Metabolic liver diseases in patients with acute pancreatitis: implications for disease management

PhD Thesis

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1. List of abbreviations:

ALD	alcoholic liver disease (ALD)
ANC	acute necrotic collection
AP	acute pancreatitis
APFC	acute peripancreatic fluid collection
BISAP	Bedside Index for Severity in Acute Pancreatitis
CAP	controlled attenuation parameter
CI	confidence interval
CRP	C-reactive protein
CT	computed tomography (CT)
CTSI	Computed Tomography Severity Index
EASL	European Association for the Study of the Liver
HCC	hepatocellular carcinoma (HCC
HPSG	Hungarian Pancreatic Study Group
IAP/APA	International Association of Pancreatology/ American Pancreatic Association
IQR	interquartile range
LOH	length of hospitalization
MAFLD	metabolic-associated fatty liver disease
MAP	moderate acute pancreatitis
MRI	magnetic resonance imaging (MRI)
MRS	Magnetic resonance spectroscopy (MRS)
MRSI	Magnetic Resonance Severity Index
MSAP	moderate-to-severe (MSAP)
MSAP	moderate-to-severe acute pancreatitis
NAFL	non-alcoholic fatty liver (NAFL
NAFLD	non-alcoholic fatty liver disease (NAFLD)
NASH	non-alcoholic steatohepatitis (NASH).
OR	odds ratio
PP	pancreatic pseudocyst
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QUIPS	Quality in Prognosis Studies
SAP	severe acute pancreatitis
SD	standard deviation

SIRS	systemic inflammatory response syndrome
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
T2DM	type 2 diabetes mellitus
VIF	Variance Inflation Factor
WMD	weighted mean difference

2. Vision

To reduce the incidence and severity of metabolic-associated fatty liver disease (MAFLD) and acute pancreatitis by identifying the underlying mechanisms contributing to their association and developing effective patient prevention and treatment strategies.

3. Mission

Our research aims to identify the biological and clinical factors contributing to the association between MAFLD and acute pancreatitis and determine the mechanisms that underlie the more severe course of acute pancreatitis in patients with MAFLD. We will achieve this through a comprehensive analysis of a prospectively collected international registry and by reviewing the current literature, utilizing cutting-edge technologies to investigate the role of the gut-liver axis, inflammation, and metabolic dysregulation in the pathogenesis of these diseases. Our ultimate goal is to develop evidence-based guidelines for the prevention and management of MAFLD and acute pancreatitis and to improve the outcomes and quality of life of patients affected by these diseases.

4. Specific goals

- To investigate the current knowledge about the association of non-alcoholic fatty liver disease on the course of acute pancreatitis.
- To investigate the prevalence of metabolic-associated fatty liver disease (MAFLD) in patients with acute pancreatitis and to determine the impact of MAFLD on the severity and clinical course of acute pancreatitis.
- To provide models for the early detection of patients with MAFLD who are at high risk of developing severe acute pancreatitis.
- To develop recommendations for preventing and managing MAFLD and acute pancreatitis and to disseminate this knowledge to healthcare providers and patients worldwide.

5. Background

5.1. What is the topic

5.1.1. Acute pancreatitis

Acute pancreatitis (AP) is a severe gastrointestinal disorder that affects a significant number of people worldwide, with an estimated incidence rate of 23-49 per 100,000 individuals every year (1, 2). This highlights the scale of the problem and its impact on public health. Unfortunately, AP is associated with high levels of mortality and morbidity, making it a significant concern.

While the disease course is usually mild in most cases, affecting 70-75% of patients, it can still cause significant discomfort and requires medical attention (3, 4). However, for the remaining 25-30% of cases, the condition becomes moderate-to-severe (MSAP) and can lead to a high mortality rate, with some instances reaching 50% (3). This emphasizes the critical importance of early diagnosis and appropriate management of AP to prevent its progression to MSAP and reduce the risk of complications. It is essential to ensure that patients receive prompt and effective treatment to prevent further complications and improve their chances of recovery.

Acute pancreatitis is a challenging gastrointestinal disease for many reasons:

1. We do not have a specific therapy (5, 6).
2. Research activity decreasing on the topic (7).
3. The yearly incidence rate is increasing, especially in Hungary (1).
4. The contributing factors to disease development are still not fully understood (8).
5. There are still questions regarding the disease development (9).
6. The mortality rate and the rate of local or systemic complications are high (3).

5.1.2. Fatty liver disease

Fatty liver disease, also known as hepatic steatosis, is a medical condition characterized by an accumulation of excess fat in the liver. There are two types of fatty liver disease: non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). Both ALD and NAFLD are serious health concerns, and their incidence is on the rise every decade (10).

ALD is primarily caused by heavy and prolonged alcohol consumption, with more than 90% of heavy drinkers developing fatty liver, while about 25% develop the more severe alcoholic hepatitis (11). Alcohol abuse is responsible for about 4% of all deaths annually and 5% of all disabilities worldwide (12). However, the incidence of NAFLD is increasing due to the prevalence of obesity, diabetes, and metabolic syndrome.

The treatment options for ALD have not changed much in the past few decades, with abstinence being the cornerstone of therapy, supported by nutritional interventions and steroids. Unfortunately, alcoholic hepatitis, the most severe manifestation of ALD, has a short-term mortality rate of up to 50% in patients who are unresponsive to corticosteroid treatment (13). Moreover, patients who are steroid non-responders or have contraindications to steroid use (such as upper gastrointestinal bleeding, impaired renal function, and sepsis) have limited treatment options available.

ALD and AP share a common etiology, namely alcohol abuse. According to a prospective acute pancreatitis registry, alcohol abuse was a contributing factor in 25% of cases (14). As a result, alcoholic AP patients typically present with some degree of ALD.

5.1.3. NAFLD

Introducing NAFLD is crucial as its incidence and prevalence are increasing with each passing decade. Currently, NAFLD affects approximately 25%-35% of the general population in Western countries and 5%-15% of the population in Asian countries (15). However, these numbers are even higher in people with type 2 diabetes, obesity, or morbid obesity, where the prevalence ranges from 60%-70% and 75%-92%, respectively, compared to the general population (16).

The prevalence of obesity in the United States has been on the rise and has increased from 10% to 60% in the last three decades (16), which is considered one of the primary factors contributing to the increasing prevalence of NAFLD. This disease has been associated with a high-calorie diet, excess consumption of saturated fats, refined carbohydrates, sugar-sweetened beverages, high fructose intake, and a Western diet, all of which can lead to weight gain and obesity (17).

NAFLD is defined by evidence of fatty liver without other factors that could explain the accumulation of liver fat, such as excessive alcohol use (>21 standard drinks/week for men and >14 for women in the USA; >30 g daily for men and >20 g for women in UK and EU), chronic viral hepatitis, or drug-induced steatosis (18, 19). The

term NAFLD covers a spectrum of liver abnormalities ranging from non-alcoholic fatty liver (NAFL, simple steatosis) to non-alcoholic steatohepatitis (NASH). These diseases begin with fatty accumulation in the liver

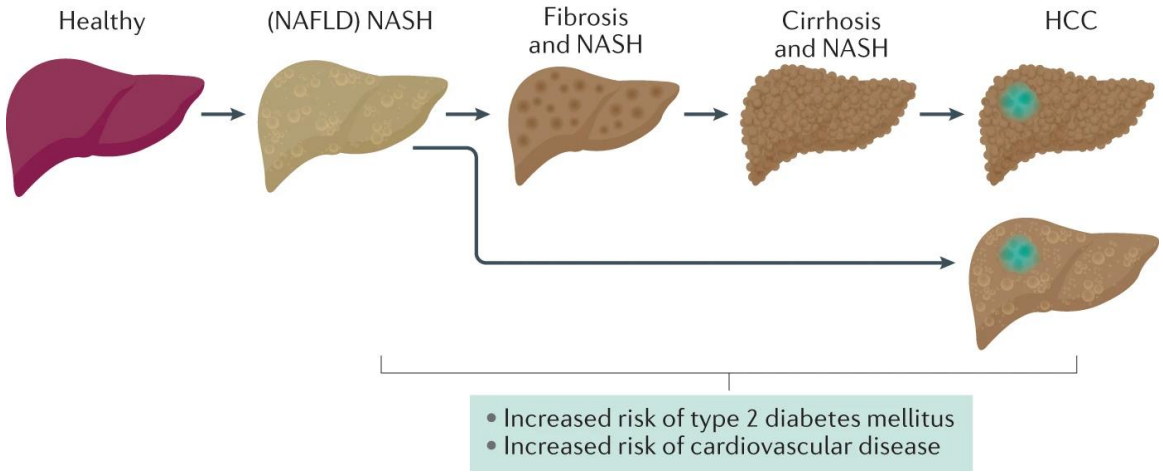

Figure 1. Shows the spectrum of NAFLD, starting from NASH to HCC (20).

(hepatic steatosis), which can remain fatty without disturbing liver function (NAFL). However, by various mechanisms and possible insults to the liver, it can progress into non-alcoholic steatohepatitis (NASH), a state in which steatosis is combined with inflammation and sometimes fibrosis (steatohepatitis). NASH can then lead to complications such as cirrhosis and hepatocellular carcinoma (HCC) (21). Therefore, early detection and management of NAFLD are crucial to prevent its progression to more severe liver diseases.

5.1.4. MAFLD

Most guidelines and recent publications currently define NAFLD as the presence of steatosis in over 5% of hepatocytes in the absence of significant alcohol consumption or other known causes of liver disease (18). However, Eslam et al.(22) proposed a new set of "positive" criteria for the diagnosis of MAFLD that does not rely on alcohol consumption or concomitant liver diseases. These criteria are based on evidence of fat accumulation in the liver through histological (biopsy), imaging, or blood biomarkers in addition to meeting one of three criteria: overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation (**Figure 1**).

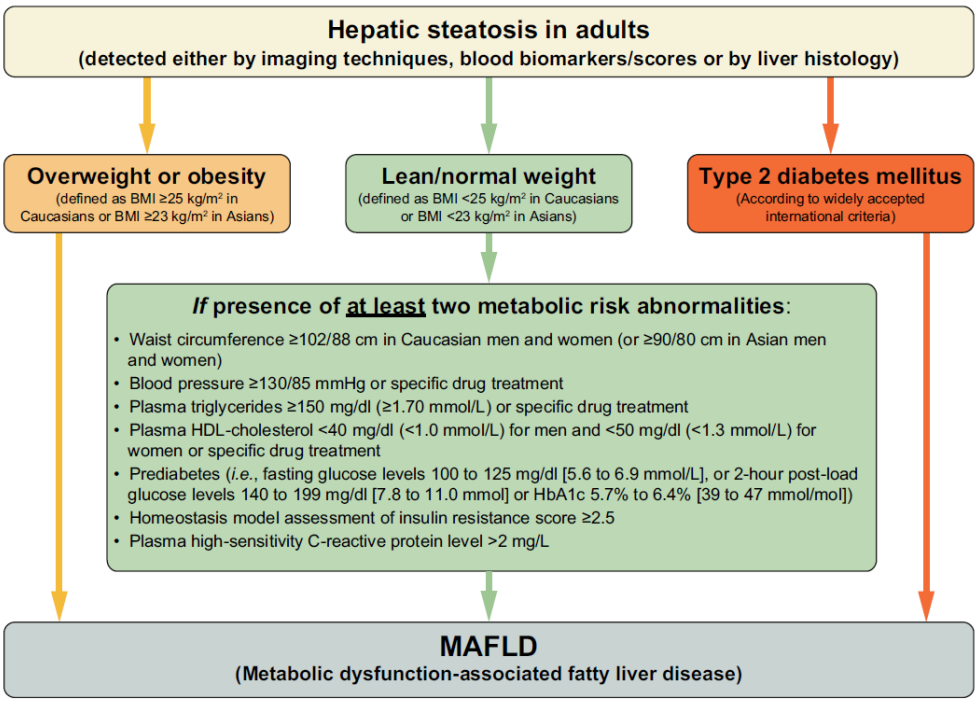

Figure 2. The proposed diagnostic criteria for MAFLD can be represented by a flowchart, outlining the steps required for a positive diagnosis (18).

Metabolic dysregulation is defined as the presence of at least two metabolic risk abnormalities. A flowchart outlining these proposed diagnostic criteria can be seen in **Figure 1**.

To detect steatosis, ultrasound is the most widely used diagnostic tool, recommended as the first-line modality. However, it should be noted that ultrasound has limited sensitivity and cannot reliably detect steatosis below 20%, and may not perform well in individuals with a BMI above 40 kg/m2. Vibration-controlled transient elastography (FibroScan) can be used to measure the controlled attenuation parameter (or similar) and is increasingly used in routine clinical practice, with an area under the receiver operating-characteristic curve of 0.87 for steatosis using biopsy as the reference standard (23). If available, computed tomography (CT) or magnetic resonance imaging (MRI) can be used to diagnose moderate and severe steatosis. Magnetic resonance spectroscopy (MRS) provides a quantitative estimate of liver fat, but it is expensive, has limited availability, and requires special software. As a result, MRI-derived proton density fat fraction is generally preferred in clinical trials as it is more practical and closely agrees with MRS (24).

5.2.Why is it important

Acute pancreatitis (AP) is a complex disease requiring a multidimensional approach to predict outcomes and manage complications accurately. Current guidelines recommend a comprehensive three-dimensional approach that considers host risk factors, clinical risk scores, and response to therapy. This approach is essential to stratify patients based on their risk and provide appropriate treatment to prevent complications (25, 26).

Host risk factors such as age, body mass index (BMI), and the presence of metabolic syndrome have been found to play a significant role in the progression of AP. Elderly patients over the age of 65 are at a higher risk of developing systemic complications (odds ratio - OR=8.93, 95% confidence interval - CI:1.20–66.80) (27), while abnormal BMI values, both >30 kg/m2 and <18.5 kg/m2, are associated with an elevated risk of mortality (OR=2.89, 95% CI: 1.10–7.36 and OR=1.82, 95% CI: 1.32–2.50, respectively) (28). The presence of metabolic syndrome can also significantly increase the harmful effects of each other on the course of AP, making it critical to identify and address these host risk factors for effective risk stratification and preventing complications in AP patients (29, 30).

Clinical risk scores such as the Bedside Index for Severity in Acute Pancreatitis (BISAP) score take into account various factors such as age, the presence of systemic inflammatory response syndrome, impaired mental status, and elevated blood urea nitrogen and serum lactate dehydrogenase levels, and can be used to predict outcomes in AP (25).

Monitoring the response to therapy is also crucial in predicting outcomes in AP (25). The persistence of systemic inflammatory response and elevated creatinine levels have been found to be associated with poor outcomes. Regular monitoring of these parameters can aid in assessing the response to therapy and the need for further intervention.

Despite these efforts, a significant number of patients with AP may still experience local or systemic complications, and a small percentage may die. Therefore, it is crucial to continue researching and developing new approaches to managing and preventing complications in AP patients.

5.3.What is the problem to solve

Our study group recently conducted a study that revealed some interesting findings regarding the relationship between FLD/ NAFLD and AP. Specifically, we found that both NAFLD and FLD independently increase the odds of MSAP with odds ratios of 3.39 (95% CI=1.52–7.56) and 3.68 (95% CI=2.16–6.29), respectively (31).

Despite the implications of these findings, NAFLD is not currently included in risk stratification. In 2020, Eslam et al.(22) proposed new diagnostic criteria for NAFLD and renamed it MAFLD based on steatosis and metabolic factors. While MAFLD has been shown to have a prognostic role in other acute diseases, its role in AP has not yet been studied (32).

Given the relationship between NAFLD and AP, MAFLD may have a similar effect on the development and prognosis of AP due to shared metabolic factors. However, further research is needed to investigate the role of MAFLD in AP.

5.4.What will happen if the research is successful

Patients with AP accompanied by MAFLD/ NAFLD will be recognized more accurately and paid special attention during the management of AP.

By identifying the relationship between MAFLD and AP, we can improve risk stratification and develop appropriate management strategies for patients with AP and MAFLD. In addition, our findings underscore the importance of recognizing and addressing metabolic factors, such as MAFLD, in managing AP, which could potentially improve patient outcomes.

5.5. Objectives and hypotheses

This thesis describes the results of our **(1) systematic review with meta-analysis (31)** and **(2) registry analysis assessing the association between MAFLD and the course of AP (33)** with the following aims:

- To summarize the current evidence on the relationship between NAFLD and the course of AP.
- To investigate the prognostic role of MAFLD in the course of AP. We hypothesized that the course of AP would be more severe in the presence of MAFLD.
- To assess the different MAFLD types. We assumed different effects on AP.

6. Literature review of the current evidence on the relationship between NAFLD/ FLD and the course of AP

6.1. Materials and methods

Our research has been conducted in compliance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2009 Statement (34, 35), and it was updated based on the PRISMA 2020 statement (36), which provides a comprehensive checklist of items to be reported when conducting and publishing systematic reviews and meta-analyses. Adhering to the PRISMA guidelines ensures the transparency, reproducibility, and accuracy of our study.

In addition, our study protocol was registered in PROSPERO, an international database of prospectively registered systematic reviews, under the registration number CRD42019123416. The PROSPERO registration provides a comprehensive record of our study's design, objectives, and methods, as well as any amendments made during the study process. By registering our study protocol in PROSPERO, we have also demonstrated our commitment to transparency and reducing potential bias in our research. You can access the PROSPERO registration at https://www.crd.york.ac.uk/prospero.

6.1.1. Information sources

To identify relevant studies for our meta-analysis, we conducted a thorough and comprehensive systematic literature search in seven major medical databases. These databases include PubMed, EMBASE, Web of Science, CENTRAL, WHO global health library, Scopus, and ClinicalTrial.gov. We searched all of these databases from their inception up until the 13th of November 2019, using a well-defined search query: “pancreatitis AND (“fatty liver” OR FLD OR NAFLD OR steatohepatitis OR steatosis)”. We imposed no language or other restrictions in our search criteria, in order to capture all relevant studies.

In addition to the electronic database search, we manually searched for relevant review articles that were published in scientific journals. We also reviewed the bibliographic reference lists of all the studies that were included in our meta-analysis, to ensure that no relevant study was missed.

6.1.2. Search strategy

Our study focused on adult (>18 years) patients (P) who were diagnosed with acute pancreatitis (AP) due to various causes. Specifically, we investigated the impact of FLD or NAFLD (E) on patient outcomes compared to those without FLD or NAFLD (C). To be included in our analysis, eligible studies had to use either abdominal imaging techniques such as ultrasound, CT scan, MRI, or liver biopsy to define FLD or NAFLD. In cases of NAFLD, the amount of alcohol consumed also had to be defined. Our primary objective was to assess in-hospital and overall mortality, while secondary outcomes included the severity of AP, local complications such as acute peripancreatic fluid collection (APFC), acute necrotic collection (ANC), pancreatic pseudocyst (PP), systemic inflammatory response syndrome (SIRS), and the length of hospitalization (LOH).

We did not have any restriction on the diagnostic criteria for AP or for local or systematic complications. However, we assessed studies in different groups based on definitions.

To ensure a comprehensive evaluation of patient outcomes, we narrowed our focus to longitudinal studies. By examining studies that followed patients over an extended period, we were able to gain a better understanding of the impact of FLD and NAFLD on AP outcomes over time.

6.1.3. Selection process

In accordance with the guidelines outlined in the Cochrane Handbook (37, 38), our study followed a rigorous selection process. Two independent investigators, were responsible for identifying eligible studies using EndNote X7.4 (Clarivate Analytics, Philadelphia, PA, US). Duplicate publications were removed, and the remaining studies were screened based on their title and abstract. Any studies that met our pre-defined eligibility criteria, known as PECO (participants, exposure, comparison, and outcomes), were selected for full-text review by the same two reviewers. To ensure a comprehensive analysis, conference abstracts containing relevant data were also included in our review.

Any discrepancies or disagreements during the selection process were resolved by third-party arbitration. This ensured that our study's findings were based on high-quality and reliable data sources.

In cases where there were multiple publications on the same cohort of patients, we selected the most recent publication to avoid any duplication of data.

6.1.4. Data collection process and data items

Our study's data extraction process was conducted meticulously by two independent investigators. Both investigators used a pre-defined Excel datasheet (Office 365, Microsoft, Redmond, WA, US) to collect data from each eligible study. The information extracted included details such as the first author's name, publication year, study period, study design, demographic data, sample sizes, mean age, and the percentage of female participants. Additionally, any data necessary for assessing the risk of bias was also collected.

To conduct statistical analyses, we extracted raw data into 2 by 2 tables that contained information on the outcome of interest (yes or no) and the presence or absence of FLD or NAFLD. For each outcome, we calculated the odds ratio (OR) using the raw data collected with 95% confidence interval (CI). By examining the ORs for each outcome, we were able to assess the impact of FLD or NAFLD on patient outcomes.

To further analyze the data, we used the GetData Graph Digitizer 2.26 software (S. Fedorov 2013, Russia, http://getdata-graph-digitizer.com) to extract graphical data from the eligible studies. This allowed us to collect more detailed and nuanced information that could be used to draw more robust conclusions from the data.

6.1.5. Study risk of bias assessment

To assess the methodological quality of the included studies, we used the Quality in Prognosis Studies (QUIPS) tool - a critical appraisal tool designed specifically for prognostic studies (39). Our study employed two independent investigators, who were responsible for assessing the risk of bias in each eligible study. Any discrepancies or disagreements that arose during the appraisal process were resolved through discussion between the two reviewers or through consultation with a third investigator.

Due to the retrospective design of the included studies, we omitted the main domain "study attrition" and other items that did not fit our meta-analysis. This was necessary as retrospective studies have inherent limitations that may differ from those of prospective studies. However, we ensured that the remaining domains were evaluated thoroughly, including the study participants, the prognostic factors, the outcome measurements, the statistical analysis, and the overall risk of bias.

6.1.6. Synthesis methods

Our meta-analytical calculations were performed using two different software programs - Stata 15.1 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA) and Comprehensive Meta-Analysis (version 3, Biostat Inc., Englewood, NJ, USA). These calculations were carried out by a trained statistician.

To compare the outcomes of patients with FLD or NAFLD to those without FLD or NAFLD, we calculated pooled odds ratios (OR) with 95% confidence interval (CI) using the random-effects model with the DerSimonian–Laird method (40). Specifically, we used this model for the outcomes of in-hospital mortality, severity of AP, risk of local complications (ANC, APFC, PP), and SIRS. Additionally, we calculated the weighted mean difference (WMD) with 95% CI for LOH. We used the Cochrane's Q and the I2 statistics to test for heterogeneity, where I2 represents the magnitude of heterogeneity (moderate: 30–60%, substantial: 50–90%, considerable: 75–100%). We considered a p-value of less than 0.10 to be suggestive of significant heterogeneity (41).

Interpreting a forest plot requires considering the overall effect size, individual study results, heterogeneity, and statistical measures. The forest plot visually presents the results of multiple studies investigating the same research question. The diamond-shaped summary estimate represents the combined effect size, with its position indicating the point estimate and width representing the confidence interval. Each study is represented by a square, reflecting its estimate of effect size and the size of the square indicating study weight. Heterogeneity is observed when there is substantial variability among study results, reflected by scattered squares and a wider confidence interval in the summary estimate. Heterogeneity can arise from differences in study design, populations, or interventions. Statistical measures, such as the I-squared statistic and p-value, help assess the degree of heterogeneity and its significance.

