< 0.01	84.9%
BMI(kg/m^2)	4	805/3008	1.42[a]	0.66,2.17	< **0.001**	< 0.01	98.2%
Obesity	2	547/2324	2.38 [b]	1.36,4.16	**0.002**	0.077	68.1%
Diabetes	2	678/2815	1.69 [b]	0.65,4.43	0.285	0.001	90.5%
Serum triglyceride (mg/dL)	2	547/2324	0.60[a]	−0.01,1.22	0.053	< 0.01	93.5%
CRP (mg/dl) — at admission	3	745/2948	1.14[a]	−1.01,3.29	0.298	< 0.01	99.8%
CRP (mg/dl) — at day three	2	265/757	0.65[a]	0.083,1.22	**0.025**	0.001	90.7%
APACHE II score	2	678/2815	0.96[a]	−0.34,2.27	0.147	< 0.01	99.4%
Systemic complications	2	547/2324	3.60 [b]	2.91,4.44	< **0.001**	0.452	0
Persistent organ failure (> 48 h)	3	325/817	2.32 [b]	1.36,3.96	**0.002**	0.257	26.4%
Respiratory failure	2	540/2251	3.43 [b]	2.76,4.26	< **0.001**	0.75	0
Mortality	2	547/2324	4.16 [b]	2.57,6.73	< **0.001**	0.40	0
SIRS	2	540/2251	2.82 [b]	2.3,3.47	< **0.001**	0.964	0
Metabolic disturbance	2	540/2251	3.90 [b]	3.09,4.91	< **0.001**	0.686	0
Pancreatic necrosis	2	547/2324	3.05 [b]	1.74,5.36	< **0.001**	0.227	31.6%
Duration of hospitalization (days)	2	547/2324	0.27[a]	0.13,0.41	< **0.001**	0.779	0
Etiology							
Alcohol-induced pancreatitis	3	607/2384	1.61 [b]	1.15,2.25	**0.006**	0.254	26.9%
Gallstone pancreatitis	3	738/2875	0.57 [b]	0.39,0.82	**0.002**	0.086	59.2%
Hyperlipidemic pancreatitis	3	738/2875	2.35 [b]	1.53,3.61	< **0.001**	0.235	30.9%
Severity by revised Atlanta classification							
Mild	3	745/2948	0.28 [b]	0.18,0.42	< **0.001**	0.021	74.2%
Moderately severe	3	745/2948	2.72 [b]	1.82,4.05	< **0.001**	0.033	70.8%
Severe	4	805/3008	3.57 [b]	2.06,6.18	< **0.001**	0.009	73.9%
Local complications							
Acute necrotic collection	2	265/757	3.45 [b]	1.87,6.36	< **0.001**	0.150	51.7%
Peripancreatic fluid collection	2	265/757	4.10 [b]	3.01,5.57	< **0.001**	0.535	0
Pancreatic pseudocyst	2	265/757	2.79 [b]	1.65,4.72	< **0.001**	0.488	0

Abbreviations: P value: P value for the overall effect; P_h: P value for heterogeneity; SIRS, systemic inflammatory response syndrome; BMI, body mass index; OR: odds ratio; HR: hazard ratio; Bold text indicates statistical significance. Obesity: BMI ≥ 25 kg/m^2, CRP: C-reactive protein; APACHE-II acute physiology and chronic health evaluation score; FLAP, fatty liver related acute pancreatitis; NFLAP, non-fatty liver related acute pancreatitis.

[a] Weighted mean differences (WMD) were used to express the continuous data.

[b] Odds ratios (OR) were used to express the event-related data.

0.36–0.23, $P = 0.127$), sex (WMD = 0.99, 95% CI: 0.59–1.68, $P = 0.981$), diabetes status (OR = 1.69, 95% CI: 0.65–4.43, $P = 0.285$), serum triglyceride (WMD = 0.60, 95% CI: 0.01-1.22, $P = 0.053$) and APACHE-II score (WMD = 0.96, 95% CI: 0.34–2.27, $P = 0.147$) (Table 2).