If at least three studies were included in an analysis, we performed sensitivity analysis using the leave-one-out method to test the effect of each study on the main association. To assess the symmetry of the funnel plot visually, we evaluated the presence of small-study effects.

Funnel plots are used to assess publication bias. In an ideal scenario, the plot is symmetrical, indicating no publication bias. Asymmetry suggests publication bias, with fewer smaller studies reporting negative or non-significant results. However, funnel plot

asymmetry can also be influenced by factors like heterogeneity and study quality. Additional analysis, such as Egger's regression test or the trim-and-fill method, can be employed to further evaluate publication bias.

6.1.7. Details of ethical approval

As this review is based solely on previously published data and does not involve any new human subjects, no ethical approval was required. Therefore, no patients were involved in the design, conduct, or interpretation of this review. The use of publicly available data from peer-reviewed journals ensured that patient confidentiality and privacy were maintained.

6.2.Results

6.2.1. Search and selection

The systematic review included a total of 15 articles, out of which 13 were included in the meta-analysis. The details of the literature search can be found in **Figure 3**. After a thorough full-text assessment, six studies were excluded due to inappropriate study design or inclusion criteria. In terms of qualitative synthesis, several exclusion criteria were applied, such as a previous meta-analysis, a review that focused on the rate of FLD/ NAFLD in AP patients, two studies that only reported on severe FLD/ NAFLD cases, and a single case-report.

Additionally, a study that used the Nationwide Inpatient Sample database of the United States of America to examine the link between NAFLD and AP severity was also excluded. This was due to the un-proportionally low rate of NAFLD cases. Two articles could not be included in the quantitative synthesis as they lacked sufficient data.

It is worth noting that only one study provided information on long-term outcomes, while only one reported on hospital readmission. Overall, the 13 studies that were included in the meta-analysis provided a robust foundation for our systematic review, and allowed us to draw meaningful conclusions about the relationship between FLD/ NAFLD and AP.

6.2.2. Characteristics of the studies included in the meta-analysis

Table 1 provides a summary of the key features of the studies included in this analysis. All studies were conducted retrospectively, utilizing a cohort study design to investigate AP. The majority of studies (11 out of the total number) utilized the Revised Atlanta Classification (42) or the Atlanta Classification of 1992 (43) to classify AP severity. However, some studies also incorporated other severity classification methods such as the CTSI (Computed Tomography Severity Index) and the MRSI (Magnetic Resonance Severity Index) (44) to provide a comprehensive assessment of the disease. These classification systems allow for a standardized approach to evaluating the severity of AP and can provide valuable insights into the disease course and potential outcomes for patients.

The main characteristics of the included studies are summarized in **Table 1**. Further details about the eligibility criteria of each included study can be found in **Appendix Table 1**. All studies were retrospective cohort studies.

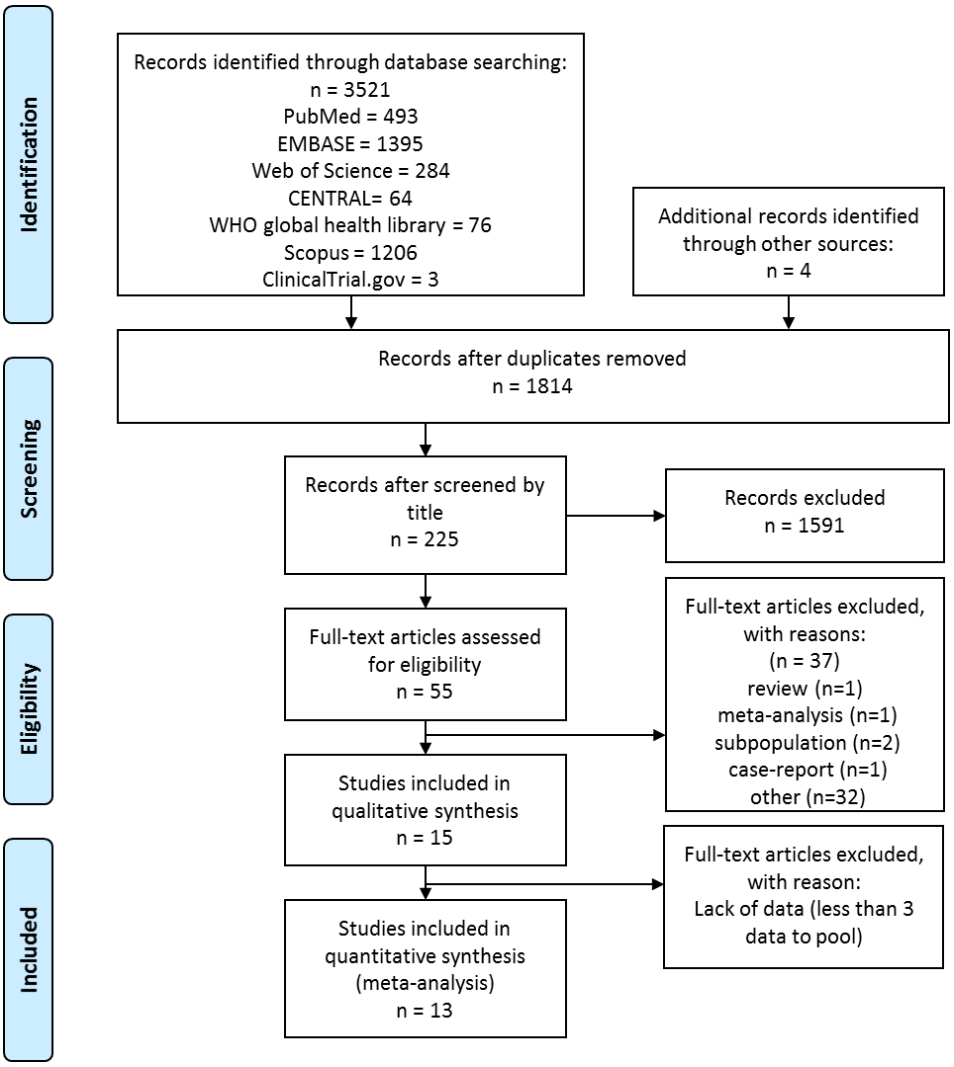

Figure 3. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart for the study selection procedure.

In this analysis, the prevalence of both FLD and NAFLD was found to vary widely across the 13 articles reviewed. Specifically, the prevalence of FLD ranged from 18% to 82%, while the prevalence of NAFLD ranged from 24% to 58%.

The diagnostic methods used to identify FLD and NAFLD also varied across the studies. In six of the articles, an unenhanced abdominal CT scan was utilized to diagnose these conditions. Meanwhile, other studies relied on abdominal ultrasound or MRI to make the diagnosis. Notably, two out of the 13 articles did not report the specific method used for diagnosis.

Table 1. Characteristics of the studies included in the systematic review and meta-analysis.

Author and year	Country (centre)	Recruitment period	AP diagnosis	Leading etiology of AP	Nr of AP cases	Fatty liver disease			Examined outcomes
						Definition	Diagnostic method (cut-off)	Nr. FLD cases (%)	
Dou J. et al., 2017 (45) (article in Chinese)	China (single-center)	2013 – 2016	2 out of 3 criteria	G 37% H 10%	251	NAFLD	US (NR)	117 (47)	AP severity (Atlanta 2012) §
Hao Y.M. et al., 2015 (46) †	China (single-center)	2011 – 2013	NR	NR	148	FLD	NR	41 (28)	AP severity (Atlanta 1992)
Jasdanwala S, 2015 (47)	USA (multicenter)	Not reported	2 out of 3 criteria	NR	574	NAFLD	CT or US (NR)	193 (34)	In-hospital mortality, AP severity (Atlanta 2012), LOH, ICU admission, BISAP
Jia J. et al., 2018 (48)	China (single-center)	2016 – 2017	2 out of 3 criteria	NR	128	FLD	CT (HAI<1)	56 (44)	AP severity (Atlanta 2012), ANC, APFC
Mikolasevic I. et al., 2016 (49)	Croatia (single-center)	2008 – 2015	2 out of 3 criteria	G 84% H 1%	822	NAFLD	CT (HA >10 HU, or LD<40 HU) or US	198 (24)	In-hospital mortality, AP severity (Atlanta 2012) §, ANC, APFC, PP, LOH, APACHE-II, CTSI
Morel C.E. et al., 2019 (50) (article in Spanish)	Mexico (single-center)	2017 – 2018	2 out of 3 criteria	G 70% A 11% H 5%	186	FLD	US (NR)	68 (37)	AP severity (Atlanta 2012), persistent SIRS
Peng Z.H. et al., 2012 (51) (article in Chinese)	China (single-center)	2010 – 2011	2 out of 3 criteria	G 57%	606	FLD	CT (HAI<1)	498 (82)	In-hospital mortality, overall complications §
Satapathy S. et al., 2011 (52) †	USA (single-center)	2002 – 2009	NR	G 39% A 18%	108	FLD	CT (HAI<0.8)	23 (21)	In-hospital mortality, ANC, PP, LOH, ICU admission, need for antibiotics, CTSI, Ranson 48 h
Suchsland T. et al., 2015 (53)	Germany (single-center)	2006-2011	ICD-10	NR	373	FLD	NR	NR	Risk of hyperglycemia after AP

Wang S. et al., 2013 (54) †	China (single-center)	2010 – 2011	NR	NR	120	FLD	NR	35 (29)	AP severity (Atlanta 1992) §, SIRS, pulmonary failure, metabolic disturbances
Wu D. et al., 2019 (55)	China (single-center)	2012 – 2016	2 out of 3 criteria	G 32% H 48%	656	NAFLD	CT (HAI<1)	378 (58)	AP severity (Atlanta 2012) §, SIRS, BISAP, Ranson score
Xiao B. et al., 2012 (56)	China (single-center)	2009 – 2011	Pain and laboratory results ‡	G 38%	50	FLD	MRI (HAI)	33 (66)	In-hospital mortality, MRSI
Xu C. et al., 2015 (57)	China (single-center)	2000 – 2014	2 out of 3 criteria	G 58% A 22% H 11%	2671	FLD/ NAFLD	CT (HAI<1)	480 (18)	In-hospital mortality, AP severity (Atlanta 2012), ANC, systemic and local complications, APACHE-II
Yoon S.B. et al., 2017 (58)	Korea (single-center)	2009 – 2016	2 out of 3 criteria	G 36% A 34% H 3%	200	FLD	CT (HAI<1)	67 (34)	In-hospital mortality, AP severity (Atlanta 2012) §, ANC, PP, APFC, LOH
Yuan L. et al., 2017 (59)	China (single-center)	2009-2013	2 out of 3 criteria	G 49% A 5% H 10%	310	FLD	NR	119 (39)	hospital readmission after the first episode of AP

†: conference abstract; ‡: AP diagnostic criteria were based on abdominal pain and serum pancreatic enzyme elevation; §: outcome assessed by adjusted analysis from logistic regression; 2 out of 3 criteria: 1. abdominal pain, 2. laboratory findings, 3. abdominal imaging;

AFLD: alcoholic fatty liver disease; ANC: acute necrotic collection; AP: acute pancreatitis; APACHE-II: "Acute Physiology, Age, Chronic Health Evaluation II"; APFC: acute peripancreatic fluid collection; BISAP: bedside index for severity in acute pancreatitis; CT: computed tomography; CTSI: CT severity index; Etiology A: alcohol abuse, G: gallstone disease, H: hypertriglyceridemia induced; ICU: intensive-care unit; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th revision; FLD: fatty liver disease; HA: hepatic attenuation; HAI: hepatic attenuation index; LD: liver density; LOH: length of hospitalization; MRI: magnetic resonance imaging; MRSI: magnetic resonance severity index; NAFLD: non-alcoholic fatty liver disease; PP: pancreatic pseudocyst; SIRS: systemic inflammatory response syndrome; US: abdominal ultrasound; USA: United States of America.

6.2.3. Findings of Meta-Analysis: FLD vs. no FLD

Table 2 presents a summary of the key findings from our analysis.

First we analyzed the subgroup of publications reporting on FLD generally. We found that in patients with AP, the presence of FLD was associated with a higher risk of in-hospital mortality, composite of moderately severe and severe AP, and severe AP alone. Specifically, the odds of in-hospital mortality were 3.56 times higher in patients with FLD than those without FLD. Similarly, the odds of composite moderately severe and severe AP were 3.14 times higher in the FLD group. In addition, the odds of severe AP alone were 2.67 times higher in patients with FLD than those without FLD (see **Figure 4-7 and Table 2**).

When studies using the Atlanta 1992 classification for AP were analyzed (**Table 2**), we found that the odds of severe AP were significantly higher in the FLD group compared to those without FLD (OR=4.70, CI: 2.65–8.32). Moreover, in multivariate analysis, we observed an independent association between FLD and the odds of moderately severe/severe AP based on five studies (OR=3.68, CI: 2.16–6.29).

Further analysis (**Table 2**) showed that AP patients with FLD had a higher proportion of acute necrotic collection (OR=3.08, CI: 2.44–3.90), acute peripancreatic collection (OR=3.27, CI: 1.97–5.42), and pancreatic pseudocyst (OR=2.69, CI: 1.64–4.40) compared to those without FLD. Additionally, SIRS was more common in AP patients with FLD (38.19% vs. 18.63%; OR=2.39, CI: 1.74-3.28). Finally, based on five articles, the length of hospital stay was longer among patients with FLD than in the non-FLD group (WMD=1.46 days, CI: 0.54–2.39, **Figure 7**).

The heterogeneity analysis for each outcome is presented in the corresponding figures. Overall heterogeneity ranged between 0 and 91.5%. However, on average, results showed moderate heterogeneity.

Table 2. Summary of findings.

Outcome	N0 of studies (N0 of pts)	Odds ratio (95% CI)	I^2 (%)	Chi^2
FLD vs no-FLD				
Mortality	7 (5031)	3.56 (1.77-8.28)	43.2	0.103
Composite of MSAP and SAP (uni)	7 (5302)	3.14 (1.87-5.25)	91.5	0
Composite of MSAP and SAP (multi) ‡	5 (NR)	3.68 (2.16-6.29)	65.6	0.020
SAP by Atlanta 2012	8 (4931)	2.67 (2.01-3.56)	32.0	0.173
SAP by Atlanta 1992	2 (268)	4.70 (2.65-8.32)	0	0.634
Acute necrotic collection	5 (3929)	3.08 (2.44-3.90)	17.5	0.303
Acute peripancreatic fluid collection	3 (1150)	3.27 (1.97-5.42)	57.9	0.093
Pancreatic pseudocyst	3 (1130)	2.69 (1.64-4.40)	0	0.715
SIRS	4 (3634)	2.39 (1.74-3.28)	47	0.129
Length of hospital stay	5 (1955)	1.46 (0.54-2.39) †	40.7	0.150
NAFLD vs. no-NAFLD				
Mortality	2 (1396)	2.81 (0.39-20.03)	68.7	0.074
Composite of MSAP and SAP (uni)	5 (4910)	2.64 (1.37-5.11)	94	0
Composite of MSAP and SAP (multi) ‡	3 (NR)	3.39 (1.52-7.56)	79.2	0.008
SAP by Atlanta 2012	3 (4085)	2.21 (1.70-2.88)	0	0.806
Length of hospital stay	3 (1647)	1.41 (0.03-2.7) †	68.5	0.042

CI = confidence interval, FLD = fatty liver disease, I2 and Chi2 = heterogeneity, MSAP = moderately severe acute pancreatitis, NAFLD = non-alcoholic fatty liver disease, SAP = severe acute pancreatitis, SIRS = systemic inflammatory response syndrome.

† Length of hospital stay results are represented as weighted mean differences with 95% CI, values represent days; ‡ parameters included in multivariate analyses in the included studies are summarized in Table 3.

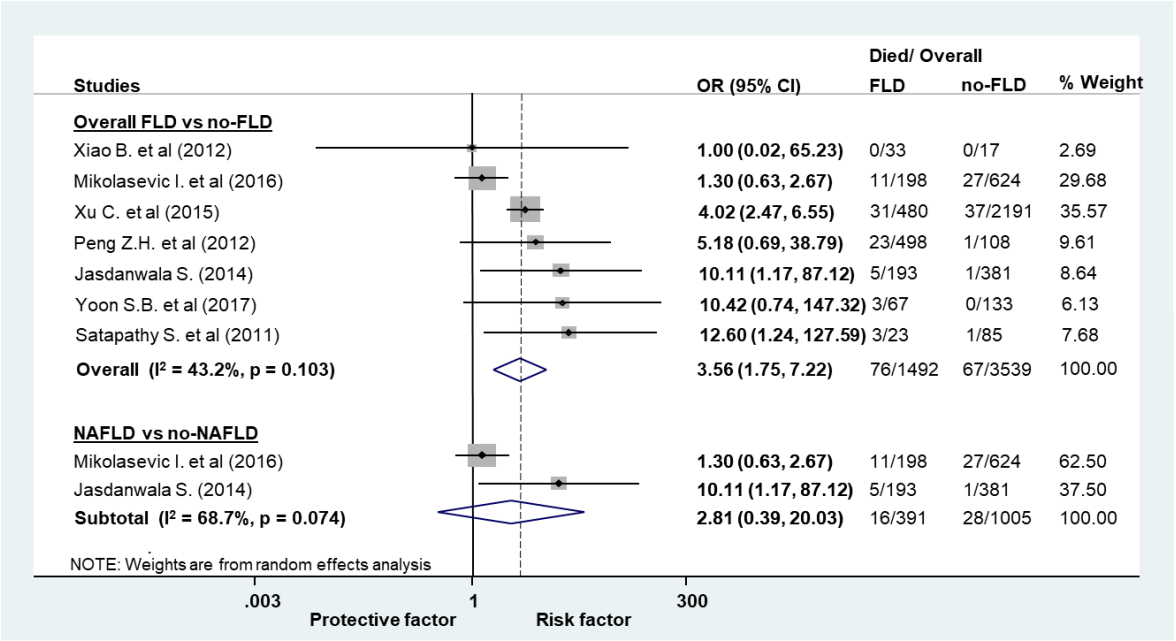

Figure 4. Forest plots of studies evaluating the association between fatty liver disease or non-alcoholic fatty liver disease and overall survival of patients with acute pancreatitis; CI: confidence interval, OR: odds ratio.

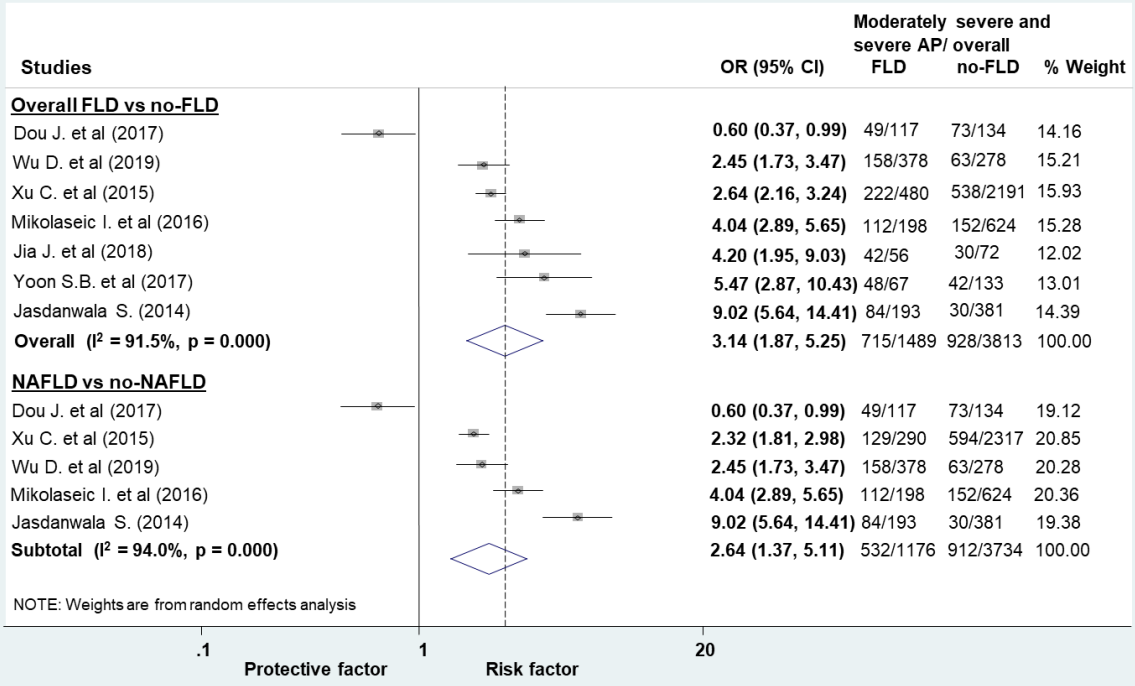

Figure 5. Forest plots of studies evaluating the association between fatty liver disease (FLD) or non-alcoholic fatty liver disease (NAFLD) and disease severity of acute pancreatitis (AP). We compared the odds of moderately severe/severe vs mild AP in patients with and without FLD/ NAFLD; CI: confidence interval, OR: odds ratio.

6.2.4. Findings of Meta-Analysis: NAFLD vs. no NAFLD

The study found that mortality rates were higher in patients with NAFLD in comparison to those without it. However, the difference did not reach statistical significance (OR=2.81, CI: 0.39–20.03; as depicted in **Figure 4**).

The severity of AP was found to be greater in patients with NAFLD based on the analysis of five articles. The odds of developing moderately severe or severe AP were 2.64 times higher in patients with NAFLD (OR=2.64, CI: 1.37–5.11; as shown in **Figure 5**). The odds of developing severe AP were also higher in the NAFLD group (OR=2.21, CI: 1.70–2.88). Additionally, analysis of three articles revealed that NAFLD was an independent predictor of severe AP (OR=3.39, CI: 1.52–7.56; as depicted in **Figure 6**).

Furthermore, patients with NAFLD tended to have a longer hospital stay compared to those without it (WMD=1.41 days, CI: 0.03–2.79). These findings suggest that NAFLD may contribute to a more severe course of AP, which can lead to prolonged hospitalization and poorer outcomes for patients.

Table 3. Factors included in multivariate logistic regression analyses.

Studies	**Factors included in the multivariate analysis**
Yoon S.B. et al, 2017 (58)	Age, gender, body mass index, alcohol consumption
Mikolasevic I. et al, 2016 (49)	Arterial hypertension, type 2 diabetes mellitus, dyslipidemia, body mass index
Wang S. et al, 2013 (54)	Age, gender, etiology, systemic complications, pulmonary failure
Wu D. et al, 2019 (55)	Age, gender, body mass index, serum triglyceride level, chronic heart disease, type 2 diabetes mellitus, arterial hypertension, smoking
Dou J. et al, 2017 (45)	Body mass index, white blood cells, serum amylase level

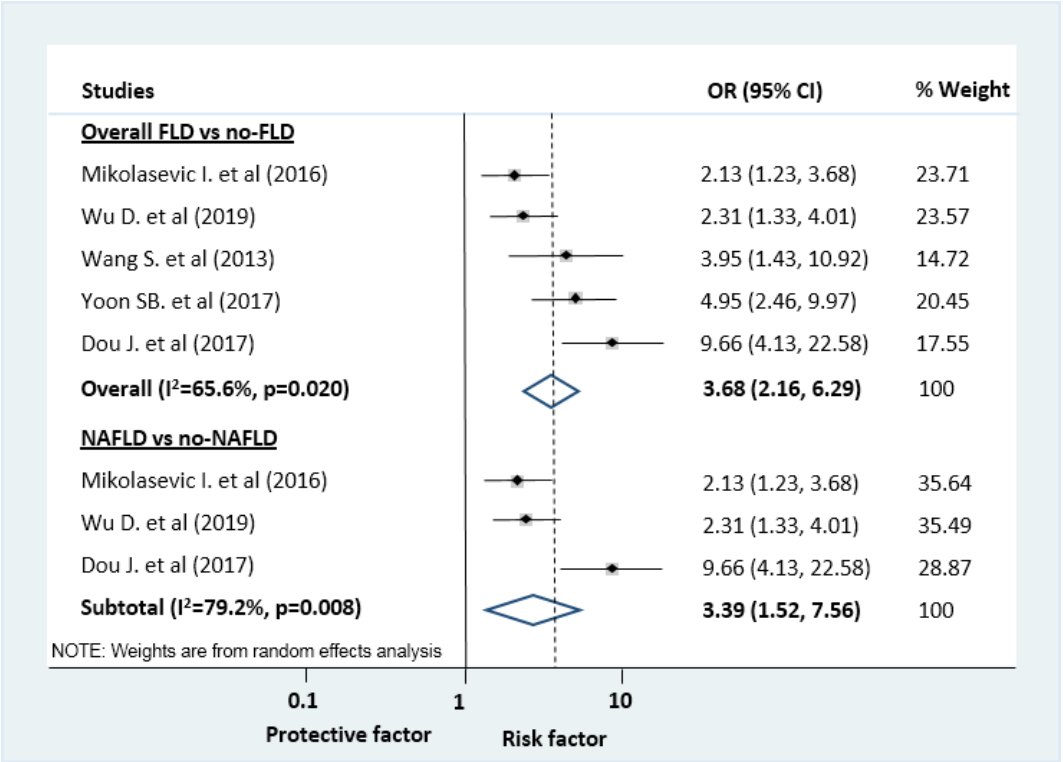

Figure 6. Forest plots of studies evaluating the association between fatty liver disease (FLD) or non-alcoholic fatty liver disease (NAFLD) and disease severity of acute pancreatitis (AP). Logistic regression analysis results were pooled, comparing the odds of moderately severe/ severe vs mild AP in patients with and without FLD/ NAFLD; CI: confidence interval, OR: odds ratio.

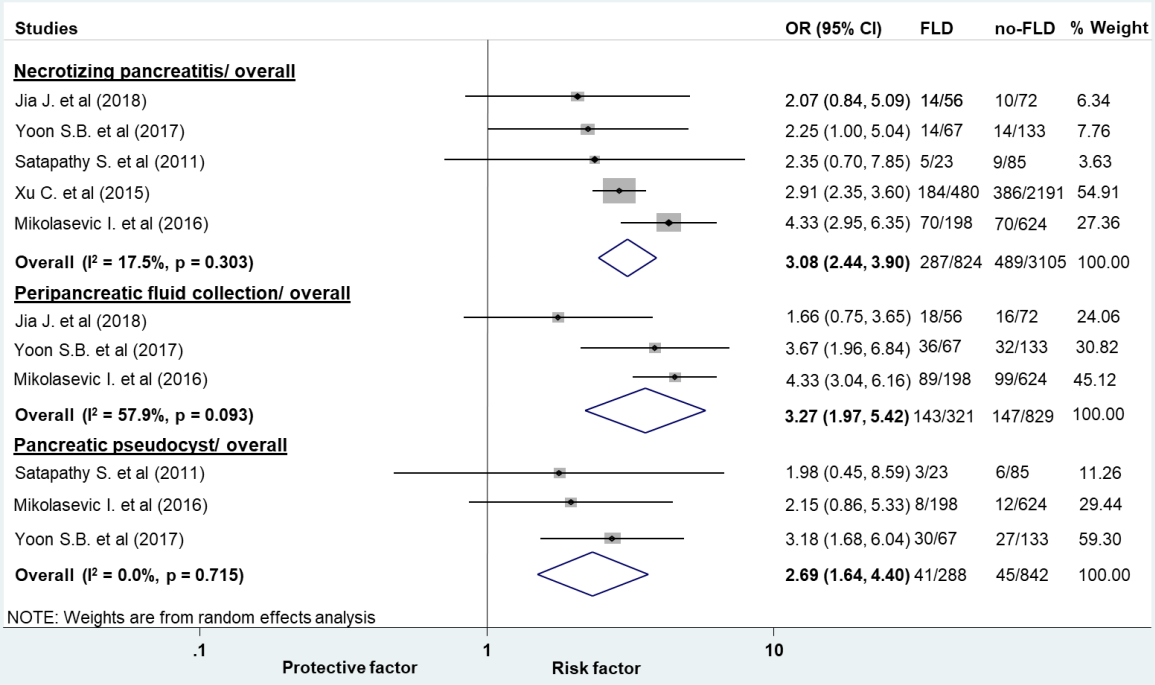

Figure 7. Forest plots of studies evaluating the association between fatty liver disease and the odds of local complications (necrotizing pancreatitis, peripancreatic fluid collection and pancreatic pseudocyst) in acute pancreatitis; CI: confidence interval, FLD: fatty liver disease, OR: odds ratio.

6.2.5. Risk of bias assessment between studies

Table 4 provides a summary of the risk of bias and quality assessment of the individual studies. The analysis revealed that Hao YM (46), Wang S. et al. (54), and Satapathy S. et al.(52) had the worst results, with multiple moderate and high-risk domains.

The domain of "study participation" received the best rating, as only one study carried a high and two studies carried moderate risk of bias. This indicates that the participation of study subjects was adequately described and reported in these studies.

However, the domain of "study confounding" received the worst rating, as multiple studies did not report how important confounders were accounted for or whether an appropriate method was used for handling missing data. This suggests that the potential influence of confounding factors on study outcomes was not adequately addressed in some of the studies, potentially compromising the validity and reliability of their findings. Therefore, future studies should focus on addressing these limitations to ensure that the results obtained are more accurate and reliable.

Table 4. Risk of bias assessment using QUIPS (Quality In Prognosis Studies) tool.

Study	1[a]	2[b]	3	4	5	6
Dou J. et al (45)		N/ A				
Hao Y.M. (46)		N/ A				
Jasdanwala S. (47)		N/ A				
Jia J. et al (48)		N/ A				
Mikolasevic I. et al (49)		N/ A				
Morel C.E. et al (50)		N/ A				
Peng Z.H. et al (51)		N/ A				
Satapathy S. et al (52)		N/ A				
Wang S. et al (54)		N/ A				
Wu D. et al (55)		N/ A				
Xiao B. et al (56)		N/ A				
Xu C. et al (57)		N/ A				
Yoon S.B. et al (58)		N/ A				

Items in columns 1: Study participation, 2: Study attrition, 3: Prognostic factor measurement, 4: Outcome measurement, 5: Study confounding, 6: Statistical analysis and reporting; Green: low risk of bias, yellow: moderate risk of bias, red: high risk of bias; a. Overall ratings for each domain was assigned as carrying 'low', 'moderate' or 'high' risk of bias, based on the items included in each domain; b. N/A: not applicable.

6.2.1. Additional Analysis

Our analysis did not detect any evidence of publication bias when we visually assessed the funnel plots, as shown in **Figure 8**. Moreover, the sensitivity analysis revealed no significant differences except for one outcome.

Specifically, when we removed the study of Yoon et al.(58) from the forest plot that assessed the odds of pancreatic pseudocyst, the results became non-significant (OR=2.09; CI: 0.97–4.55). This suggests that the inclusion of the study by Yoon et al.(58) may have had a significant impact on the overall results for this outcome, and caution should be exercised when interpreting these findings.

Overall, our analysis suggests that the results obtained are generally reliable and robust, and that the risk of publication bias was minimal. However, the sensitivity analysis highlights the importance of considering the potential impact of individual studies on overall results, and the need for caution when interpreting findings that rely heavily on a single study.

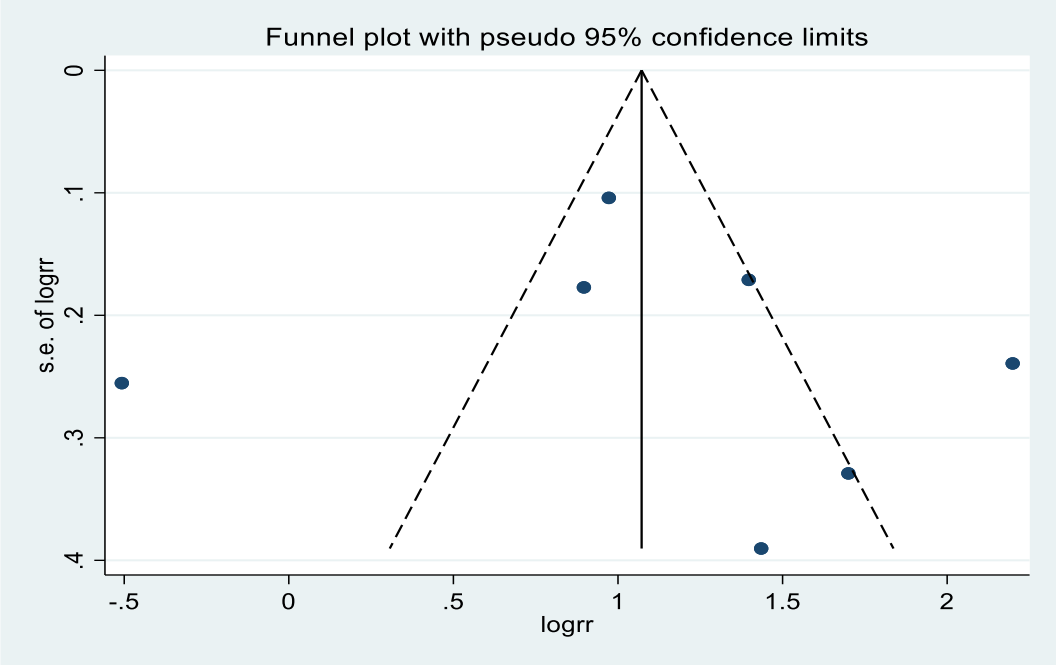

Figure 8. Funnel plot with pseudo 95% confidence intervals with included studies on Figure 2.

6.3. Discussion

6.3.1. Summary of findings

At the time of its publication, this meta-analysis stood out as the first of its kind to examine the risk of multiple outcomes in AP patients who also had FLD or NAFLD. We found that both FLD and NAFLD increased the odds of in-hospital mortality. However, the differences were non-significant. Furthermore, we found increased odds of moderately severe AP and local complications. Importantly, patients with both FLD and NAFLD spent more time hospitalized compared to patients without FLD or NAFLD. Most importantly, we found an independent association between the disease course of AP and FLD/ NAFLD.

Prior to our study, only one meta-analysis had been conducted, but it included a limited number of articles and solely focused on the increased severity of AP in patients with fatty liver disease (FLD) (60). The previous meta-analysis did not distinguish between different etiologies of FLD, such as alcoholic, non-alcoholic, or metabolic, although this could have significantly impacted the severity of AP. Furthermore, while the analysis did report on the severity of AP in patients with and without FLD, one of the included articles specifically examined the association between severe FLD and AP severity, indicating that a more detailed examination of the relationship between these two conditions was warranted.

Therefore, this current meta-analysis represents a more comprehensive and nuanced investigation of the link between NAFLD and AP, examining the potential impact of different FLD etiologies on AP severity and analyzing multiple outcomes. As such, it provides a valuable contribution to the existing literature on this topic.

6.3.2. Explanation and elaboration

Prior research has demonstrated that FLD is linked to a higher risk of cardiovascular mortality and an elevated incidence of chronic kidney disease (61). However, the impact of FLD and its non-alcoholic variant (NAFLD) on the severity of AP is not yet fully understood. One possible explanation for the association between FLD/NAFLD and increased severity of AP is their shared risk factors. Both conditions are often found in individuals who suffer from obesity, alcohol abuse, or hyperlipidemia. As a result, the prevalence of FLD is high among AP patients. However, whether FLD or NAFLD has a significant impact on the prognosis of AP remains uncertain.

Clinical guidelines recommend that a contrast-enhanced CT scan should be performed between 72-96 hours after the onset of AP symptoms (25). In cases where both AP and FLD are suspected, combined unenhanced and enhanced CT scans can provide valuable information about the status of both conditions (58). Additionally, various studies have demonstrated that imaging techniques such as CT scan and ultrasound elastography or MRI can be highly effective in detecting FLD (18, 62). International guidelines typically recommend using US as the primary diagnostic tool for detecting FLD due to its widespread availability and lower cost compared to the gold-standard MRI. However, US has limited specificity and may not reliably detect steatosis when the fat content in the liver is less than 20%. In contrast, MRI can detect as little as 5% fat in the liver, making it a highly sensitive diagnostic tool for FLD. Another clinically available imaging technique called controlled attenuation parameter (CAP) can also be used to diagnose FLD. This non-invasive method classifies the degree of steatosis into three grades based on the amount of liver tissue with fatty change (18). By using a combination of these imaging techniques, healthcare professionals can more accurately diagnose and assess the severity of both AP and FLD, which can ultimately lead to more effective treatment and management strategies for patients.

There is considerable heterogeneity in the causes of AP and FLD. However, despite this heterogeneity, studies have consistently demonstrated a strong association between the presence of FLD and increased AP severity. According to research by Yoon et al.(58), this trend is observed regardless of the underlying cause of pancreatitis, whether it is alcohol-related or non-alcoholic. Similarly, research by Xu et al.(57) found that the severity of AP was similar in patients with alcoholic FLD and those with non-alcoholic FLD. However, in both cases, patients with FLD had a worse course of AP compared to those without FLD. These findings suggest that the presence of FLD may be a significant risk factor for increased AP severity, irrespective of the underlying cause of the pancreatitis.

According to four different research articles (51, 55, 57, 63), the severity of FLD can significantly impact the outcomes of AP. These studies all suggest that the severity of FLD is associated with a worse course of AP, with negative effects on the overall prognosis. In particular, Wang et al.(64) found a higher rate of severe AP in patients with severe FLD. This suggests that patients with more severe FLD may be at a higher risk for experiencing a more severe form of AP. However, it is important to note that the course

of AP may be further complicated in patients with cirrhosis. Research by Yuan et al.(65) demonstrated that patients with cirrhosis experienced more severe cases of AP compared to those without cirrhosis. However, the higher rate of mortality observed in these patients was attributed to the complications of cirrhosis rather than AP itself. These findings highlight the importance of evaluating the severity of FLD and any potential co-occurring liver conditions in patients with AP.

Five of the studies included in this analysis reported results regarding the severity of AP as defined by various scoring systems. These findings can provide valuable insight into the impact of FLD on the severity of AP. One study found that FLD patients had significantly higher BISAP scores compared to non-FLD patients (mean BISAP 0.813 vs. 0.544, $p<0.01$) (47). BISAP scores are a widely used scoring system that helps predict the severity of AP based on clinical parameters such as blood urea nitrogen levels, impaired mental status, and other factors. Two other studies reported significantly higher CTSI scores in FLD patients compared to non-FLD patients (mean CTSI 2.9 vs. 1.1, $p<0.01$ and 4 vs. 2.2, $p<0.05$) (49, 52). CTSI scores are another scoring system that assesses the severity of AP based on CT scan findings. Furthermore, one of the studies included in this analysis found that FLD patients had significantly higher APACHE-II scores compared to non-FLD patients (mean APACHE-II 8.4 vs. 7.2, $p<0.01$) (49). The APACHE-II score is a commonly used scoring system that evaluates the severity of disease based on various physiological parameters. Overall, these findings suggest that FLD may be associated with a more severe course of AP, as reflected in higher scores on various severity scoring systems.

Four studies included in the analysis suggested the integration of FLD into prognostic tools for AP. However, only one study, conducted by Hao et al.(46), evaluated the effect of incorporating FLD into the APACHE-II score system. This study reported that adding FLD to the APACHE-II score system increased the sensitivity and specificity for predicting severe AP. Specifically, the sensitivity increased from 78.1% to 85.4%, and the specificity increased from 75.5% to 86.2%. This suggests that including FLD in the APACHE-II score system can improve its ability to predict severe AP in patients with FLD.

Several studies have investigated the impact of FLD on pancreatic necrosis infection and the need for antibiotics in AP patients. Ding et al.(66) found no significant effect of FLD on pancreatic necrosis infection (OR=0.971; 95% CI: 0.45–2.08). However,

Xu et al.(57) reported an increased risk of infection in AP patients with FLD (46.5% vs. 38%, $p < 0.05$). Furthermore, Satapathy et al.(52) reported a higher need for antibiotics in AP patients with FLD (69.6% vs. 30.6%). While these findings suggest a potential association between FLD and increased risk of pancreatic necrosis infection and antibiotic use in AP patients, the data was only represented in a few articles and, therefore, unsuitable for quantitative analysis. It is important to note that pancreatic necrosis infection is a severe complication of AP that can lead to mortality. Prompt and adequate use of antibiotics is crucial in preventing and treating this complication. Therefore, the potential association between FLD and increased risk of infection and antibiotic use in AP patients highlights the importance of considering FLD in the management and treatment of AP.

FLD was found to have a significant association with increased hospital readmission of patients with AP. One study reported an OR of 3.48, with a 95% CI of 1.70–7.11 (53). However, it should be noted that the data were collected retrospectively, and the admission diagnosis of acute or chronic pancreatitis was screened together regarding later readmission with a pancreatitis-related diagnosis. This limitation may have affected the accuracy of the findings. Further studies with prospective designs are needed to confirm this association.

It is well established that NAFLD is a risk factor for the development of type 2 diabetes and other metabolic disorders (18). Studies have shown that individuals with NAFLD are more likely to develop insulin resistance, impaired glucose tolerance, and type 2 diabetes, even in the absence of other risk factors such as obesity or physical inactivity (67-69). Yuan et al.(59) found that FLD was a significant risk factor for abnormal fasting blood glucose levels after the first episode of AP, with a hazard ratio (HR) of 1.869 (95% CI: 1.16-3.01). The study had a median follow-up period of three years, but did not report the definition of FLD used. None of the included studies in the analysis discussed long-term complications such as diabetes or cardiovascular disease, which are known to be associated with FLD.

Several pathogenetic theories have been proposed to explain how fatty liver can aggravate pancreatitis, but the exact mechanisms remain unclear. One proposed theory is that fatty liver often coexists with hyperlipidemia, which can cause the accumulation of free radicals, microcirculatory disturbances, oxidative stress, and acinar necrosis in AP (70-72). Hyperlipidemia can also decrease red blood cell velocity, leading to an increase

in hemoglobin-oxygen affinity in the microcirculation, which can further exacerbate tissue hypoxia (73). Additionally, the interstitial release of triglyceride degradation products and the accumulation of free radicals may contribute to cellular disruption (70). A recent study suggested that the PPARα signaling pathway and the fatty acid degradation pathway may also play a role in the pathogenesis of APFL, indicating that fatty liver can aggravate pancreatitis through these pathways (74).

Furthermore, a chronic proinflammatory state in patients with fatty liver may also exacerbate the course of AP. Previous studies have shown that in rat and human AP models, fatty liver reduced alpha1-antitrypsin levels, which have significant anti-inflammatory properties that affect a wide range of inflammatory cells such as neutrophils, monocytes, macrophages, and mast cells (64). Thus, a decrease in serum AAT levels can lead to excessive inflammation activation. Additionally, the pooled results of our analysis showed that the occurrence of SIRS was significantly higher in FLD-AP patients than in non FLD-AP patients. Therefore, an excessive SIRS response may be one of the mechanisms by which fatty liver aggravates pancreatitis.

6.4.Strengths and limitations

Our meta-analysis has been conducted with a rigorous methodology, which involved a systematic search and reproducible selection and data extraction processes. One of the key strengths of this study is that we adjusted for covariates to account for AP severity, and included a high number of AP cases, which increases the statistical power of our analysis.

However, several limitations need to be considered while interpreting the results of our study. Firstly, we included conference abstracts, which are often lacking in details, and hence may be subjected to potential bias. Although we aimed to reduce the risk of publication bias, we could not test if publication bias affects the results due to the small number of studies included in our analysis.

Another potential limitation is that all the included studies were retrospective, single-center cohort studies, and most of the study populations were from Asia. Hence, our findings may not be generalizable to other world regions. Furthermore, the diagnosis of AP and FLD was inconsistent among the studies, and none confirmed FLD through liver biopsy. Additionally, the timing of repeated abdominal imaging was not reported uniformly in all the studies, which may have led to heterogeneity in the rate of local

complications. There was significant heterogeneity in some of the results, including severity, independent risk, and peripancreatic fluid collection. However, sensitivity analysis revealed a significant difference only in the case of one outcome (the odds of pancreatic pseudocyst). Lastly, the risk factors included in the individual logistic regression analysis were not uniform among the studies. Therefore, caution should be exercised while interpreting the results of our analysis.

6.5.Conclusion

In summary, our analysis indicates that patients with AP and FLD or NAFLD are likely to experience a more severe disease progression, a higher likelihood of developing local and systemic complications, and a longer hospital stay.

6.6.Implication for practice

According to our findings, FLD and NAFLD exacerbate the progression of AP. Since FLD and NAFLD can be detected through affordable and non-invasive abdominal US or highly sensitive and specific abdominal CT scans, we recommend that AP patients undergo an initial assessment of not only the pancreas but also the liver to identify fatty liver. This approach could lead to more personalized patient care and improve outcomes for AP patients compared to current practices.

6.7.Implication for research

Given the significant impact of FLD and NAFLD on AP outcomes, we propose that the assessment of these conditions be integrated into prognostic tools used in AP management. It is important to note that long-term complications were not evaluated in the studies we reviewed, highlighting the need for follow-up research. Moreover, potential treatment options should be explored to reduce the heightened risks of AP complications in patients with FLD and NAFLD. Furthermore, it is unclear whether the presence of NAFLD or FLD impacts the prevalence of AP.

6.8.Implication for policymakers

By including FLD as a factor in prognostic tools, healthcare providers can better predict the severity of AP in patients with this condition and provide appropriate treatment and management. Additionally, AP associated with FLD and NAFLD may lead to higher healthcare utilization and associated costs. Therefore, the economic impact of these conditions should be investigated further in patients with AP.

7. Prospective international registry analysis about the relationship between MAFLD and the course of AP

7.1. Materials and methods

Our results are presented following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (75).

Using data from the international, prospective, multicenter Acute Pancreatitis Registry of the Hungarian Pancreatic Study Group (HPSG), we conducted a post hoc cross-sectional analysis. The registry received approval from the Hungarian Scientific and Research Ethics Committee of the Medical Research Council (22254-1/2012/EKU and 17787-8/2020/EÜIG) and was conducted in accordance with the Declaration of Helsinki revised in 2013. Furthermore, all participants provided written informed consent.