3.4. Comparison of severity in AP patients with and without fatty liver

Based on the 2012 revision of the Atlanta classification, the severity of AP was subdivided into three types: mild AP (MAP), moderately severe AP (MSAP), and severe AP (SAP). The incidences of MSAP and SAP were still higher in the FL group than those in non-FL group (OR = 3.57, 95% CI: 2.06–6.18, $P < 0.001$; OR = 2.72, 95% CI: 1.82–4.05, $P < 0.001$, respectively) (Fig. 2A and B). However, the incidences of MAP in the FL group were lower than non-FL group (OR = 0.28, 95% CI: 0.18–0.42, $P < 0.001$) (Fig. 3).

3.5. Subgroup analysis according to obesity

When sub-classified the AP patients according to the occurrence of obesity, a worse prognosis was found both in obese patients and non-obese patients with FL. Specifically, in obese patients, the incidences of MSAP (pooled HR = 2.91, 95% CI: 1.98–4.26) and SAP (pooled HR = 1.70, 95% CI: 1.14–2.53) were significantly higher in FL group than in non-FL group. In contrast, the incidence of MAP in the FL group was less frequent than non-FL group (pooled HR = 0.31, 95% CI: 0.19–0.50). Similarly, in non-obese patients, the incidences of MSAP and SAP were still higher in the FL group than those in non-FL group. The odds ratio of MSAP was 1.87 (95% CI: 1.40–2.48), and SAP was 3.30 (95% CI: 2.23,4.89). But the incidences of MAP were higher in non-FL group than those in the FL group (pooled HR = 3.58, 95% CI: 1.45–8.87). In AP patients with FL, whether obese or not, the incidences of MSAP and SAP were higher in patients with fatty liver than those without fatty liver (Table 3).

3.6. Subgroup analysis according to the cause of pancreatitis

It is well known that alcohol abuse is closely related to fatty liver. Therefore, subgroup analyses were done for cause of pancreatitis (alcoholic pancreatitis vs non-alcoholic pancreatitis). Strong trends in fatty liver and severity of AP were also CI: 0.68–1.50, P = 0.966), MSAP (OR = 0.92, 95% CI: 0.60–1.39, P = 0.685) and SAP observed regardless of the cause of pancreatitis. The incidences of MAP (OR = 1.01, 95% (OR = 1.13, 95% CI: 0.67–1.91, P = 0.644) were comparable between alcoholic pancreatitis group and non-alcoholic pancreatitis group (Table 3).

4. Discussion

In the present study, we mainly investigated the prognostic impact of fatty liver on the prognosis of acute pancreatitis by the method of meta-analysis. According to the revised Atlanta classification, the severity of AP was subdivided into three types: mild AP (MAP), moderately severe AP (MSAP), and severe AP (SAP). And patients were classified as SAP if remote organ failure was present for more than 48 h [12]. Our results demonstrated that fatty liver could influence the severity and clinical outcome and may play a prognostic role in patients with AP. The incidences of MSAP and SAP were statistically significantly higher in the FLAP group than those in NFLAP group. Stratified analyses were performed, and significant results pertaining to the relationship of fatty liver to a worse prognosis were found in all subgroups on the basis of obesity and alcohol abuse. These findings suggest