We collected patient data from the establishment of the registry in 2012 until December 31, 2019, using electronic case report forms that underwent a four-level data monitoring protocol for validation. Párniczky et al.(76) describe the data collection and validation processes in detail. Our registry implemented four quality control checkpoints. Firstly, the local clinical research assistant electronically uploaded the data and ensured its equivalence with the hard copy. Secondly, the local institutional principal investigator, who holds a medical doctoral degree, verified and confirmed the validity and accuracy of the uploaded data. Thirdly, the central data administrator, based at the headquarters of HPSG, conducted a final accuracy check. Finally, the registry leader reviewed and verified the presented data in-house. Patients with inadequate or insufficient data were excluded from the analysis. **Table 5.** provides a summary of the contributing centers.

Table 5. Contributing centers to the acute pancreatitis registry. The last column represents the number of patients enrolled in each center.

Hospital	City	Country	N
First Department of Medicine, University of Pécs	Pécs	Hungary	795
Department of Gastroenterology, Szent György University Teaching Hospital of County Fejér	Székesfehérvár	Hungary	356
Department of Medicine, University of Szeged	Szeged	Hungary	355
Department of Internal Medicine, University of Debrecen	Debrecen	Hungary	148
Bajcsy-Zsilinszky Hospital	Budapest	Hungary	124
Dr Réthy Pál Hospital of County Békés	Békéscsaba	Hungary	56
Targu Mures County Emergency Hospital, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Targu Mures	Targu Mures	Romania	34

Hospital	City	Country	N
Vilnius University Hospital Santariskiu Klinikos (Santariškių Klinikos)	Vilnius	Lithuania	25
Pándy Kálmán Hospital of County Békés	Gyula	Hungary	22
Dr Bugyi István Hospital	Szentes	Hungary	21
Markusovszky University Teaching Hospital	Szombathely	Hungary	15
Borsod-Abaúj-Zemplén County and Teaching Hospital	Miskolc	Hungary	11
Saint Luke Clinical Hospital	St Petersburg	Russia	11
Centrum péče o zažívací trakt, Vítkovická nemocnice a.s.	Ostrava	Czech Republic	10
Clinical Hospital Center Rijeka	Rijeka	Croatia	9
Csongrád County Health Center	Makó	Hungary	9
Bogomolets National Medical University	Kiev	Ukraine	8
Helsinki University Central Hospital	Helsinki	Finland	8
Bács Kiskun County Hospital	Kecskemét	Hungary	7
Department of Surgery, University of Debrecen	Debrecen	Hungary	7
Gomel Regional Clinical Hospital	Gomel	Belarus	7
Gastroenterology, Hepatology and Nutritional Centre, Pauls Stradins Clinical University Hospital	Riga	Latvia	6
Buda Hospital of the Hospitaller Order of Saint John of God	Budapest	Hungary	3
Hospital of Bezmialem Vakif University, School of Medicine	Istanbul	Turkey	3
Second Department of Medicine, Semmelweis University	Budapest	Hungary	2
General Surgery, Consorci Sanitari del Garrof, Sant Pere de Ribe	Barcelona	Spain	1
Total			**2053**

7.1.1. Definition of MAFLD

We retrospectively diagnosed MAFLD based on prospectively collected data, utilizing the criteria and definition established by Eslam et al.(22) The diagnosis of MAFLD was made in the presence of liver steatosis on any abdominal imaging (ultrasound, computed tomography - CT, magnetic resonance imaging - MRI, and endoscopic ultrasound - EUS) and at least one of the following criteria: (1) BMI ≥25 and ≥30 kg/m2 indicating overweight or obesity, (2) type 2 diabetes mellitus (T2DM) (77), and/or (3) the presence of two or more metabolic risk abnormalities (hypertension, hypertriglyceridemia, hypercholesterolemia, or pre-diabetes). The third criterion included glycated hemoglobin (HbA1c), high blood pressure, hyperlipidemia, and hypercholesterolemia, which were collected from patient history, drug intake, or in-hospital laboratory analysis. However, C-reactive protein (CRP) was excluded due to the acute inflammatory state in AP. Waist circumference measurements were also not available since this is not routinely collected in any of the enrolling centers.

Alcohol consumption is not considered an exclusion criterion in the definition of MAFLD. Consequently, we stratified the participants into subgroups based on the presence or absence of alcohol abuse, as outlined below.

7.1.2. Patient selection

All the included adult (≥18 years) AP patients were diagnosed using the IAP/APA guidelines (25).AP was defined by meeting at least two out of the following three criteria: (1) experiencing upper abdominal pain (clinical), (2) having serum amylase or lipase levels exceeding three times the upper limit of normal (laboratory), (3) and/or meeting imaging criteria through CT, MRI, or ultrasonography (imaging).

Initially, we identified patients with AP and subsequently assessed whether they had undergone abdominal imaging (such as ultrasound, CT, MRI, or EUS) and had liver descriptions available. We assessed every abdominal imaging during hospitalization, not only the admission imaging. Fat accumulation in the liver noted in any imaging during the hospitalization was categorized as steatosis, while an unequivocal description of the liver without steatosis was categorized as non-steatosis (=non-MAFLD group). We excluded patients without abdominal imaging during hospitalization, those with equivocal liver descriptions, or patients with a history of other chronic liver diseases like cirrhosis and chronic hepatitis B or C.

Next, patients were categorized into the MAFLD groups if any of the three diagnostic criteria were met, whereas patients were categorized into the non-MAFLD group if all three criteria could be assessed and found to be negative. Finally, patients were excluded if any criteria for the diagnosis of MAFLD were missing, and all others were negative.

Patients were monitored from admission until discharge or mortality, with a focus on the relief of symptoms, decreasing inflammation, and/or restoration of oral feeding.

7.1.3. Outcomes and variables

Our study had several outcomes. The primary outcome was all-cause in-hospital mortality. We also examined the severity of AP using the revised Atlanta 2012 classification (42), which categorizes AP as mild, moderate (MAP), or severe (SAP) based on the presence of local, systemic complications, and/ or multi-organ failure (MOF). In addition, we analyzed moderate-to-severe AP as a separate outcome (MSAP), which combines the moderate and severe AP groups. Additionally, we evaluated the incidence of overall and individual local complications (42) (such as acute peripancreatic fluid collections, pancreas necrosis defined as an acute necrotic collection or walled of necrosis, and pseudocyst), MOF (42) (such as renal, respiratory, and cardiovascular

failure), diabetes as a complication (abnormal fasting glucose at discharge) (78), length of hospital stay (LOH) (from admission until discharge or mortality), and maximum CRP level.

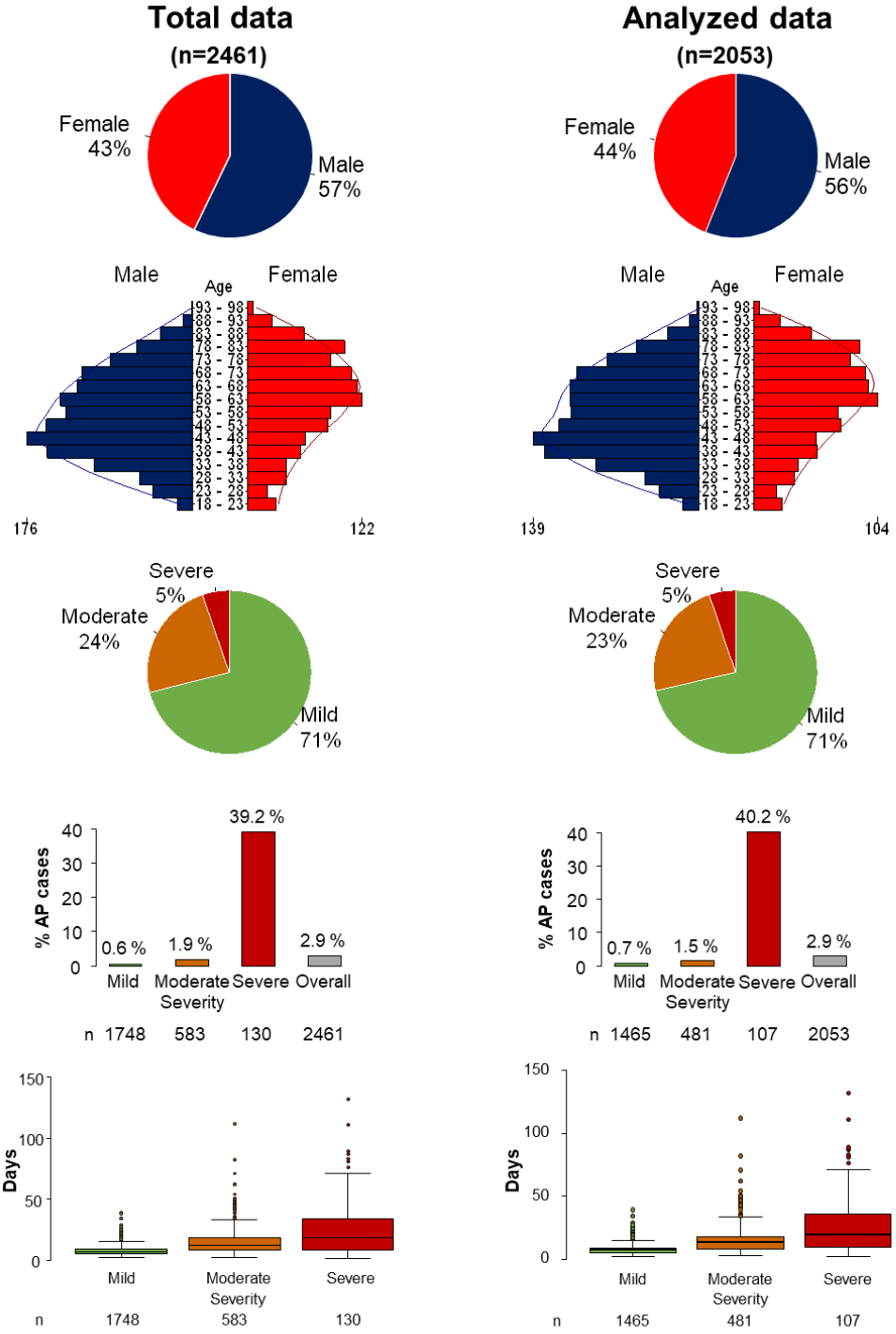

Figure 9. Representativeness analysis. Group one represents the total number of patients with AP in our registry, while the analyzed data represents the group of patients after the selection based on our eligibility criteria. None of the assessed parameters showed a difference between the two groups ($p>0.05$), meaning that our analyzed cohort is representative of the overall patient population.

We further detailed the definitions of included variables in **Appendix Table 2**. Alcohol abuse was defined based on the European Association for the Study of the Liver (EASL) NAFLD guideline as ≥20g/day for females and ≥30g/day for males (18).

7.1.4. Data quality and representativeness

Appendix Table 2. summarizes the proportion of available data for each parameter. We compared the characteristics of the original cohort (n=2,461) with those of our analyzed cohort (n=2,053) and found no discrepancies in terms of gender, age, severity distribution, and LOH (**Figure 9**). Our cohort selection process is illustrated in **Figure 10**.

7.1.5. Statistical analysis

Our research involved a post hoc cross-sectional analysis of the prospective acute pancreatitis registry. We used the R statistical software, version 4.0.2 (R Core Team, 2020, Vienna, Austria) to conduct this analysis.

For our descriptive statistics, we presented median with 25% and 75% percentiles (interquartile range - IQR) or mean with standard deviation (SD) for continuous variables and frequencies and relative frequencies (%) for categorical variables. We used the Chi2 test or Fisher's exact test for categorical variables and Welch's two-sample t-test or Kruskal-Wallis test, followed by Dunn's post hoc test for continuous variables.

We conducted a multivariate binary logistic regression analysis to identify the risk factors that are independently associated with in-hospital mortality, MSAP, and SAP. Our analysis included MAFLD, age ≥60, gender, smoking, alcohol abuse, T2DM, and overweight/obesity as variables. These variables were selected based on the univariate analysis. We also performed analyses that excluded T2DM or overweight/obesity due to the level in the variance inflation factor. Adjusted odds ratios (OR) with 95% confidence intervals (CIs) were calculated. We report the Variance Inflation Factor (VIF) along with the ORs.

To determine statistical significance, we considered $p<0.05$, except for the Kruskal-Wallis test, followed by Dunn's post hoc test, where $p<0.025$ was considered statistically significant.

Additionally, we conducted subgroup analyses based on the diagnostic criteria of MAFLD (MAFLD BMI, MAFLD T2DM, and MAFLD other), the number of positive

criteria in MAFLD (1, 2, or 3), age < and ≥60 years, abdominal imaging with CT and ultrasound, and patients with and without alcohol abuse. These subgroup analyses allowed us to explore the potential differences in our findings across different patient populations and criteria.

Our study utilized advanced statistical methods to analyze a prospective acute pancreatitis registry, identify significant risk factors associated with in-hospital mortality, MSAP, and SAP, and conduct subgroup analyses to explore differences across patient populations.

7.2. Results

7.2.1. One in three patients suffering from AP has MAFLD

In accordance with our selection criteria, we selected a total of 2,053 patients with acute pancreatitis for our study. Of these, 801 patients (39%, 95% CI: 37-41.1%) were included in the MAFLD group, while 1,252 patients (61%) were categorized into the non-MAFLD group, as presented in **Figure 10**. We conducted a thorough analysis of the data collected and reported the descriptive statistics of the included AP patients in **Table 6.** Overall, there were more males (56%) and patients aged <60 (55%) in our cohort, while the mean age was 57 (±17). Interestingly, 52 patients with steatosis were not eligible for the MAFLD group and were therefore included in the non-MAFLD group. The mean BMI of patients was 28.4 (±5.9), meaning that, on average, the analyzed population was overweight. On the other hand, 71% (n=1,349/1,898) of the patients had a BMI over 25 kg/m2. Regarding comorbidities, 578/1,850 (31%) had no comorbidities based on the Charlson comorbidity index (CCI). However, 69% of the patients had a CCI≥1, while almost 20% had a CCI≥3.

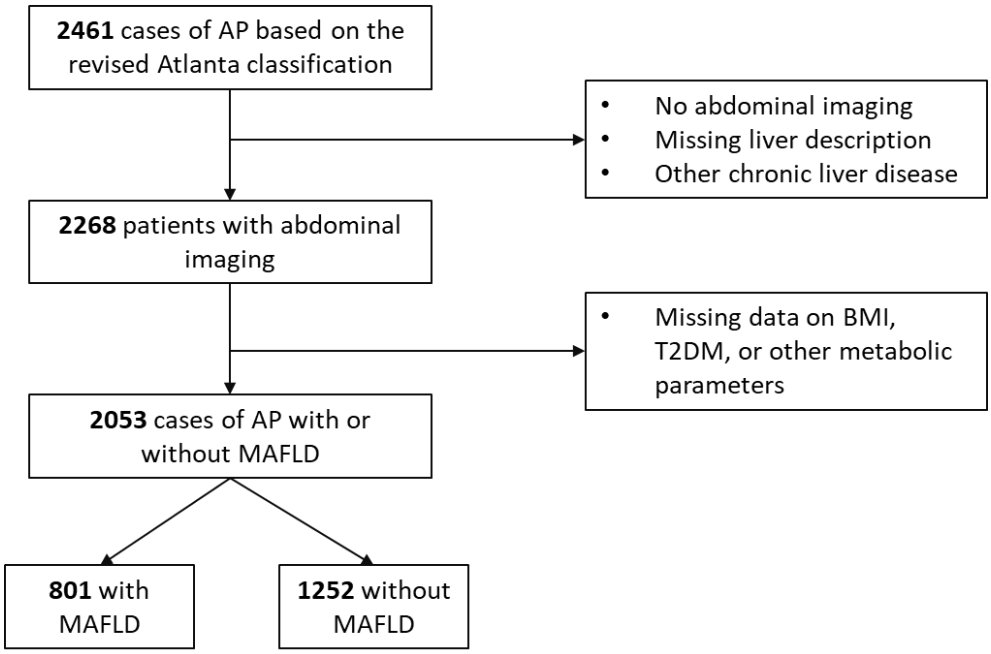

Figure 10. The selection process of the analyzed dataset. As a first step, we excluded patients with no abdominal imaging, missing or equivocal liver descriptions on imaging, and other chronic liver diseases. Next, we assessed the three diagnostic criteria for MAFLD. If we had missing information regarding body-mass index (BMI), type-2 diabetes mellitus (T2DM), or other metabolic parameters, we excluded these patients from our analysis.

Regarding the course of the disease, 913/2,053 (44%) had biliary etiology and 432/2,053 (21%) of the patiens had AP due to alcohol abuse. Only a small percentage, 60/2,053 (2.9%) of the patients, died during the hospitalization, while in 1465/2,053 (71.4%) cases, the disease course was mild.

Lastly, on the median, patients reached their maximum CRP on day 3 (IQR 2-4) while the mean LOS was 10.62 (±9.9).

Specifically, our study revealed that 1,818 patients (89%) underwent at least one abdominal ultrasound, with 1,624 of these scans being conducted within the first two days of admission. In addition, 1,099 patients relied solely on ultrasound imaging. Furthermore, 952 patients (46%) underwent at least one CT scan, with 606 scans being conducted during the first two days of admission and 233 relying solely on CT imaging. Additionally, 23 patients (1%) underwent at least one magnetic resonance imaging, while 36 patients (2%) underwent at least one endoscopic ultrasound.

7.2.2. Patients in the MAFLD group have more comorbidities compared to the non-MFLD group

In our subsequent analysis, we compared AP patients with and without MAFLD and discovered notable differences. Specifically, AP patients with MAFLD had a lower proportion of females compared to those without (34% vs. 50%, $p<0.001$), and a higher percentage of patients below the age of 60 (59% vs. 52%, $p<0.001$). Additionally, patients with MAFLD showed higher rates of comorbidities, the highest being hypertension (83 vs. 72%, $p<0.001$) and overweight/ obesity (93 vs. 56%, $p<0.001$). Furthermore, MAFLD patients consumed alcohol (23 vs. 12%, $p<0.001$) in a higher proportion but showed a similar smoking rate with non-MAFLD patients (31 vs. 28%, $p=0.195$) (**Table 6**).

Furthermore, we observed that MAFLD was associated with elevated rates of severity, local and systemic complications, and diabetes as a complication. However, we did not find any significant differences in the rate of in-hospital mortality, cardiovascular failure, and pseudocysts between the two groups ($p=0.874$, $p=0.214$, and $p=0.065$, respectively) (see **Table 6** and **Figures 11 and 12**). **Figures 11 and 12** illustrate the rate of various outcomes observed in the analyzed MAFLD subgroups. The highest event rates were observed in the MAFLD other subgroup and MAFLD patients with all three diagnostic criteria positive.

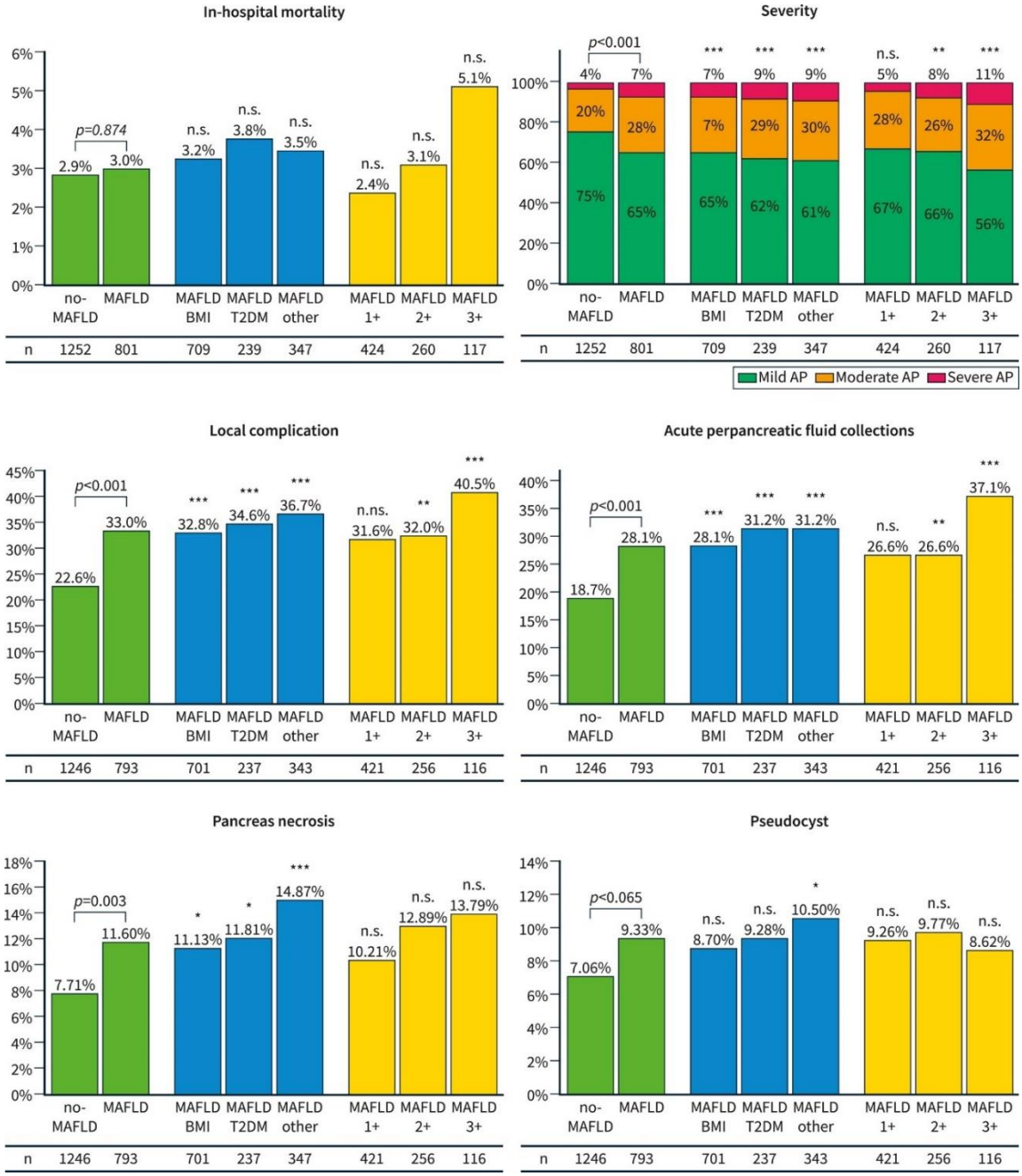

Figure 11. Summary figure showing the rate of in-hospital mortality, severity, local complications, acute peripancreatic fluid collection, pancreas necrosis, and pseudocysts based on the different MAFLD groups. Colors for severity show mild (green), moderate (yellow), and severe (red) acute pancreatitis. Significance was either presented between the groups by the exact value or with symbols *, **, *** (<0.05, <0.01, <0.001, respectively). Non-significant differences compared to the non-MAFLD group were marked as 'n.s.'

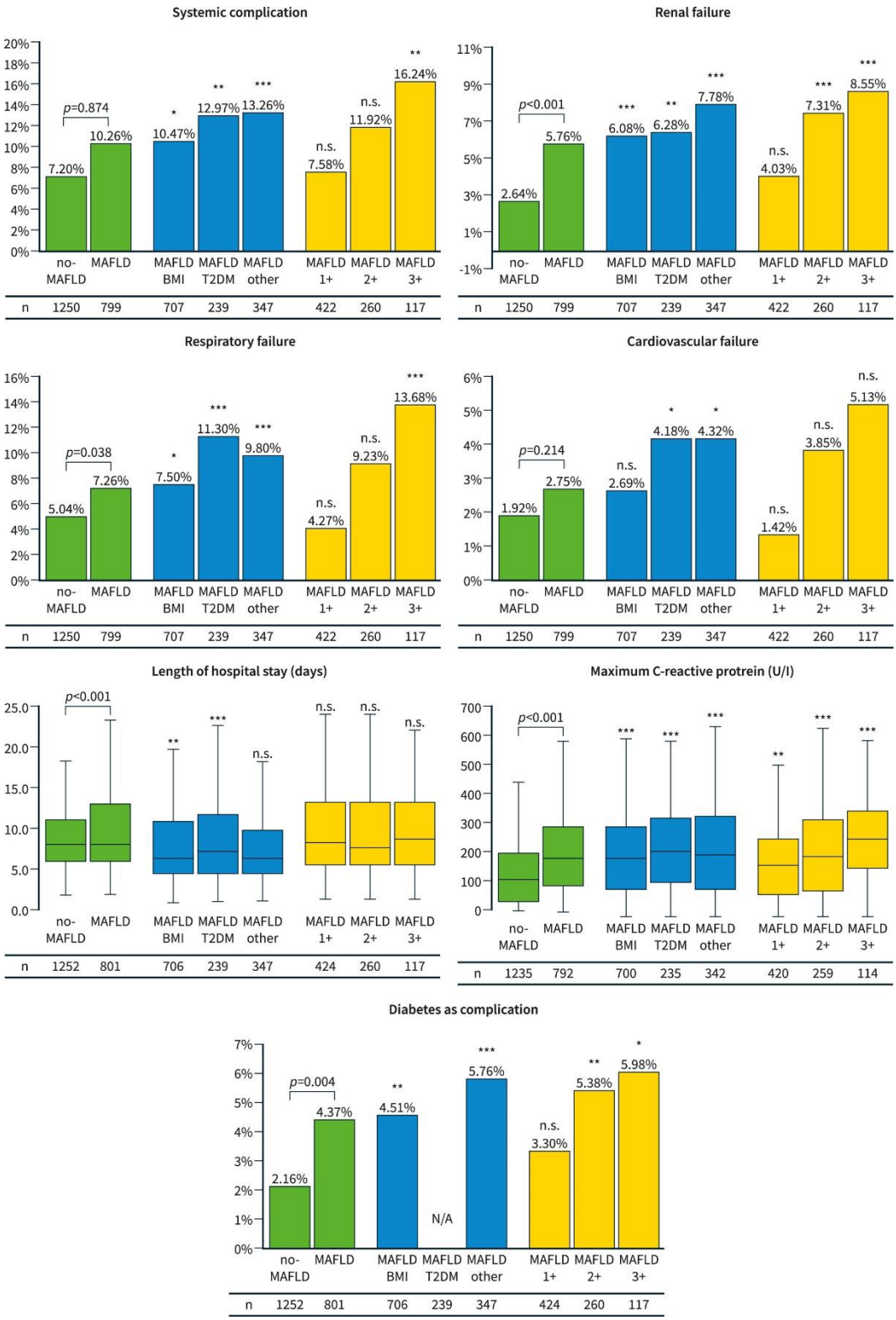

Figure 12. Summary figure showing the rate of multi-organ failure, renal failure, respiratory failure, cardiovascular failure, and diabetes as a complication, and the boxplots for the length of hospital stay and maximum C-reactive protein based on the different MAFLD groups. In the subgroup of MAFLD T2DM diabetes as a complication was not applicable (N/A). On the boxplots, the box represents the median with the 25 and 75% quartile (Q1 and Q3), while the whiskers represent the 1.5 x interquartile (IQR) range compared to Q1 and Q3. Significance was either presented between the groups by the exact value or with symbols *, **, *** (<0.05, <0.01, <0.001, respectively).

7.2.3. MAFLD is an independent risk factor of AP severity but not for in-hospital mortality

According to the results of a multivariate-adjusted logistic regression analysis presented in **Table 7**, individuals with MAFLD had higher odds of developing MSAP independently (OR=1.39, 95% CI: 1.05-1.84), but there was no significant increase in the odds of in-hospital mortality (OR=0.87, 95% CI: 0.40-1.83) or SAP (OR=1.63, 95% CI: 0.93-2.89) in the MAFLD group. Further detailed multivariate logistic regression analyses for these outcomes are provided in **Table 8**, and the VIF values for each parameter were found to be acceptable.

We also analyzed the diagnostic criteria for MAFLD and found significant differences in their impact on disease outcomes. MAFLD based on overweight/obesity only increased the odds of SAP (OR=1.71, 95% CI: 1.03-2.83) and MSAP (OR=1.50, 95% CI: 1.17-1.92) when overweight/obesity was excluded from the multivariate model. In contrast, MAFLD based on T2DM only remained a significant predictor of MSAP (OR=2.37, 95% CI: 1.33-4.33) if T2DM was included in the multivariate model. When T2DM was excluded, the odds of MSAP were no longer significant (Model 2 OR=1.36, 95% CI: 0.93-1.96).

Finally, MAFLD based on metabolic risk abnormalities was found to be an independent predictor for both SAP (OR=2.53, 95% CI: 1.31-4.82) and MSAP (OR=1.72, 95% CI: 1.21-2.44), according to **Table 7**. These findings suggest that the specific diagnostic criteria used to define MAFLD may have different impacts on disease outcomes.

Table 6. Basic characteristics of the included patients and comparison between MAFLD and non-MAFLD groups

Parameter	**All patients**	**MAFLD**	**non-MAFLD**	**p-value**
Age	57 (±17) (2053)	56 (±14) (801)	57 (±18) (1252)	0.162[1]
Age ≥60 years	932/2,053 (45%)	332/801 (41%)	600/1,252 (48%)	<0.001[2]
Female	902/2,053 (44%)	276/801 (34%)	626/1,252 (50%)	<0.001[2]
Comorbidities				
Steatosis	853/2,053 (42%)	801/801 (100%)	52/1,252 (4%)	<0.001[2]
Hypertension	1196/1,563 (77%)	537/647 (83%)	659/916 (72%)	<0.001[2]
Type 2 diabetes mellitus	426/2,039 (21%)	239/797 (30%)	187/1,242 (15%)	<0.001[2]
Obesity/ overweight	1,349/1,898 (71%)	709/765 (93%)	640/1,133 (56%)	<0.001[2]
Body mass index	28.4 (±5.9) (1898)	31.10 (±5.53) (765)	26.57 (±5.41) (1,133)	<0.001[1]
Hypertriglyceridemia	440/1,393 (32%)	273/592 (46%)	167/801 (21%)	<0.001[2]
Hypercholesterinemia	410/1,285 (32%)	223/527 (42%)	187/758 (25%)	<0.001[2]
CCI 0	578/1,850 (31%)	0/716 (0%)	578/1,134 (51%)	<0.001[2]
CCI 1-2	918/1,850 (50%)	533/716 (74%)	385/1,134 (34%)	<0.001[2]
CCI 3-4	253/1,850 (14%)	126/716 (18%)	127/1,134 (11%)	<0.001[2]
CCI ≥5	101/1,850 (5.5%)	57/716 (8%)	44/1,134 (4%)	<0.001[2]
Smoking	596/2,041 (29%)	246/798 (31%)	350/1,243 (28%)	0.195[2]
Alcohol consumption	236/1,457 (16%)	125/548 (23%)	111/909 (12%)	<0.001[2]
Laboratory values				
Admission amylase (U/ l)	722 (300-1,518) (1,910)	595 (228-1,305) (748)	773 (346-1,643) (1,162)	<0.001[1]
Admission lipase (U/ l)	1,448 (573-3,387) (1,512)	1,324 (471-3,322) (596)	1,499 (635-3,429) (916)	0.593[1]
Max CRP (U/ l)	139 (51-237) (2,027)	184 (88-286) (792)	109 (38-200) (1,235)	<0.001[1]
Max CRP day	3 (2-4) (2,027)	3 (2-4) (792)	3 (2-4) (1,235)	0.218[1]
Admission HbA1C (%)	5.60 (5.30-6.20) (685)	5.90 (5.50-7.00) (269)	5.50 (5.20-5.80) (416)	<0.001[1]
Admission glucose (mmol/l)	7.5 (6.1-9.6) (1,799)	8.39 (6.70-10.79) (702)	7.00 (5.83-8.93) (1,097)	<0.001[1]
Etiology				
Biliary	913/2,053 (44%)	297/801 (37%)	616/1,252 (49%)	<0.001[2]

Alcohol	432/2,053 (21%)	226/801 (28%)	206/1,252 (17%)	<0.001[2]
Hypertrigliceridaemia	140/2,053 (7%)	108/801(14%)	32/1,252 (3%)	<0.001[2]
Other	568/2,053 (28%)	170/801 (21%)	398/1,252 (31%)	<0.001[2]
Outcomes				
In-hospital mortality	60/2,053 (2.9%)	24/801 (3%)	36/1,252 (2.9%)	0.874[2]
Mild AP	1465/2,053 (71.4%)	520/801 (65%)	945/1,252 (75.5%)	<0.001[2]
Moderate AP	481/2,053 (23.4%)	225/801 (28%)	256/1,252 (20.5%)	
Severe AP	107/2,053 (5.2%)	56/801 (7%)	51/1,252 (4%)	
Local complications	543/2,039 (26.6%)	262/793 (33%)	281/1,246 (22.5)	<0.001[2]
Peripancreatic fluid collection	456/2,039 (22.4%)	223/793 (28.1%)	233/1,246 (18.7%)	<0.001[2]
Pancreas necrosis	188/2,038 (9.2%)	92/793 (11.6%)	96/1,245 (7.7%)	0.003[2]
Pseudocyst	162/2,039 (7.9%)	74/793 (9.3%)	88/1,246 (7.1%)	0.065[2]
Multi-organ failure	172/2,049 (8.4%)	82/799 (10.3%)	90/1,250 (7.2%)	0.015[2]
Renal failure	79/2,049 (3.9%)	46/799 (5.8%)	33/1,250 (2.6%)	<0.001[2]
Respiratory failure	121/2,048 (5.9%)	58/799 (7.3%)	63/1,249 (5%)	0.038[2]
Cardiovascular failure	46/2,049 (2.2%)	22/799 (2.8%)	24/1,250 (1.9%)	0.214[2]
Diabetes as complication	62/2,053 (3%)	35/801 (4.4%)	27/1,252 (2.2%)	0.004[2]
Length of hospital stay	10.62 (±9.9) (2,053)	11.54 (±11.24) (801)	10.03 (±8.91) (1,252)	<0.001[1]

AP: acute pancreatitis; CCI: Charlson Comorbidity Index; CRP: C-reactive protein;

Categorical variables were described as event/total (%), continuous variables as mean or median with standard deviation (SD) or 25% and 75% percentiles (IQR)

[1]Welch Two Sample t-test; [2]Pearson's Chi-squared test

Table 7. Multivariable adjusted logistic regression analysis for MAFLD vs. non-MAFLD comparison and different MAFLD groups compared to non-MAFLD in patients with AP.

Comparison	In-hospital mortality	Moderate-to-severe AP	Severe AP
MAFLD vs non-MAFLD	0.87 (0.40-1.83)	**1.39 (1.05-1.84)**	1.63 (0.93-2.89)
MAFLD based on obesity or overweight model 1	0.95 (0.43-2.10)	**1.35 (1.01-1.81)**	1.56 (0.87-2.87)
MAFLD based on obesity or overweight model 2	0.96 (0.47-1.86)	**1.50 (1.17-1.92)**	**1.71 (1.03-2.83)**
MAFLD based on T2DM model 1	3.52 (0.50-70.2)	**2.37 (1.33-4.33)**	2.49 (0.82-9.26)
MAFLD based on T2DM model 2	0.78 (0.23-2.07)	1.36 (0.93-1.96)	1.53 (0.75-2.92)
MAFLD based on metabolic risk abnormalities	1.69 (0.66-3.99)	**1.72 (1.21-2.44)**	**2.53 (1.31-4.82)**
MAFLD meets one criteria†	0.50 (0.16-1.31)	1.23 (0.88-1.70)	1.13 (0.54-2.27)
MAFLD meets two criteria†	1.29 (0.43-3.39)	1.38 (0.93-2.04)	2.08 (0.97-4.35)
MAFLD meets three criteria†	6.00 (0.88-50.9)	**3.04 (1.63-5.70)**	**4.76 (1.50-15.4)**
MAFLD alcohol consumption excluded	0.97 (0.42-2.16)	**1.51 (1.11-2.03)**	**1.89 (1.03-3.54)**
MAFLD alcohol consumers	0.61 (0.09-4.04)	0.87 (0.42-1.79)	0.82 (0.22-3.27)
MAFLD below <60 years	3.03 (0.73-15.0)	**1.53 (1.03-2.28)**	**3.16 (1.17-9.41)**
MAFLD above ≥60 years	0.46 (0.16-1.21)	1.17 (0.78-1.74)	1.09 (0.52-2.24)
MAFLD based on abdominal CT	0.75 (0.33-1.69)	1.12 (0.78-1.63)	1.26 (0.67-2.36)
MAFLD based on abdominal ultrasound	1.17 (0.46-2.98)	**1.61 (1.19-2.18)**	**1.97 (1.04, 3.82)**

All the bold values highlight those with $p<0.05$

Data are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) tested by multivariable logistic regression analyses.

Multivariate analyses were adjusted for MAFLD, age ≥60, gender, smoking, alcohol abuse, T2DM, and overweight/ obesity.

Model 1: obesity/ overweight and T2DM are included in the models

Model 2: obesity/ overweight or T2DM are excluded from the models

† overweight/obesity, T2DM or/and ≥two metabolic risk abnormalities

AP: acute pancreatitis; **CT:** computed tomography; **MAFLD:** metabolic associated fatty liver disease; **T2DM:** type 2 diabetes mellitus.

Table 8. Multivariate logistic regression analysis comparing overall MAFLD and non-MAFLD groups regarding the odds of in-hospital mortality, moderately severe AP (MAP), and moderate-to-severe AP (MSAP). We performed a similar analysis for each comparison in Table 7.

Variable	Nº	Event	OR	95% CI	p-value	VIF
In-hospital mortality						
MAFLD vs non-MAFLD	1,309	36				1.22
No-MAFLD	792	22	1.00	—		
MAFLD	517	14	0.865	0.400, 1.83	0.707	
Age ≥60	1,309	36				1.11
No	684	12	1.00	—		
Yes	625	24	2.14	1.04, 4.66	0.044	
Gender	1,309	36				1.12
Male	656	23	1.00	—		
Female	653	13	0.451	0.212, 0.930	0.033	
Smoking	1,309	36				1.22
No	968	32	1.00	—		
Yes	341	4	0.307	0.083, 0.890	0.046	
Alcohol abuse	1,309	36				1.24
No	1,102	29	1.00	—		
Yes	207	7	1.74	0.634, 4.29	0.252	
Overweight/ obesity	1,309	36				1.18
No	373	8	1.00	—		
Yes	936	28	1.27	0.553, 3.21	0.585	
Type 2 diabetes mellitus	1,309	36				1.03
No	1,031	31	1.00	—		
Yes	278	5	0.463	0.154, 1.13	0.121	
Moderately severe AP (MAP)						
MAFLD vs non-MAFLD	1,309	357				1.25
No-MAFLD	792	185	1.00	—		
MAFLD	517	172	1.39	1.05, 1.84	0.020	
Age ≥60	1,309	357				1.15
No	684	195	1.00	—		
Yes	625	162	0.871	0.668, 1.13	0.306	
Gender	1,309	357				1.20
Male	656	201	1.00	—		
Female	653	156	0.774	0.591, 1.01	0.063	
Smoking	1,309	357				1.32
No	968	270	1.00	—		
Yes	341	87	0.702	0.504, 0.97	0.034	
Alcohol abuse	1,309	357				1.27
No	1,102	285	1.00	—		
Yes	207	72	1.47	1.02, 2.11	0.036	
Overweight/ obesity	1,309	357				1.23
No	373	79	1.00	—		
Yes	936	278	1.36	0.99, 1.88	0.057	
Type 2 diabetes mellitus	1,309	357				1.05
No	1,031	283	1.00	—		
Yes	278	74	0.871	0.635, 1.18	0.383	
Moderate-to-severe AP (MSAP)						
MAFLD vs non-MAFLD	1,309	64				1.25
No-MAFLD	792	29	1.00	—		
MAFLD	517	35	1.63	0.925, 2.89	0.093	
Age ≥60	1,309	64				1.11

Variable	Nº	Event	OR	95% CI	p-value	VIF
No	684	27	1.00	—		
Yes	625	37	1.39	0.811, 2.40	0.237	
Gender	1,309	64				1.19
Male	656	36	1.00	—		
Female	653	28	0.783	0.448, 1.37	0.388	
Smoking	1,309	64				1.21
No	968	55	1.00	—		
Yes	341	9	0.387	0.166, 0.819	0.019	
Alcohol abuse	1,309	64				1.27
No	1,102	50	1.00	—		
Yes	207	14	1.86	0.903, 3.69	0.081	
Overweight/ obesity	1,309	64				1.19
No	373	11	1.00	—		
Yes	936	53	1.37	0.682, 2.94	0.397	
Type 2 diabetes mellitus	1,309	64				1.04
No	1,031	48	1.00	—		
Yes	278	16	0.99	0.529, 1.77	0.976	

CI = Confidence Interval, OR = Odds Ratio, VIF = Variance Inflation Factor

7.2.4. MAFLD dose-dependently increases the odds of SAP

In our study, we conducted a comprehensive analysis to investigate the impact of multiple positive MAFLD criteria on patients with acute pancreatitis (AP) compared to those without MAFLD. We observed that the presence of one, two, and three diagnostic criteria for MAFLD led to a gradual increase in the odds of developing moderate-severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) in a dose-dependent manner (**Table 7**).

The ORs for MSAP were 1.23 (95% CI: 0.88-1.70) with one MAFLD criterion, 1.38 (95% CI: 0.93-2.04) with two criteria, and 3.04 (95% CI: 1.63-5.70) with three criteria. Similarly, the ORs for SAP were 1.13 (95% CI: 0.54-2.27) with one MAFLD criterion, 2.08 (95% CI: 0.97-4.35) with two criteria, and 4.76 (95% CI: 1.50-15.4) with three criteria.

7.2.5. The effect of MAFLD is more substantial in patients without alcohol abuse, age <60 years, and with steatosis diagnosed based on abdominal ultrasound

We performed a subgroup analysis to explore the effect of MAFLD on acute pancreatitis based on age, alcohol abuse, and diagnostic methods. Interestingly, we found that the impact of MAFLD on acute pancreatitis varied significantly in different patient subgroups.

In the subgroup analysis of patients below and above 60 years, we observed a significant difference in the effect of MAFLD. MAFLD was associated with increased odds of MSAP (OR=1.53, 95% CI: 1.03-2.28) and SAP (OR=3.16, 95% CI: 1.17-9.41) in patients below 60 years, but not in patients above 60 years (OR=1.17, 95% CI: 0.78-1.74 and OR=1.09, 95% CI: 0.52-2.24, respectively).

Additionally, in the subgroup analysis of patients with and without alcohol abuse, the effect of MAFLD on acute pancreatitis differed significantly. The odds of MSAP (OR=1.51, 95% CI: 1.11-2.03) and SAP (OR=1.89, 95% CI: 1.03-3.54) were higher in MAFLD patients without alcohol abuse but not in MAFLD patients with alcohol abuse (OR=0.87, 95% CI: 0.42-1.79 and OR=0.82, 95% CI: 0.22-3.27, respectively).

Furthermore, we found that the diagnostic method used to detect MAFLD also had a significant impact on the odds of developing MSAP and SAP. MAFLD diagnosed by abdominal ultrasound was associated with increased odds of MSAP (OR=1.61, 95% CI: 1.19-2.18) and SAP (OR=1.97, 95% CI: 1.04-3.82). However, MAFLD diagnosed by abdominal CT was not associated with a worse outcome.

7.3. Discussion

7.3.1. Summary of findings

Until now, only a limited number of studies have investigated the impact of MAFLD on other diseases, and this number is constantly growing. However, this current study represents a groundbreaking effort to explore the correlation between MAFLD and the severity of AP. The findings of our research revealed that nearly 39% of AP patients also suffer from MAFLD, which has a significant effect on the severity of AP, but does not impact the chances of in-hospital mortality.

To assess the relationship between MAFLD and the severity of AP, we used a variety of diagnostic criteria for MAFLD. Our analysis identified that individuals with other metabolic risk abnormalities had the highest odds of developing a more severe form of AP. Additionally, the number of positive MAFLD criteria showed a dose-dependent association with increased chances of in-hospital mortality, as well as the development of moderate and severe AP. Furthermore, we found that the effect of MAFLD on AP was more pronounced in patients under 60 years of age and without alcohol abuse. Finally, we observed that the type of abdominal imaging method used may also affect the relationship between MAFLD and AP severity.

7.3.2. Explanation and elaboration

Our study findings align with the most comprehensive meta-analysis available on this topic, which included 13 articles (31). The meta-analysis showed that NAFLD/ FLD increased the chances of developing a more severe form of AP but did not impact in-hospital mortality rates. However, this could be attributed to the fact that mortality rates in AP patients increase rapidly after the age of 59 (27, 79), and a majority of our patients with MAFLD were below 60 years of age. It is worth noting that the average age of our study participants was consistent with other European cohorts (80). This indicates that our study results are generalizable to a broader population and can be used to inform clinical practice and management of AP patients with MAFLD.

A recent study examining all-cause mortality due to MAFLD in a general population found a lower prevalence of MAFLD, at 25.9% (95% CI 23.6-28.3), compared to our cohort, which reported a rate of 39% (CI: 37-41.1%) (81). The higher prevalence of MAFLD in our study population may be attributed to the shared etiology of MAFLD and AP, or MAFLD may increase the incidence of AP. Our results also indicated that

alcohol and hypertriglyceridemia-induced AP were more prevalent in patients with MAFLD compared to those without. Interestingly, the current definition of MAFLD does not exclude individuals who consume alcohol (22), given the heterogeneity of NAFLD and emerging evidence suggesting that even moderate alcohol consumption may pose risks for individuals with NAFLD (82). Furthermore, the high prevalence of MAFLD in Eastern Europe may partly explain the elevated rates of MAFLD observed in our study (83). This finding emphasizes the importance of region-specific studies in understanding the epidemiology of MAFLD and its associated diseases.