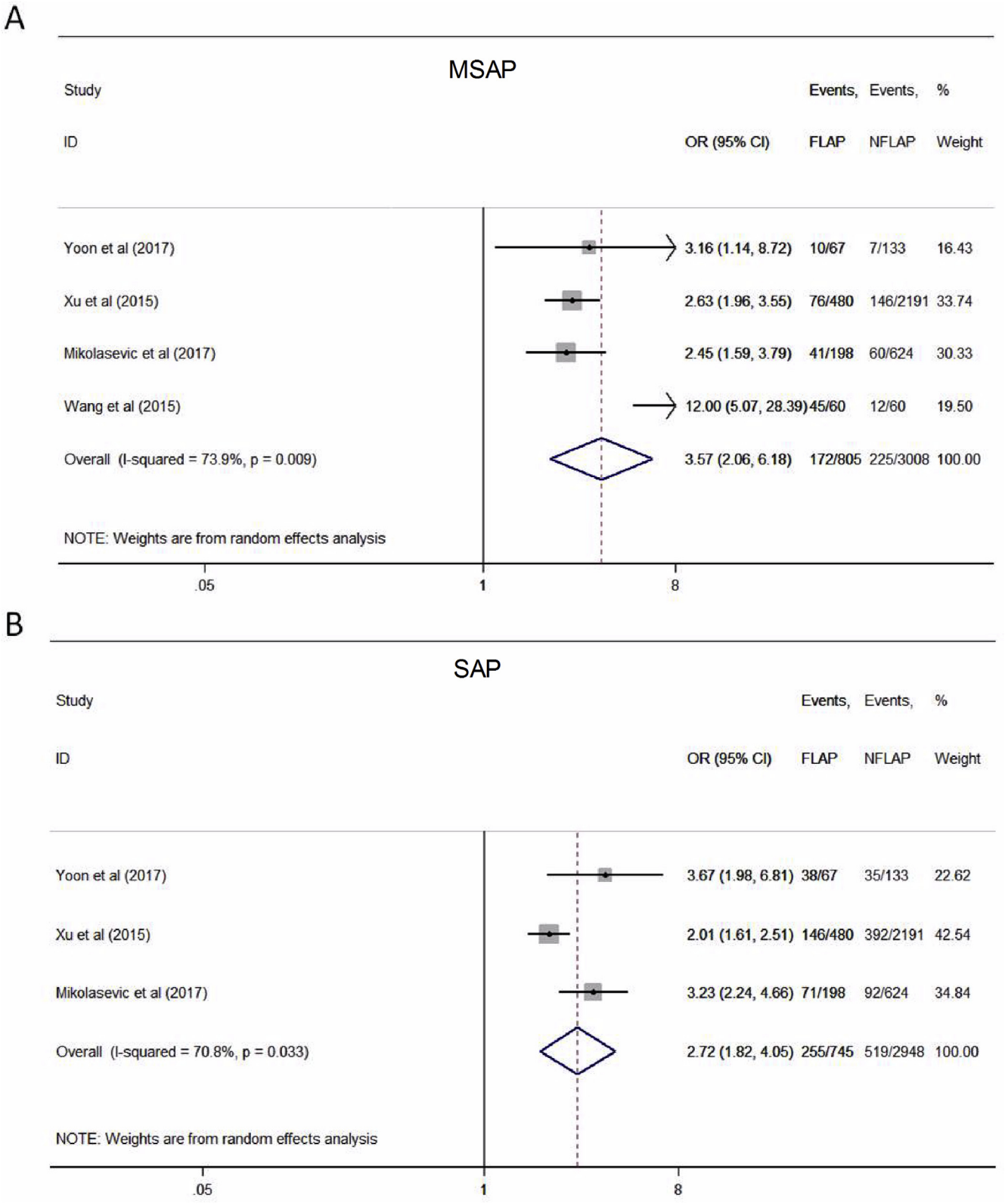

Fig. 2. Comparison of the incidences of MSAP (A) and SAP (B) between the FLAP group and NFLAP group. CI indicates confidence interval; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; FLAP, fatty liver-related acute pancreatitis; NFLAP, non fatty liver-related acute pancreatitis; OR, odds ratio.

that fatty liver by itself may be an independent risk factor for severe clinical course of AP. In addition, the meta-analysis also demonstrated that a higher mortality in FLAP group than in NFLAP group, as well as the occurrence of SIRS and local complications. To our knowledge, this is the first meta-analysis to show that fatty liver is significantly related with the severity of AP.