The prediction of severe AP has been extensively studied in the past. However, our study group recently developed a novel early prediction tool using machine learning, which involved a large number of AP cases. This tool has the ability to predict severe AP with an impressive area under the curve (AUC) of 0.81±0.03 (84). Several other prognostic tools have been developed with similar AUC values, which can also predict a more severe course in AP. However, none of these tools have assessed or included the presence of NAFLD/ MAFLD as a possible prognostic factor (85-88).

In our study, we found that compared to other metabolic risk factors, the presence of MAFLD increased the odds of a more severe AP dose-dependently. The odds ratios for a more severe AP increased with the number of positive MAFLD criteria, with odds ratios of 1.13, 2.08, and 4.76 for one, two, or three positive criteria, respectively. Other studies have also investigated the impact of metabolic risk factors on AP outcomes. For example, Dobszai et al.(28) found that having a BMI greater than 25 increased the odds of severe AP almost three-fold compared to those with a normal BMI. The effect of BMI on AP severity also increased with the degree of obesity. Additionally, our research group found that T2DM, which is a component of the MAFLD diagnosis, increased the odds of intensive care unit admission, renal failure, and overall complications in patients with AP (89). Lastly, hypertriglyceridemia, another component of the metabolic syndrome, dose-dependently increased the odds of local complications and organ failure in patients with AP (90).

Our study aimed to investigate how different types of MAFLD groups may impact the course of AP in distinct ways. We particularly focused on the non-obese, non-T2DM MAFLD patients, who are also known as metabolically unhealthy lean (non-obese) patients (22). This group of patients with MAFLD has been found to have a greater accumulation of ectopic fat, particularly in visceral fat format, which can contribute to

peripancreatic fat infiltration in AP. In addition, hypertriglyceridemia in this group may lead to the formation of toxic unsaturated fatty acids and an increase in chylomicron concentration, elevating blood viscosity and leading to complications (91). Moreover, it was found that obesity was associated with increased intrapancreatic fat and visceral fat around the pancreas in obese MAFLD patients (92). This finding is consistent with previous research that suggests obesity is a significant risk factor for AP (28). Additionally, our study found that hyperglycemic states, a factor included in the diagnosis of T2DM MAFLD, were previously linked to direct pancreatotoxic effects, mainly through the intracellular increase of reactive oxygen species (93). This can lead to complications such as renal failure, intensive care unit admission, and overall complications, as found in another study by our research group (93). Overall, our research highlights the importance of considering different types of MAFLD groups and their associated metabolic risk factors when investigating the impact of MAFLD on AP.

Further investigation is required to better understand how MAFLD exacerbates the course of AP. Currently, few studies have explored this relationship in depth. One notable study by Wang et al.(74) conducted on AP rat fatty liver models identified several dysregulated genes that contribute to the aggravation of AP. Specifically, the study found that the inhibition of the Peroxisome Proliferator-Activated Receptor alpha (PPAR-α) signaling pathway and the fatty acid degradation pathway may lead to the exacerbation of AP. In another study, Wang et al.(64) found lower levels of alpha-1-antitrypsin in both human and rat AP models. This protein is an inhibitor of several pancreatic proteases that can cause tissue damage in AP. Therefore, the lower levels of alpha-1-antitrypsin may contribute to the severity of AP in patients with MAFLD. Lastly, Lin et al.(94) conducted a recent study on FLD rat models and found increased bacterial translocation in the liver and pancreas. This suggests that gut microbiota may play a role in the pathogenesis of AP in patients with MAFLD. Overall, while these studies provide some insights into the mechanisms underlying the effect of MAFLD on AP, further research is needed to fully elucidate this relationship.

In our study, we utilized multiple types of abdominal imaging to diagnose MAFLD. Interestingly, we found that the diagnosis of MAFLD using abdominal ultrasound resulted in increased severity of AP, whereas the diagnosis of MAFLD using abdominal CT did not show a significant association. This difference in results could be attributed to the varying levels of steatosis that can be detected by each imaging modality.

It is worth noting that one of the diagnostic criteria for AP is based on abdominal imaging, but current guidelines do not require imaging to confirm the diagnosis (25). Ultrasound is currently the most widely available tool for diagnosing steatosis, but its diagnostic accuracy decreases when the fat percentage is below 20% (22). Moreover, high abdominal fat can further decrease its diagnostic performance. On the other hand, abdominal CT or MRI can detect lower levels of steatosis, but AP guidelines recommend their use at least 72 hours after the onset of the disease (25). The most recent cohort analysis published in 2022 investigated liver spontaneous attenuation (LSA) measured with abdominal CT as a possible predictive factor (95). The authors found 3.23 (95% CI: 1.33−51.2) and 8.82 (95% CI: 1.91−69.7) odds of severe AP in the third and fourth quartile LSA groups. They concluded that LSA on CT is associated with AP severity. Overall, the use of different imaging modalities to diagnose MAFLD and AP can yield different results, and the appropriate choice of imaging modality should be based on the patient's specific clinical scenario. These findings highlight the importance of using appropriate imaging modalities to diagnose MAFLD and AP accurately.

The incidence of diabetes as a complication was found to be significantly higher in the MAFLD group in our study, with a rate of 4.4% compared to 2.2% in the non-MAFLD group (p=0.004). In our study, diabetes was diagnosed based on abnormal fasting glucose levels at discharge. However, other studies recommend following the diagnostic criteria for diabetes established by the American Diabetes Association (77), as Petrov MS et al.(78) stated in a review. Yuan et al.(59) also found that fatty liver was a risk factor for abnormal fasting blood glucose levels (HR=1.87, 95% CI=1.16-3.01) after the first episode of AP. This finding supports our observation that MAFLD is associated with a higher incidence of diabetes as a complication in patients with AP. However, it is worth noting that in our meta-analysis (31) we found that only Yuan et al.(59) evaluated long-term complications, with a median follow-up of three years. Therefore, further research is needed to investigate the long-term impact of MAFLD on the development of diabetes in patients with AP.

Although we were unable to evaluate the readmission rate in our study, a previous investigation reported an increased likelihood of hospital readmission for patients with fatty liver disease and AP (OR=3.48, 95% CI: 1.70–7.11). However, this study had a retrospective design, and the authors did not distinguish between patients with the first episode of AP or those with chronic pancreatitis (53).

We could not assess the rate of readmission. However, a previous study found that patients with fatty liver disease had increased odds of hospital readmission with AP (OR = 3.48, 95% CI: 1.70–7.11). In this study, the data were collected retrospectively, and the authors did not differentiate between patients with the first AP episode or chronic pancreatitis (53). This highlights the importance of patient education during the first course of AP. Patient education can be effective during hospitalization. Nagy et al.(96) analyzed the same database as this research. They found that a brief psychological intervention in alcohol-induced AP can decrease alcohol consumption and, consequently, the readmission rate. However, these results need to be validated in randomized controlled trials.

There is currently no evidence to suggest that AP patients with MAFLD require a unique treatment approach. Thus, as per current guidelines, the recommended course of action in the acute phase is to initiate fluid resuscitation and early refeeding as soon as possible. However, given the higher incidence of patients with T2DM, preventing hyperglycemia is crucial due to its toxic effects (93). Additionally, AP induced by hypertriglyceridemia occurs more frequently in the MAFLD group. Therefore, it is recommended that TG levels are assessed upon admission.

Lastly, it must be highlighted that the diagnostic criteria of MAFLD need further validation. However, it was already endorsed by multiple expert boards (97, 98). In a research letter, Fouad et al.(99) emphasized that both patients and physicians tend to underestimate the severity of FLD. Despite the diagnosis, management, and treatment of patients with NAFLD/NASH (non-alcoholic steatohepatitis), there is a significant lack of knowledge regarding the differences between the two conditions, often resulting in non-compliance with current guidelines. However, the shift from NAFLD to MAFLD appears to increase physicians' awareness of the condition. Additionally, most participants favor the recent proposal to consider MAFLD as a continuous disease rather than a binary classification based solely on the presence of steatohepatitis. Thus, this report contributes to the growing number of voices supporting the transition from NAFLD to MAFLD.

7.3.3. Strengths and limitations

As the **strength of our study**, we have to mention that:

a. Our analysis is one of the first to analyze the usability of the MAFLD definition; most centers are still using the negative diagnostic criteria of NAFLD
b. This is the largest registry analysis of prospectively collected patients with acute pancreatitis. Patient data were collected on admission and during the hospitalization.
c. The data quality for the outcomes was 100% for almost all of them.
d. We performed multiple subgroup analyses using multivariate logistic regression analysis, showing the independent effect of MAFLD on the course of acute pancreatitis.
e. We followed the international recommendations when reporting our results.

On the other hand, the **limitations of our study** have to be mentioned:

a. Although patient data were collected prospectively, the presence of MAFLD was determined retrospectively based on the collected data. This was because the definition of MAFLD was introduced after the start of the acute pancreatitis registry.
b. In some cases, we did not have the details (e.g., liver imaging) to determine the presence of MAFLD, which may result in selection bias. However, our representativeness analysis did not show a difference between the analyzed and the original patient group.
c. We could not analyze long-term outcomes, like 30-day or 1-year mortality or readmission.
d. Although the number of patients was high, we could only include a small number of patients in some subgroups.
e. The gold standard for measuring liver steatosis is a biopsy, which was not performed in any acute pancreatitis cases. However, the definition of MAFLD does not require the performance of a biopsy.
f. We did not analyze the effectiveness of acute pancreatitis therapy based on the presence of MAFLD. On the other hand, MAFLD does not have a therapy for acute illnesses.

7.4.Conclusion

Our research indicates that MAFLD is common in patients with AP and is linked to greater severity of the condition. However, it does not appear to impact in-hospital mortality rates significantly. Our findings suggest that the effect of MAFLD on AP severity can be influenced by several factors, including the diagnostic criteria used, patient age, alcohol consumption, and the type of abdominal imaging employed.

7.5.Implication for practice

Assessing patients with AP for the presence of MAFLD is crucial from a clinical perspective. Incorporating this evaluation both during acute care and after discharge could lead to better severity predictions on admission and facilitate education for patients on the significance of reducing or eliminating the extent of MAFLD after AP. Our findings emphasize the importance of including MAFLD screening in routine care for AP patients. This approach could improve patient outcomes by identifying those at high risk of complications and allowing for early interventions to manage MAFLD and prevent AP progression.

7.6.Implication for research

The long-term effects of MAFLD in patients with AP are not well understood, and further investigation is needed to determine the impact of this condition on the course and development of AP. In addition, additional research is necessary to identify the molecular and cellular mechanisms underlying the association between MAFLD and acute pancreatitis, focusing on the role of gut-liver axis dysfunction, inflammation, and metabolic dysregulation. This could inform the development of more effective treatments and prevention strategies.

7.7.Implication for policymakers

On the first hand, policymakers should emphasize the use of MAFLD instead of NAFLD. This may help the detection of liver steatosis more accurately and help in the early diagnosis of MAFLD in patients with AP. However, there is still a lack of data regarding the additional healthcare cost of AP treatment in the presence of MAFLD. Therefore, analyzing the financial impact of MAFLD on AP is essential.

The need for immediate implementation of scientific results in patient care has been previously demonstrated in patients with AP (100, 101).

8. Own work and future carrier plan

During my PhD training, I participated in Translational Medicine PhD training at the University of Péscs and Semmelweis University. I was not only a student in the program, but I also participated as a Science Methodology Supervisor for several PhD and undergraduate students. During this work, I led several PhD projects, undergraduate student research projects and student conference presentations, and finally supervised several graduation theses. This helped me acquire significant clinical methodologies knowledge, which was essential for my PhD. On the other hand, I took part in Pathophysiology training at the Institute of Translational Medicine, which helped me to deepen my educational skills.

I also actively participated in clinical work starting in 2019, during which I learned many aspects of acute pancreatitis care but also other fields of gastroenterology. I enrolled patients into many prospective registries and randomized clinical trials during my work. On the other hand, I participated in the follow-up of the patients. Besides acute pancreatitis-related research, I was part of the hepatology work group at the Institute of Translational Medicine. We worked on the Wilson disease and NAFLD registries.

During the COVID-19 pandemic, I was lucky to participate in many COVID-19-related research, resulting in significant scientific output.

After finishing my PhD, I plan to start my gastroenterology residency training, during which I intend to continue clinical research. During my training, I want to develop my own research group. Furthermore, I want to continue my work with future PhD students. For this, I plan to develop a unique platform that will guide other researchers through the steps of any research. Furthermore, I want to deepen my basic science knowledge, which will help me conduct more advanced translational medicine research.

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11. Publications

11.1. Scientific metrics (as of 2023.06.16)

Number of publications **related to the subject of the thesis**: Cumulative impact factor of publications related to the thesis: Q1: 1, Q2: 0, Q3: 0, Q4: 0, SJR not classified: 1	2 11.108
Number of **other first or last author accepted/published** articles: Cumulative impact factor of the published articles: Q1: 6, Q2: 0, Q3: 0, Q4: 0	6 29.091
Number of **other accepted/published** articles: Cumulative impact factor of the published articles: Q1: 34, Q2: 3, Q3: 0, Q4: 1	38 255.518
Number of total citation by **Google Scholar**: https://scholar.google.com/citations?user=XTt5lw8AAAAJ&hl=en Hirsch Index:	635 14
Number of total citation by **MTMT**: https://m2.mtmt.hu/gui2/?type=authors&mode=browse&sel=10071961 Hirsch Index:	433 10

11.2. Publications related to the subject of the thesis

n=2, cumulative impact factor: 11.108

1. **Váncsa S**, Sipos Z, Váradi A, Nagy R, Ocskay K, Juhász MF, Márta K, Teutsch B, Mikó A,…, Hegyi P. Metabolic-associated fatty liver disease is associated with acute pancreatitis with more severe course: post hoc analysis of a prospectively collected international registry. UEG Journal. 2023 Apr 16;11(4):371-382. doi: 10.1002/ueg2.12389 (**Q1, IF: 6.866**)
2. **Váncsa S**, Németh D, Hegyi P, Szakács Z, Hegyi PJ, Pécsi D, Mikó A, Erőss B, Erős A, Pár G. Fatty Liver Disease and Non-Alcoholic Fatty Liver Disease Worsen the Outcome in Acute Pancreatitis: A Systematic Review and Meta-Analysis. J Clin Med. 2020 Aug 20;9(9):2698. doi: 10.3390/jcm9092698. (**in 2020 not classified in SJR, IF: 4.242**)

11.3. Other first or last author accepted/ published articles

n=6, cumulative impact factor: 29.091

1. Matis D, Hegyi P, Teutsch B, Tornai T, Erőss B, Pár G*, **Vancsa S*.** Improved body composition decreases the fat content in non-alcoholic fatty liver disease, a meta-analysis and systematic review of longitudinal studies. Front Med (Lausanne). 2023 Apr 13;10:1114836. doi: 10.3389/fmed.2023.1114836. (**D1/Q1, IF: 5.058**)
2. Sebők J, Édel Z, Dembrovszky F, Farkas N, Török Z, Balogh G, …, Wittmann I, **Váncsa S***, Vigh L*, Hegyi P*. Effect of HEAT therapy in patiEnts with type 2 Diabetes mellitus (HEATED): protocol for a randomised controlled trial. BMJ Open. 2022 Jul 12;12(7):e062122. doi: 10.1136/bmjopen-2022-062122. (**Q1, IF: 3.006**)
3. **Váncsa S**, Németh D, Hegyi P, Szakács Z, Farkas Á, Kiss S, Hegyi PJ, Kanjo A, Sarlós P, Erőss B, Pár G. Diabetes Mellitus Increases the Risk of Hepatocellular Carcinoma After Direct-Acting Antiviral Therapy: Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021 Oct 18;8:744512. doi: 10.3389/fmed.2021.744512. (**Q1, IF: 5.058**)
4. **Váncsa S**, Dembrovszky F, Farkas N, Szakó L, Teutsch B, Bunduc S, Nagy R, …, Erőss B, Péterfi Z, Hegyi P. Repeated SARS-CoV-2 Positivity: Analysis of 123 Cases. Viruses. 2021 Mar 19;13(3):512. doi: 10.3390/v13030512. (**Q1, IF: 5.818**)
5. Hegyi PJ*, **Váncsa S*,** Ocskay K, Dembrovszky F, Kiss S, Farkas N, Erőss B, Szakács Z, Hegyi P, Pár G. Metabolic Associated Fatty Liver Disease Is Associated With an Increased Risk of Severe COVID-19: A Systematic Review With Meta-Analysis. Front Med (Lausanne). 2021 March 12;8:626425. doi: 10.3389/fmed.2021.626425. (**Q1, IF: 5.058**)
6. **Váncsa S,** Hegyi PJ, Zádori N, Szakó L, Vörhendi N, …, Kiss S, Szakács Z, Németh D, Hegyi P, Pár G. Pre-existing Liver Diseases and On-Admission Liver-Related Laboratory Tests in COVID-19: A Prognostic Accuracy Meta-Analysis With Systematic Review. Front Med (Lausanne). 2020 Nov 13;7:572115. doi: 10.3389/fmed.2020.572115. PMID: 33282888; PMCID: PMC7691431. (**Q1, IF: 5.093**)

11.4. Other accepted/published articles:

n=38, cummulative impact factor: 255.518

1. Czapári D, Váradi A, Farkas N, Nyári G, Márta K, **Váncsa S**, Nagy R, Teutsch B, Bunduc S, …, Hegyi P; Hungarian Pancreatic Study Group. Detailed characteristics of post-discharge mortality in acute pancreatitis. Gastroenterology. 2023 May 27:S0016-5085(23)00801-6. doi: 10.1053/j.gastro.2023.05.028. (**D1/Q1, IF: 33.883**)
2. Solyom E, Szalai E, Czumbel ML, Szabo B, **Váncsa S**, Mikulas K, …, Varga G, Hegyi P, Molnar B, Fazekas R. The use of autogenous tooth bone graft is an efficient method of alveolar ridge preservation - meta-analysis and systematic review. BMC Oral Health. 2023 Apr 19;23(1):226. doi: 10.1186/s12903-023-02930-2.(**Q1, IF: 3.747**)
3. Pethő B, Mátrai Á, Agócs G, Veres DS, Harnos A, **Váncsa S,** Bánhidy F, Hegyi P, Ács N. Maternal age is highly associated with non-chromosomal congenital anomalies: Analysis of a population-based case-control database. BJOG. 2023. Online version. doi: 10.1111/1471-0528.17461. (**D1/Q1, IF: 7.331**)
4. Teutsch B, **Váncsa S**, Farkas N, …, Vörhendi N, Boros E, Szabó I, Hágendorn R, Alizadeh H, Hegyi P, Erőss B. Intravenous ferric carboxymaltose versus oral ferrous sulfate replacement in elderly patients after acute non-variceal gastrointestinal bleeding (FIERCE): protocol of a multicentre, open-label, randomised controlled trial. BMJ Open. 2023 Mar 14;13(3):e063554. doi: 10.1136/bmjopen-2022-063554. (**Q1, IF: 3.006**)
5. Bajzát D, Kéri AF, Imrei M, Kói T, Párniczky A, Hegyi P, Kovács K, **Váncsa S,** Müller KE. Safety Analysis of Preoperative Anti-TNF-α Therapy in Pediatric IBD After Intestinal Resection: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2023 Feb 15:izac274. doi: 10.1093/ibd/izac274. (**D1/Q1, IF: 7.290**)
6. Greff D, Juhász AE, **Váncsa S**, Váradi A, Sipos Z, …, Hegyi P, Nyirády P, Ács N, Várbíró S, Horváth EM. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2023 Jan 26;21(1):10. doi: 10.1186/s12958-023-01055-z. (**Q1, IF: 4.982**)

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8. Mátrai Á, Teutsch B, Váradi A, Hegyi P, Pethő B, Fujisawa A, **Váncsa S**, Lintner B, Melczer Z, Ács N. First-Trimester Influenza Infection Increases the Odds of Non-Chromosomal Birth Defects: A Systematic Review and Meta-Analysis. Viruses. 2022 Dec 2;14(12):2708. doi: 10.3390/v14122708. (**Q1, IF: 5.818**)
9. Széles Á, Fazekas T, **Váncsa S**, Váradi M, Kovács PT, …, Csizmarik A, Hegyi P, Váradi A, Nyirády P, Szarvas T. Pre-treatment soluble PD-L1 as a predictor of overall survival for immune checkpoint inhibitor therapy: a systematic review and meta-analysis. Cancer Immunol Immunother. 2022 November 16. doi: 10.1007/s00262-022-03328-9. (**D1/Q1, IF: 6.630**)
10. Széles Á, Kovács PT, Csizmarik A, …, **Váncsa S**, Hegyi P, …, Grünwald V, Hadaschik B, Horváth O, Nyirády P, Szarvas T. High Pretreatment Serum PD-L1 Levels Are Associated with Muscle Invasion and Shorter Survival in Upper Tract Urothelial Carcinoma. Biomedicines. 2022 Oct 13;10(10):2560. doi: 10.3390/biomedicines10102560. (**Q1, IF: 4.757**)
11. Horváth IL, Bunduc S, Fehérvári P, **Váncsa S**, Nagy R, Garmaa G, Kleiner D, Hegyi P, Erőss B, Csupor D. The combination of ulinastatin and somatostatin reduces complication rates in acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials. Sci Rep. 2022 Oct 26;12(1):17979. doi: 10.1038/s41598-022-22341-7. (**D1/Q1, IF: 4.996**)
12. Zádori N, Németh D, Frim L, Vörhendi N, Szakó L, **Váncsa S**, Hegyi P, Czimmer J. Dyspepsia-Like Symptoms in Helicobacter pylori-Negative Chronic Gastritis are Associated with ASCA-, ANCA-, and Celiac Seropositivity but Not with Other Autoimmune Parameters: A Single-Centre, Retrospective Cross-Sectional Study. Int J Gen Med. 2022 October 12;15:7789-7796. doi: 10.2147/IJGM.S380419. (**Q2, IF: 2.145**)
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multicentre, exact-matched cohort analysis. Pancreatology. 2022 Dec;22(8):1071-1078. doi: 10.1016/j.pan.2022.09.241. (**Q1, IF: 3.977**)

14. Dezso F, Birkás B, Vizin G, **Váncsa S**, Szőcs H, Erőss A, …, Gede N, Molnar Z, Hegyi P, Csathó Á. Examining the mental health adversity among healthcare providers during the two waves of the COVID-19 pandemic: results from a cross-sectional, survey-based study. BMJ Open. 2022 Aug 23;12(8):e059493. doi: 10.1136/bmjopen-2021-059493. (**Q1, IF: 3.006**)
15. Tóth B, Jávorházy A, Nyirády P, Csupor-Löffler B, Birinyi P, …, Vörhendi N, Gede N, **Váncsa S**, Hegyi P, Csupor D. Bearberry in the treatment of acute uncomplicated cystitis (BRUMI): protocol of a multicentre, randomised double-blind clinical trial. BMJ Open. 2022 Jun 24;12(6):e057982. doi: 10.1136/bmjopen-2021-057982. (**Q1, IF: 3.006**)
16. Kui B, Pintér J, Molontay R, Nagy M, Farkas N, …, **Váncsa S**, …, Gómez-Jurado MJ, Tantau A, Szentesi A, Hegyi P; Hungarian Pancreatic Study Group. EASY-APP: An artificial intelligence model and application for early and easy prediction of severity in acute pancreatitis. Clin Transl Med. 2022 Jun;12(6):e842. doi: 10.1002/ctm2.842. (**D1/Q1, IF: 8.554**)
17. Zádori N, Németh D, Szakó L, **Váncsa S**, Vörhendi N, Szakács Z, Frim L, Hegyi P, Czimmer J. Prevalence of Autoimmune-phenomena behind Chronic Gastritis of Unknown Origin, and their Role in the Poor Histological Outcome of the Stomach: A Single-centre, Retrospective Cross-sectional Study. J Gastrointestin Liver Dis. 2022 June 12;31(2):168-175. doi: 10.15403/jgld-4218. (**Q2, IF: 2.142**)
18. Kiss S, Pintér J, Molontay R, Nagy M, Farkas N, …, **Váncsa S**, …, Molnár Z, Párniczky A, Hegyi P, Szentesi A; Hungarian Pancreatic Study Group. Early prediction of acute necrotizing pancreatitis by artificial intelligence: a prospective cohort-analysis of 2387 cases. Sci Rep. 2022 May 12;12(1):7827. doi: 10.1038/s41598-022-11517-w. (**D1/Q1, IF: 4.996**)
19. Bunduc S, Gede N, **Váncsa S**, Lillik V, …, Juhász MF, Erőss B, Szakács Z, Gheorghe C, Mikó A, Hegyi P. Exosomes as prognostic biomarkers in pancreatic ductal adenocarcinoma-a systematic review and meta-analysis. Transl Res. 2022 Jun;244:126-136. doi: 10.1016/j.trsl.2022.01.001. (**D1/Q1, IF: 10.171**)
20. Szentesi A, Farkas N, Sipos Z, Mátrai P, Vincze Á, Izbéki F, Párniczky A, Hegyi P; Hungarian Pancreatic Study Group. Alcohol consumption and smoking dose-

dependently and synergistically worsen local pancreas damage. Gut. 2022 Dec;71(12):2601-2602. doi: 10.1136/gutjnl-2021-326853. (**D1/Q1, IF: 31.793**)

21. Bunduc S, Gede N, **Váncsa S**, Lillik V, …, Dembrovszky F, Erőss B, Szakács Z, Gheorghe C, Mikó A, Hegyi P. Prognostic role of cell-free DNA biomarkers in pancreatic adenocarcinoma: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2022 Jan;169:103548. doi: 10.1016/j.critrevonc.2021.103548. (**Q1, IF: 6.625**)
22. Zádori N, Szakó L, **Váncsa S**, Vörhendi N, Oštarijaš E, Kiss S, Frim L, Hegyi P, Czimmer J. Six Autoimmune Disorders Are Associated With Increased Incidence of Gastric Cancer: A Systematic Review and Meta-Analysis of Half a Million Patients. Front Immunol. 2021 Nov 23;12:750533. doi: 10.3389/fimmu.2021.750533. (**Q1, IF: 8.786**)
23. Sebők J, Édel Z, **Váncsa S**, Farkas N, …, Hooper PL, Geiger PC, Wittmann I, Vigh L, Dembrovszky F, Hegyi P. Heat therapy shows benefit in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Int J Hyperthermia. 2021;38(1):1650-1659. doi: 10.1080/02656736.2021.2003445. (**Q2, IF: 3.753**)
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25. Teutsch B, Boros E, **Váncsa S,** Váradi A, Frim L, …, Dembrovszky F, Helyes Z, Patrícia S, Péter H, Erőss B. Mucoprotective drugs can prevent and treat nonsteroidal anti-inflammatory drug-induced small bowel enteropathy: a systematic review and meta-analysis of randomized controlled trials. Therap Adv Gastroenterol. 2021 September 30;14:17562848211038772. doi: 10.1177/17562848211038772. (**Q1, IF: 4.802**)
26. Martonosi ÁR, Soós A, Rumbus Z, Hegyi P, Izsák V, Pázmány P, Imrei M, Váncsa S, Szakács Z, Párniczky A. Non-invasive Diagnostic Tests in Cystic Fibrosis- Related Liver Disease: A Diagnostic Test Accuracy Network Meta-Analysis. Front Med (Lausanne). 2021 Jul 27;8:598382. doi: 10.3389/fmed.2021.598382. (**Q1, IF: 5.058**)

27. Nagy A, Juhász MF, Görbe A, Váradi A, Izbéki F, Vincze Á, …, **Váncsa S,** …, Szentesi A, Hegyi P, Párniczky A. Glucose levels show independent and dose-dependent association with worsening acute pancreatitis outcomes: Post-hoc analysis of a prospective, international cohort of 2250 acute pancreatitis cases. Pancreatology. 2021 Oct;21(7):1237-1246. doi: 10.1016/j.pan.2021.06.003. (**Q1, IF: 3.977**)
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12. Appendixes

Appendix Table 1. Inclusion and/or exclusion criteria in each included study in the systematic review and meta-analysis.

Study	Acute pancreatitis eligibility („verbatim")	Fatty liver disease eligibility („verbatim")
Dou J. et al., 2017 (45)	**Exclusion:** "(1) previous history of pancreatic disease, including acute pancreatitis, chronic pancreatitis, pancreatic cancer; (2) those with chronic heart disease; (3) those with chronic renal failure; (4) with chronic liver Those with dysfunction; (5) those with a history of malignancy; (6) those with a history of diabetes; (7) those with missing or incomplete data."	"Guidelines for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Diseases 2010"(102)
Hao Y.M. et al, 2015 (46)	Not reported	Not reported
Jasdanwala S, 2015 (47)	Not reported	"Significant alcohol consumption: more than 21 drinks per week in men and more than 14 drinks per week for women over a minimum 2 years period"
Jia J. et al, 2018 (48)	**Inclusion:** "diagnosis based on the two out of three criteria;" **Exclusion: "**a) no abdominal CT scan was performed within 24 hours; b) incomplete clinical data; c) Splenectomy patients."	Not reported
Mikolasevic I. et al, 2016 (49)	**Exclusion: "**relapse of acute pancreatitis or with an exacerbation of chronic pancreatitis, patients with incomplete medical data, patients with active malignancy, those who were younger than 18 years and those who were receiving medications that can cause liver steatosis (corticosteroids, amiodarone, etc.) **unknown etiology"(103)**	**Exclusion: "**other causes of chronic steatosis; consummation of more than 14 alcohol drinks/week in women and more than 21 alcohol drinks/week in men was considered as excessive alcohol consumption; laboratory results indicating on possible alcohol consumption"
Morel C.E. et al, 2019 (50)	**Exclusion: "**chronic hepatitis, chronic pancreatitis, pancreatic cancer, incomplete data"	Not reported

Study	Acute pancreatitis eligibility („verbatim")	Fatty liver disease eligibility („verbatim")
Peng Z.H. et al, 2012 (51)	**Exclusion: "**CT not performed, abdominal surgery, decompensated cirrhosis, hypoproteinaemia (<30g/l), heart failure, infectious disease, malignancy, bleeding disorder"	Not reported
Satapathy S. et al, 2011 (52)	Not reported	Not reported
Suchsland T. et al, 2015 (53)	**Inclusion:** "patients that were treated at University Medicine Greifswald with the main diagnosis acute pancreatitis (ICD-10-GM: K85.xx) or chronic pancreatitis ICD-10-GM: K86.0 (alcoholic chronic pancreatitis) or K.86.1 (chronic pancreatitis by other origin) between 2006 and 2011." **Exclusion:** "Patients with incomplete or inconsistent information from the HIS were excluded. When data from the questionnaire were incomplete, the existing information was still analyzed in bivariate analyses but could not include in multivariate analyses because of the test design."	Not reported
Wang S. et al, 2013 (54)	Not reported	Not reported
Wu D. et al, 2019 (55)	**Exclusion:** "patients suffering from cirrhosis, hepatocellular carcinoma, alcoholic fatty liver, or chronic pancreatitis as well as those who had undergone splenectomy, were pregnant, were younger than 18 or older than 60 years, had been hospitalized repeatedly, or had incomplete medical"	**Exclusion: "**history of alcoholic consumption (history of drinking or equivalent alcohol consumption of more than 140 g/week for men and more than 70 g/week for women), viral hepatitis, drug-induced hepatitis, total parenteral nutrition, hepatolenticular degeneration, autoimmune liver disease, and other specific diseases that can lead to fatty liver"(104)
Xiao B. et al, 2012 (56)	**Exclusion: "**patients with a history of diabetes mellitus, obesity (body mass index Q28 kg/m2), alcohol consumption (960 g/d for 91	**Inclusion: "**MRI performed within 72 hours after the onset of symptoms, MRI was followed

Study	Acute pancreatitis eligibility („verbatim”)	Fatty liver disease eligibility („verbatim”)
	year), type B/type C viral hepatitis, hepatic cirrhosis, or cancer proved by clinical, imaging, or histological evidence”	by collection of blood samples, 1 or more MRI follow-ups, including a review of the results”
Xu C. et al, 2015 (57)	**Exclusion: “**chronic cardiac and pulmonary diseases; previous history of pancreatic diseases, including acute pancreatitis, chronic pancreatitis and pancreatic cancer; chronic renal failure; chronic liver dysfunction; a history of malignancy.”	**“Non-alcoholic fatty liver disease (NAFLD)** was diagnosed by the presence of following findings: (1) steatosis was detected either by imaging or histology; (2) the alcoholic liver disease was excluded, and alcohol consumption was less than 140g per week in men (70g in women) in the past 12 months; (3) specific diseases that could lead to steatosis were excluded as mentioned above”
Yoon S.B. et al, 2017 (58)	**Exclusion: “**ERCP, reffered cases from other hospitals without u CT, missing BMI data”	**Exclusion: “**referred cases from other hospitals without an initial CT study, cases without CT scan or unenhanced CT phase”
Yuan L. et al, 2017 (59)	**Inclusion: “**contact telephone number and met the diagnostic criteria of a first attack of AP were included in the study. **Exclusion:** (1) previous diagnosis of DM, impaired fasting glucose (IFG), or impaired glucose tolerance; (2) abnormal glycosylated hemoglobin (HbA1c) during the course of hospitalization; (3) previous AP attack before the beginning of the cohort and history of other pancreatic injury, including chronic, autoimmune, or hereditary pancreatitis, trauma, treatment of pancreatectomy or debridement, pancreatic neoplasm, cystic fibrosis, hemochromatosis, or fibrocalculous pancreatopathy; (4) previous history of hyperthyroidism, decompensated cirrhosis, ormalignant neoplasm; (5) lack of regular monitoring of FBG before or after AP; (6) history of gestational DM; (7) death during hospitalization; and (8) loss to follow-up.”	Not reported

Appendix Table 2. Data quality of the analyzed cohort and variable definitions

Parameters	**Uploaded data**	**%**
Age	2053	100.00%
Sex	2053	100.00%
Comorbidities		
Smoking	2012	98.00%
Smoking amount (cigarettes/day)	2012	98.00%
Alcohol consumption	1457	70.97%
Alcohol amount (g/day)	1457	70.97%
Hypertension	1563	76.13%
Body mass index (kg/m2)	1898	92.45%
Steatosis	2053	100.00%
Type 2 diabetes mellitus	2039	99.32%
Hypertriglyceridemia	1393	67.85%
Hypercholesterinemia	1285	62.59%
Charlson Comorbidity Index	1850	90.11%
Previous pancreatitis	2053	100.00%
Laboratory parameters		
Admission triglyceride level (mmol/l)	801	39.02%
Admission cholesterol level (mmol/l)	695	33.85%
Admission amylase (U/ l)	1910	93.03%
Admission lipase (U/ l)	1512	73.65%
HbA1C level (%)	685	33.37%
Admission glucose (mmol/l)	1799	87.63%
Admission white blood cell count (10^9/l)	1918	93.42%
Maximum C-reactive protein (U/l)	2027	98.73%
Maximum C-reactive protein day	2027	98.73%
Maximum white blood cell count (10^9/l)	2036	99.17%
Maximum white blood cell count day	2036	99.17%
Admission albumin (g/L)	723	35.22%
Acute pancreatitis outcomes		
Acute pancreatitis etiology	2053	100.00%
Severity	2053	100.00%
In-hospital mortality	2053	100.00%
Local complications	2053	100.00%
Peri-pancreatic fluid collection	2053	100.00%
Pseudocyst	2053	100.00%
Pancreas necrosis	2053	100.00%
Diabetes as complication	2053	100.00%
Systemic complications	2053	100.00%
Renal failure	2053	100.00%
Respiratory failure	2053	100.00%
Cardiovascular failure	2053	100.00%

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Review

Fatty Liver Disease and Non-Alcoholic Fatty Liver Disease Worsen the Outcome in Acute Pancreatitis: A Systematic Review and Meta-Analysis

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Abstract: The prevalence of fatty liver disease (FLD) and that of non-alcoholic fatty liver disease (NAFLD) share some risk factors known to exacerbate the course of acute pancreatitis (AP). This meta-analysis aimed to investigate whether FLD or NAFLD carry a higher risk of untoward outcomes in AP. In accordance with PRISMA guidelines, we performed a systematic search in seven medical databases for cohort studies that compared the outcomes of AP for the presence of FLD or NAFLD, and we calculated pooled odds ratio (OR) or weighted mean difference (WMD) with 95% confidence interval (CI). We included 13 articles in our meta-analysis. AP patients with FLD were more likely to die (5.09% vs 1.89%, OR = 3.56, CI = 1.75–7.22), develop severe AP (16.33% vs 7.87%, OR = 2.67, CI = 2.01–3.56), necrotizing pancreatitis (34.83% vs 15.75%, OR = 3.08, CI = 2.44–3.90) and had longer in-hospital stay (10.8 vs 9.2 days, WMD = 1.46, OR = 0.54–2.39). Patients with NAFLD were more likely to have severe AP and longer hospital stay. Both FLD and NAFLD proved to be independent risk factors of a more severe disease course (OR = 3.68, CI = 2.16–6.29 and OR = 3.39, CI = 1.52–7.56 for moderate/ severe vs. mild AP, respectively). FLD and NAFLD worsen the outcomes of AP, which suggests that incorporating FLD or NAFLD into prognostic scoring systems of AP outcomes might improve the prediction of severity and contribute to a more individualized patient care.

Keywords: acute pancreatitis; fatty liver disease; non-alcoholic fatty liver disease; hepatology; pancreatology; prognosis

1. Introduction

Fatty liver disease (FLD) is becoming increasingly common in the Western world, affecting about 25% of the population globally [1]. FLD is a clinicopathologic entity with a histological spectrum that includes simple steatosis and steatohepatitis, also it encompasses a broad variety of etiology. The most common causes of FLD are non-alcoholic fatty liver disease (NAFLD) associated with metabolic syndrome (MetS), alcohol abuse alone or in association with hypertriglyceridemia, and the combination of the causes above. It is widely known that there is a bidirectional association between NAFLD and

components of MetS [2]. The presence of NAFLD increases the risk of cardiovascular diseases, type 2 diabetes mellitus, chronic kidney disease, liver cirrhosis, and liver cancer [3].

Acute pancreatitis (AP) is a common acute gastrointestinal disease, posing a substantial social and economic burden [4]. Although the mortality of AP has been decreasing in the past decades, it is still between 2–5% and it remains high, up to 15–25% in subgroups of patients with severe AP, depending on the extent of necrosis and systemic complications [5].

Based on the guidelines issued by the International Association of Pancreatology (IAP) and the American Pancreatic Association (APA), on admission of patients with AP, a three-dimensional approach is recommended for predicting the outcome of AP, combining host risk factors, clinical risk stratification and response to initial therapy [6]. Several prognostic tools have been developed for the early prediction of severe AP and mortality, based on demography, clinical signs and symptoms, laboratory studies and imaging, composing numerous scoring systems (e.g., Bedside Index of Severity in Acute Pancreatitis—BISAP [7], 48 h Acute Physiology and Chronic Health Evaluation—APACHE II score [8], Ranson scores [9], Computed Tomography Severity Index—CTSI [10]). A recent meta-analysis showed that scoring systems have comparable diagnostic accuracy to predict severe AP with area under the curve ranging from 0.73 to 0.83 [11].

The presence of MetS is a proven risk factor of severe AP [12,13]. Pre-existing diabetes mellitus negatively influences the outcome of AP and increases the risk of renal failure, local complications, intensive care compared with the non-diabetic group [14]. Obesity is another risk factor in AP; obese patients have a three-fold increased risk of mortality compared to those with a BMI < 30 [15]. High triglyceride level is also a risk factor, serum triglyceride level higher than 5.6 mmol/L significantly increases the mortality rate (OR = 2.75, 95% CI = 1.28–5.92, $p < 0.01$) [16]. An experimental study in rat AP model demonstrated that the presence of FLD increased pro-inflammatory cytokine production, which may worsen the course of the disease [17]. Cross-sectional studies confirmed that AP is often accompanied by FLD, with a prevalence between 18–43% [18,19].

Since FLD or NAFLD is common in diabetes or obesity worsening the course of AP, it may also act as a potential risk factor in AP. This meta-analysis aimed to investigate whether FLD or NAFLD is associated with a less favorable disease course in AP.

2. Methods and Materials

Our study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2019 Statement [20]. The study protocol was registered in PROSPERO under registration number *CRD42019123416* (see *https://www.crd.york.ac.uk/prospero*).

2.1. Literature Search

A systematic literature search was performed in seven medical databases (PubMed, EMBASE, Web of Science, CENTRAL, WHO global health library, Scopus, and ClinicalTrial.gov) from inception to 13th of November 2019 with the query *pancreatitis AND ("fatty liver" OR FLD OR NAFLD OR steatohepatitis OR steatosis)*. We used no language or other restrictions. Additionally, we manually searched for relevant review articles and checked the bibliographic reference lists of studies selected for inclusion in our meta-analysis.

We included studies, discussing adult patients ***(P)*** with AP of different etiologies. We compared patients with FLD or NAFLD ***(E)*** to those without FLD or NAFLD ***(C).*** The eligible studies were supposed to define FLD or NAFLD based on abdominal imaging (ultrasound—US, computed tomography—CT scan, magnetic resonance imaging—MRI) or liver biopsy. In NAFLD the amount of alcohol consumed should also be defined. The primary outcome ***(O)*** was in-hospital mortality, secondary outcomes included AP severity [4], local complications (acute peripancreatic fluid collection—APFC, acute necrotic collection—ANC, pancreatic pseudocyst—PP), systemic inflammatory response syndrome (SIRS), and the length of hospitalization (LOH). We narrowed the focus to longitudinal studies.

2.2. Study Selection and Data Collection

We followed the recommendation of the Cochrane Handbook [21]. Two independent investigators (S.V., S.Z.) selected the studies, using EndNote X7.4 (Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates, publications were screened for title and abstract. Two reviewers (S.V., S.Z.) assessed the studies meeting the eligibility criteria (PECO) for full-text. Conference abstracts reporting relevant data were also included. Disagreements were resolved by third party arbitration (P.H.).

The most recent publication was chosen in the case of multiple publications on the same cohort of patients.

Data were extracted independently by two investigators (S.V., Z.S.) into a pre-defined Excel datasheet (Office 365, Microsoft, Redmond, WA, USA). The following data were collected: first author, year of publication, study period, study design, demographic data, sample sizes, mean age, female percentage, details on the PECO question and data necessary for risk of bias assessment. For statistical analysis, we extracted raw data into 2 by 2 tables (outcome yes/no, FLD or NAFLD yes/no) and odds ratios (OR) for each outcome.

Graphical data were also extracted using GetData Graph Digitizer 2.26 software (S. Fedorov 2013, Russia, http://getdata-graph-digitizer.com).

2.3. Statistical Analysis

Meta-analytical calculations were performed in Stata 15.1 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA) and Comprehensive Meta-Analysis (version 3, Biostat Inc., Englewood, NJ, USA) by a statistician (D.N.). For FLD vs. no-FLD and NAFLD vs no-NAFLD comparisons, we calculated pooled OR with 95% confidence interval (CI) with the random-effects model using the DerSimonian–Laird method [22] for in-hospital mortality, severity of AP, risk of local complications (ANC, APFC, PP) and SIRS, and weighted mean difference (WMD) with 95%CI for LOH.

Heterogeneity was tested by using the Cochrane's Q and the I^2 statistics, where $I^2 = 100\% \times (Q - df)/Q$, and represents the magnitude of the heterogeneity (moderate: 30–60%, substantial: 50–90%, considerable: 75–100%). A p-value of less than 0.10 was considered suggestive of significant heterogeneity [23].

We performed sensitivity analysis (leave-one-out method) if at least three studies were included in an analysis by testing the effect of each study on the main association.

To test the presence of small-study effect we assessed the symmetry of the funnel plot visually.

2.4. Risk of Bias and Quality Assessment of the Individual Studies

A critical appraisal tool for prognostic studies, the Quality in Prognosis Studies (QUIPS) tool was used to assess the methodological quality of the included studies [24]. Two independent investigators (S.V., Z.S.) assessed the risk of bias; disagreements were resolved by discussion or by a third investigator. The main domain "study attrition" and further items not fitting our meta-analysis were omitted due to the retrospective design of the included studies.

2.5. Details of Ethical Approval

No ethical approval was required for this review as all data were already published in peer reviewed journals. No patients were involved in the design, conduct or interpretation of our review.

3. Results

3.1. Search and Selection

Altogether 15 articles were eligible to be included in the systematic review, 13 of which in the meta-analysis. The details of the literature search are included in Figure 1. On full-text assessment we excluded six studies due to inappropriate study design; details are presented in Appendix S1.