The mechanisms by which fatty liver aggravating pancreatitis has not been elucidated so far, however, several pathogenetic theories have been proposed. Fatty liver is commonly accompanied with hyperlipidemia, which would induce free radical accumulation, microcirculatory

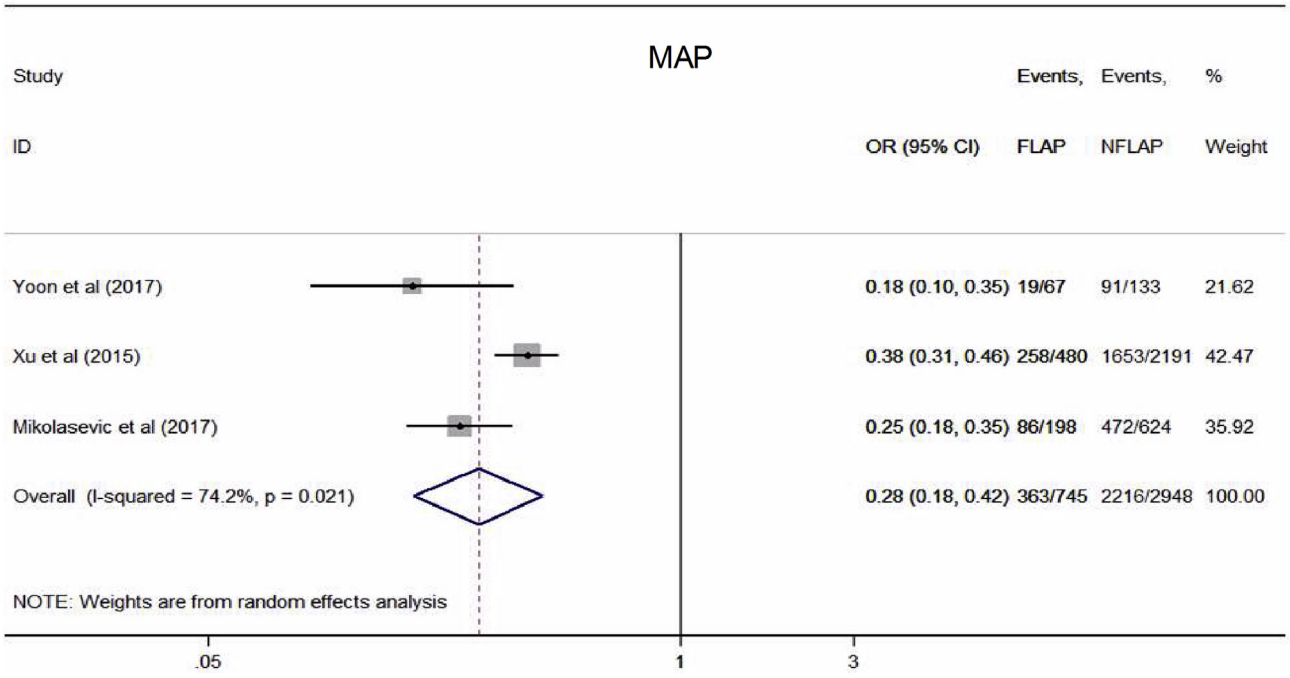

Fig. 3. Comparison of the incidences of MAP between the FLAP group and NFLAP group. CI indicates the confidence interval; MAP, mild acute pancreatitis; FLAP, fatty liver-related acute pancreatitis; NFLAP, non fatty liver-related acute pancreatitis; OR, odds ratio.

Table 3
Subgroup analysis according to BMI and the cause of pancreatitis.

Subgroups	Patients (n)	OR (95% CI)	P_0	P_h	I^2(%)
BMI ≥ 25 kg/m^2	1050				
Fatty liver	272				
Mild	125	0.31 (0.19,0.50)[a]	< **0.001**	0.245	26.0%
Moderately severe	103	2.91 (1.98,4.26)[a]	< **0.001**	0.292	9.8%
Severe	44	1.70 (1.14,2.53)[a]	**0.009**	0.504	0
Nonfatty liver	778				
Mild	570	3.25 (1.98,5.33)[a]	< **0.001**	0.245	26.0%
Moderately severe	129	0.34 (0.23,0.50)[a]	< **0.001**	0.292	9.8%
Severe	79	0.59 (0.39,0.88)[a]	**0.009**	0.504	0
BMI < 25 kg/m^2	1821				
Fatty liver	275				
Mild	141	0.28 (0.11,0.69)[a]	**0.006**	0.066	70.5%
Moderately severe	89	1.87 (1.40,2.48)[a]	< **0.001**	0.409	0
Severe	45	3.30 (2.23,4.89)[a]	< **0.001**	0.799	0
Nonfatty liver	1546				
Mild	1157	3.58 (1.45,8.87)[a]	**0.006**	0.066	70.5%
Moderately severe	306	0.54 (0.40,0.71)[a]	< **0.001**	0.409	0
Severe	83	0.30 (0.20,0.45)[a]	< **0.001**	0.799	0
Alcoholic pancreatitis vs non-alcoholic pancreatitis	156				
Mild	76	1.01 (0.68,1.50)[a]	0.966	0.918	0
Moderately severe	54	0.92 (0.60,1.39)[a]	0.685	0.992	0
Severe	26	1.13 (0.67,1.91)[a]	0.644	0.922	0

Abbreviations: MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; BMI, body mass index. I^2, I^2 value for heterogeneity within each subgroup; P_h, P value for heterogeneity between subgroups; Po, test for over effect.

[a] Odds ratios (OR) were used to express the event-related data.

disturbances, oxidative stress, and acinar necrosis in AP [21–23]. Hyperlipidemia may reduce red blood cell velocity, resulting in the increase of hemoglobin-oxygen affinity in the microcirculation, which may further aggravate tissue hypoxia [24]. The interstitial release of triglyceride degradation products and increasing free radical accumulation may exacerbate cellular disruption [21]. A recent study suggested that PPARα signalling pathway and fatty acid degradation pathway was involved in the pathological process of APFL, which indicated that fatty liver could aggravate pancreatitis through these pathways [25].

In addition, a chronic proinflammatory state in fatty liver patients may aggravate the course of AP. Our previous studies showed that, in rat and human AP models, fatty liver depressed alpha1-antitrypsin levels, which have significant anti-inflammatory properties due to their effects on a wide range of inflammatory cells such as neutrophils, monocytes, macrophages, and mast cells [20]. Thus decrease of serum AAT levels may lead to the excessive activation of inflammation. Furthermore, our pooled results showed that the occurrence of SIRS in FLAP patients was significantly higher than in NFLAP patients. Therefore, excessive SIRS response may be one of the mechanisms by which fatty liver aggravates pancreatitis.

Over that last few decades, many biomarkers and clinical scoring

systems, such as the Glasgow, APACHE II and Ranson scoring systems, have been developed and validated to monitoring changes in AP patients [13]. However, a fast, simple and accurate method is still necessary for the early evaluation of potential SAP, particularly in an emergency room [13]. Fatty liver may be confirmed as a risk factor for a more severe form of AP, and can be measured at the very early stage. In view of the significant difference in clinical outcomes between patients with FLAP and patients with NFLAP, it is important for clinicians to identify these high-risk patients. Patients with fatty liver presenting with AP should be given more active symptomatic treatment and should be strictly monitored.

This meta-analysis has potential limitations. The researches on the prognostic role of fatty liver in AP are relatively limited and the sample sizes of eligible studies in our study are relatively small. However, the findings of this meta-analysis are of clinical significance. The findings of this meta-analysis need to be confirmed by more well-designed and large-scale investigations.

To summarise, we have found that fatty liver is associated with the severity of acute pancreatitis, which would be helpful for clinicians to identify these high-risk patients.

Data statement

We declare that submitted manuscript does not contain previously published material, and are not under consideration for publication elsewhere. Each author has made an important scientific contribution to the study and is thoroughly familiar with the primary data. All authors listed have read the complete manuscript and have approved submission of the paper. The manuscript is truthful original work without fabrication, fraud or plagiarism. All authors declare that there are no conflicts of interest.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Disclosure of potential conflicts of interest

The authors disclose no potential conflicts of interest.

Ethical approval

The ethical approval was given by the ethics committee of fourth military medical university.

Sources of funding

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Authors' contributions

SH participated in the design of this study, XYT and HXC acquired the data and performed the analysis, CXL contributed to the data analysis, YS revised and drafted the paper.

Conflicts of interest

The authors disclose no potential conflicts of interest.

Research registration number

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.04.003.

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