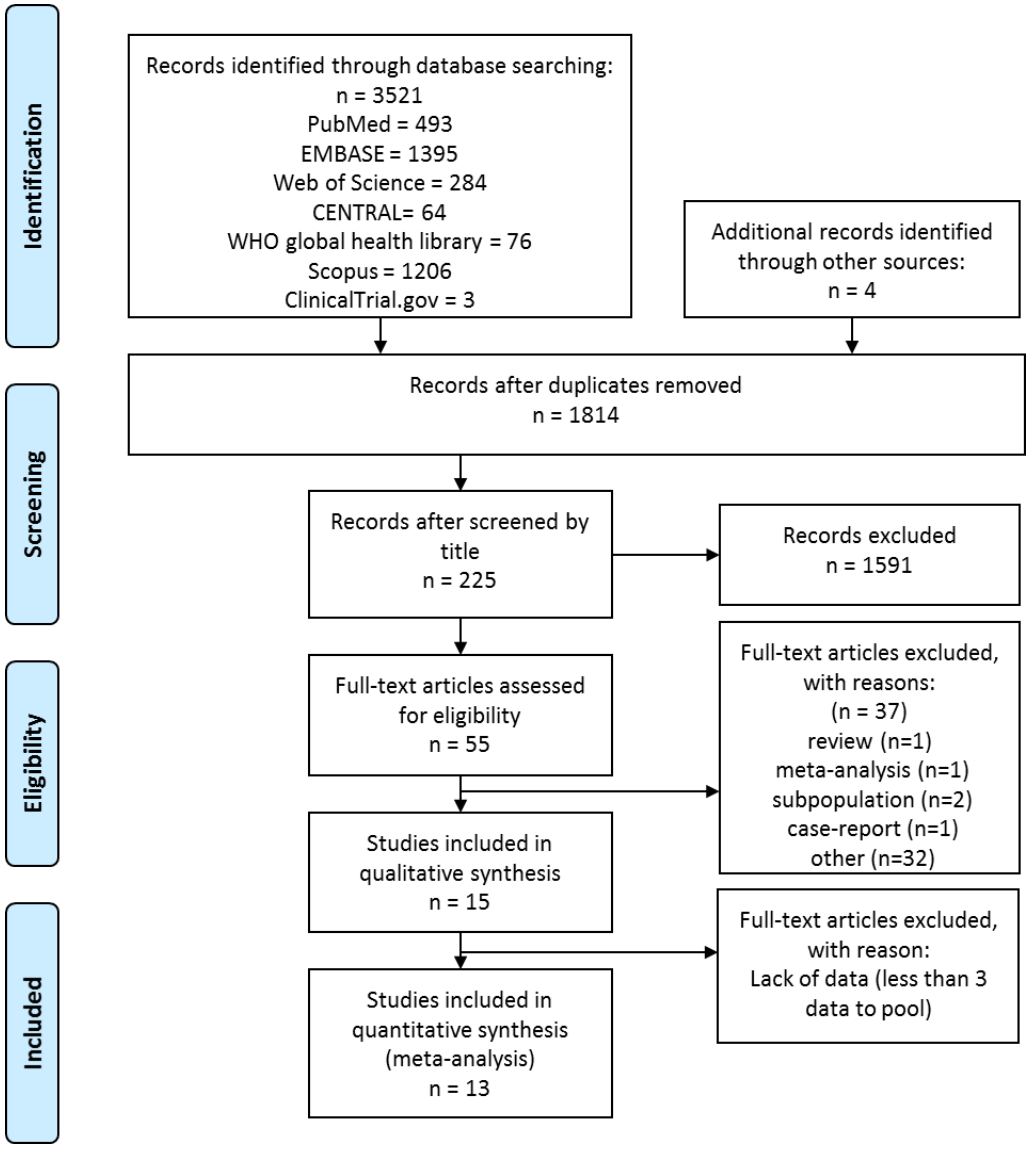

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart for the study selection procedure.

3.2. Characteristics of the Studies Included in the Meta-Analysis

The main characteristics of the included studies are summarized in Table 1. All studies were retrospective cohort studies.

The Revised Atlanta Classification [4] and the Atlanta Classification of 1992 [25] were used in 11 of the included articles; furthermore, CTSI and magnetic resonance severity index—MRSI [10] were also used for AP severity classification.

The prevalence of FLD and NAFLD ranged from 18 to 82%, and from 24 to 58%, respectively. FLD and NAFLD was diagnosed using an unenhanced abdominal CT scan in 6 of 13 articles. Other studies used abdominal US or MRI to diagnose FLD or NAFLD, 2 out of 13 articles did not report the used method. Eligibility criteria from the studies included are summarized in Table S2.

Table 1. Characteristics of the studies included in the systematic review and meta-analysis.

Author and Year	Country (Centre)	Recruitment Period	Acute Pancreatitis Diagnosis	Leading Etiology of Acute Pancreatitis	Nr. of Acute Pancreatitis Cases	Fatty Liver Disease			Examined Outcomes
						Definition	Diagnostic Method (Cut-Off)	Nr. FLD Cases (%)	
Dou J. et al., 2017 [26] (article in Chinese)	China (single-center)	2013–2016	2 out of 3 criteria	G 37% H 10%	251	NAFLD	US (NR)	117 (47)	AP severity (Atlanta 2012) §
Hao Y.M. et al., 2015 [27] †	China (single-center)	2011–2013	NR	NR	148	FLD	NR	41 (28)	AP severity (Atlanta 1992)
Jasdanwala S, 2015 [28]	USA (multicenter)	Not reported	2 out of 3 criteria	NR	574	NAFLD	CT or US (NR)	193 (34)	In-hospital mortality, AP severity (Atlanta 2012), LOH, ICU admission, BISAP
Jia J. et al., 2018 [29]	China (single-center)	2016–2017	2 out of 3 criteria	NR	128	FLD	CT (HAI<1)	56 (44)	AP severity (Atlanta 2012), ANC, APFC
Mikolasevic I. et al., 2016 [30]	Croatia (single-center)	2008–2015	2 out of 3 criteria	G 84% H 1%	822	NAFLD	CT (HA > 10 HU, or LD < 40 HU) or US	198 (24)	In-hospital mortality, AP severity (Atlanta 2012) §, ANC, APFC, PP, LOH, APACHE-II, CTSI
Morel C.E. et al., 2019 [31] (article in Spanish)	Mexico (single-center)	2017–2018	2 out of 3 criteria	G 70% A 11% H 5%	186	FLD	US (NR)	68 (37)	AP severity (Atlanta 2012), persistent SIRS
Peng Z.H. et al., 2012 [32] (article in Chinese)	China (single-center)	2010–2011	2 out of 3 criteria	G 57%	606	FLD	CT (HAI < 1)	498 (82)	In-hospital mortality, overall complications §
Satapathy S. et al., 2011 [33] †	USA (single-center)	2002–2009	NR	G 39% A 18%	108	FLD	CT (HAI < 0.8)	23 (21)	In-hospital mortality, ANC, PP, LOH, ICU admission, need for antibiotics, CTSI, Ranson 48 h
Suchsland T. et al., 2015 [34]	Germany (single-center)	2006–2011	ICD-10	NR	373	FLD	NR	NR	Risk of hyperglycemia after AP
Wang S. et al., 2013 [35] †	China (single-center)	2010–2011	NR	NR	120	FLD	NR	35 (29)	AP severity (Atlanta 1992) §, SIRS, pulmonary failure, metabolic disturbances
Wu D. et al., 2019 [19]	China (single-center)	2012–2016	2 out of 3 criteria	G 32% H 48%	656	NAFLD	CT (HAI < 1)	378 (58)	AP severity (Atlanta 2012) §, SIRS, BISAP, Ranson score
Xiao B. et al., 2012 [36]	China (single-center)	2009–2011	Pain and laboratory results ‡	G 38%	50	FLD	MRI (HAI)	33 (66)	In-hospital mortality, MRSI

Table 1. *Cont.*

Author and Year	Country (Centre)	Recruitment Period	Acute Pancreatitis Diagnosis	Leading Etiology of Acute Pancreatitis	Nr. of Acute Pancreatitis Cases	Fatty Liver Disease			Examined Outcomes
						Definition	Diagnostic Method (Cut-Off)	Nr. FLD Cases (%)	
Xu C. et al., 2015 [18]	China (single-center)	2000–2014	2 out of 3 criteria	G 58% A 22% H 11%	2671	FLD/ NAFLD	CT (HAI < 1)	480 (18)	In-hospital mortality, AP severity (Atlanta 2012), ANC, systemic and local complications, APACHE-II
Yoon S.B. et al., 2017 [37]	Korea (single-center)	2009–2016	2 out of 3 criteria	G 36% A 34% H 3%	200	FLD	CT (HAI < 1)	67 (34)	In-hospital mortality, AP severity (Atlanta 2012) [§], ANC, PP, APFC, LOH
Yuan L. et al., 2017 [38]	China (single-center)	2009–2013	2 out of 3 criteria	G 49% A 5% H 10%	310	FLD	NR	119 (39)	hospital readmission after the first episode of AP

[†]: conference abstract; [‡]: AP diagnostic criteria were based on abdominal pain and serum pancreatic enzyme elevation; [§]: outcome assessed by adjusted analysis from logistic regression; 2 out of 3 criteria: 1. abdominal pain, 2. laboratory findings, 3. abdominal imaging [4]; AFLD: alcoholic fatty liver disease; ANC: acute necrotic collection; AP: acute pancreatitis; APACHE-II: "Acute Physiology, Age, Chronic Health Evaluation II"; APFC: acute peripancreatic fluid collection; BISAP: bedside index for severity in acute pancreatitis; CT: computed tomography; CTSI: CT severity index; Etiology A: alcohol abuse, G: gallstone disease, H: hypertriglyceridemia induced; ICU: intensive-care unit; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th revision; FLD: fatty liver disease; HA: hepatic attenuation; HAI: hepatic attenuation index; LD: liver density; LOH: length of hospitalization; MRI: magnetic resonance imaging; MRSI: magnetic resonance severity index; NAFLD: non-alcoholic fatty liver disease; PP: pancreatic pseudocyst; SIRS: systemic inflammatory response syndrome; US: abdominal ultrasound; USA: United States of America.

3.3. Findings of Meta-Analysis: FLD vs. No FLD

Our findings are summarized in Table 2.

In patients with AP, the odds of in-hospital mortality (5.09 vs. 1.89%; OR = 3.56, CI: 1.77–8.28; Figure 2), composite of moderately severe and severe AP (48.02 vs. 24.34%; OR = 3.14, CI: 1.87–5.25; Figure 3), and the odds of severe AP alone (16.33 vs. 7.87%; OR = 2.67, CI: 2.01–3.56; Figure S1) was higher in the FLD group compared with those without FLD.

In the subgroup of studies using the Atlanta 1992 classification for AP classification, in the FLD group the odds of severe AP was significantly higher (OR = 4.70, CI: 2.65–8.32; Figure S2).

In multivariate analysis (Figure 4), there was an independent association between FLD and the odds of moderately severe/ severe AP based on five studies (OR = 3.68, CI: 2.16–6.29). Details of the multivariate analysis adjustments in the included studies are summarized in Table S3.

The proportion of acute necrotic collection (34.83 vs. 15.75%), acute peripancreatic collection (44.55 vs 17.73%), and peripancreatic pseudocyst (14.24 vs. 5.34) was higher in AP patients with FLD compared with the group without FLD (Figure 5). SIRS was also more frequent in AP patients with FLD (38.19 vs 18.63%; Figure S4).

Based on five articles, LOH was longer among patients with FLD than in the non-FLD patient group (WMD = 1.46 days, CI: 0.54–2.39 days; Figure S5).

The results of the heterogeneity analysis are presented in the figures corresponding to the assessed outcomes (Figures 2–5; Figures S1–S5).

Table 2. Summary of findings.

Outcome	N0 of Studies (N0 of PTS)	Odds Ratio (95% CI)	I^2 (%)	Chi^2
FLD vs no-FLD				
Mortality	7 (5031)	3.56 (1.77–8.28)	43.2	0.103
Composite of MSAP and SAP (uni)	7 (5302)	3.14 (1.87–5.25)	91.5	0
Composite of MSAP and SAP (multi) ‡	5 (NR)	3.68 (2.16–6.29)	65.6	0.020
SAP by Atlanta 2012	8 (4931)	2.67 (2.01–3.56)	32.0	0.173
SAP by Atlanta 1992	2 (268)	4.70 (2.65–8.32)	0	0.634
Acute necrotic collection	5 (3929)	3.08 (2.44–3.90)	17.5	0.303
Acute peripancreatic fluid collection	3 (1150)	3.27 (1.97–5.42)	57.9	0.093
Pancreatic pseudocyst	3 (1130)	2.69 (1.64–4.40)	0	0.715
SIRS	4 (3634)	2.39 (1.74–3.28)	47	0.129
Length of hospital stay	5 (1955)	1.46 (0.54–2.39) †	40.7	0.150
NAFLD vs no-NAFLD				
Mortality	2 (1396)	2.81 (0.39–20.03)	68.7	0.074
Composite of MSAP and SAP (uni)	5 (4910)	2.64 (1.37–5.11)	94	0
Composite of MSAP and SAP (multi) ‡	3 (NR)	3.39 (1.52–7.56)	79.2	0.008
SAP by Atlanta 2012	3 (4085)	2.21 (1.70–2.88)	0	0.806
Length of hospital stay	3 (1647)	1.41 (0.03–2.7) †	68.5	0.042

CI = confidence interval, FLD = fatty liver disease, I2 and Chi2 = heterogeneity, MSAP = moderately severe acute pancreatitis, NAFLD = non-alcoholic fatty liver disease, SAP = severe acute pancreatitis, SIRS = systemic inflammatory response syndrome; † Length of hospital stay results are represented as weighted mean differences with 95% CI, values represent days; ‡ parameters included in multivariate analyses in the included studies are summarized in Table S3.

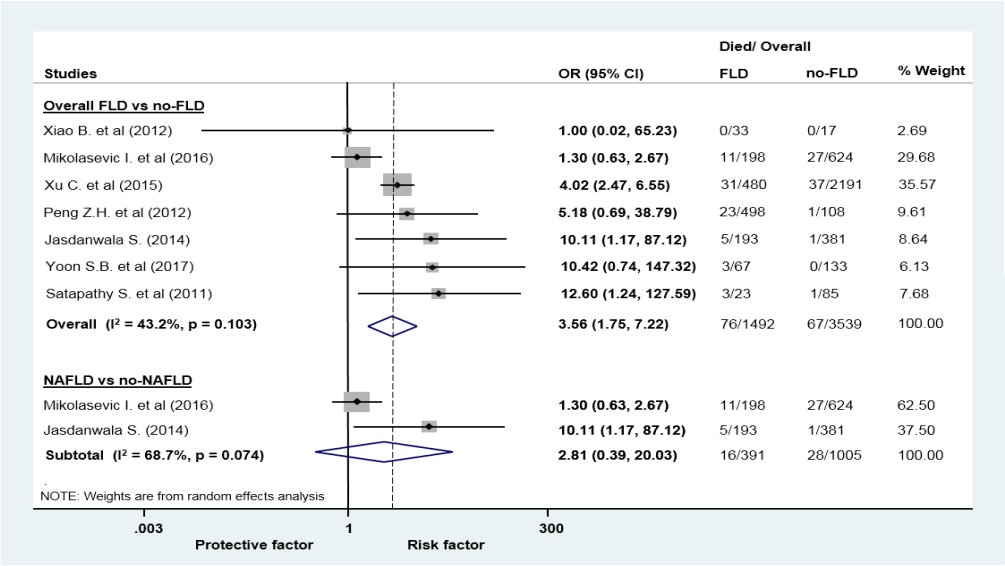

Figure 2. Forest plots of studies evaluating the association between fatty liver disease or non-alcoholic fatty liver disease and overall survival of patients with acute pancreatitis; CI: confidence interval, OR: odds ratio.

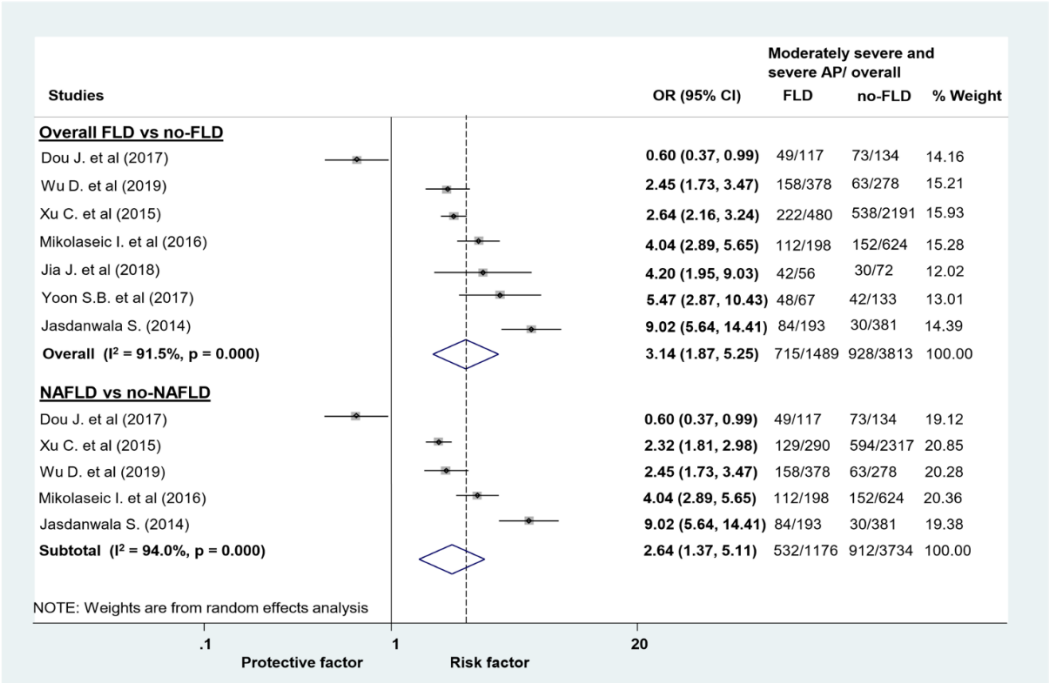

Figure 3. Forest plots of studies evaluating the association between fatty liver disease (FLD) or non-alcoholic fatty liver disease (NAFLD) and disease severity of acute pancreatitis (AP). We compared the odds of moderately severe/severe vs mild AP in patients with and without FLD/NAFLD; CI: confidence interval, OR: odds ratio.

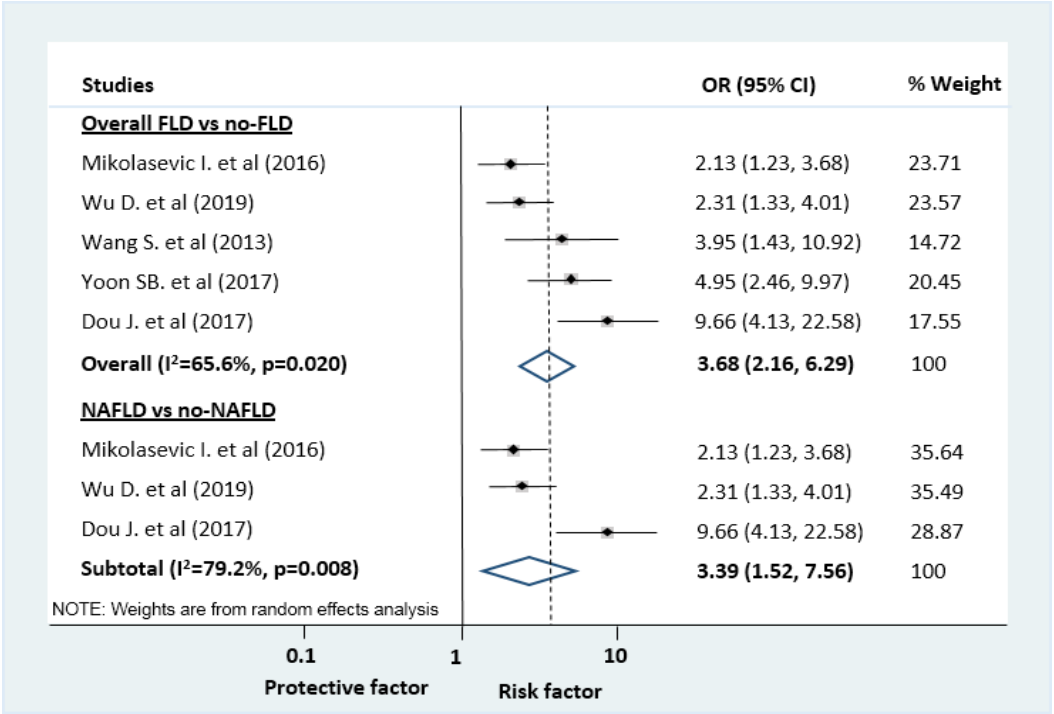

Figure 4. Forest plots of studies evaluating the association between fatty liver disease (FLD) or non-alcoholic fatty liver disease (NAFLD) and disease severity of acute pancreatitis (AP). Logistic regression analysis results were pooled, comparing the odds of moderately severe/severe vs mild AP in patients with and without FLD/ NAFLD; CI: confidence interval, OR: odds ratio.

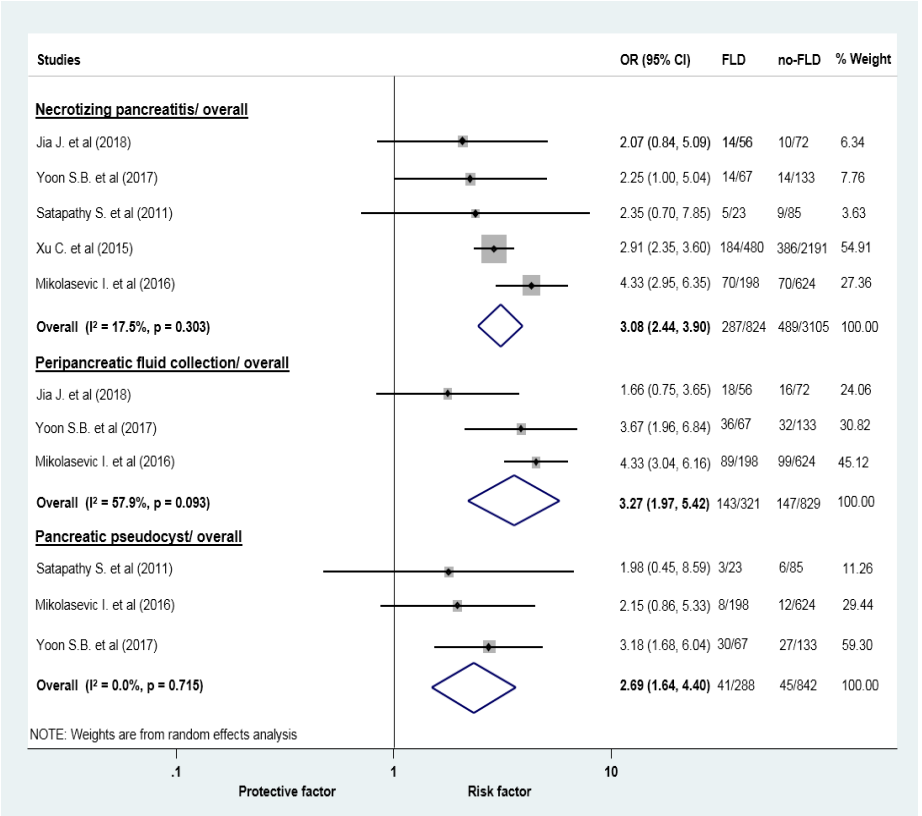

Figure 5. Forest plots of studies evaluating the association between fatty liver disease and the odds of local complications (necrotizing pancreatitis, peripancreatic fluid collection and pancreatic pseudocyst) in acute pancreatitis; CI: confidence interval, FLD: fatty liver disease, OR: odds ratio.

3.4. Findings of Meta-Analysis: NAFLD vs. No NAFLD

Although mortality in the NAFLD group was higher compared to those without it, the difference failed to attain the level of significance (OR = 2.81, CI: 0.39–20.03; Figure 2). Based on five articles, the course of AP was more severe in patients with NAFLD, the odds of moderately severe/severe AP was 2.64 higher (OR = 2.64, CI: 1.37–5.11; Figure 3). The odds to develop severe AP was also higher in the NAFLD group (OR = 2.21, CI: 1.70–2.88; Figure S3).

Based on 3 articles, NAFLD was an independent predictor of severe AP (OR = 3.39, CI: 1.52–7.56; Figure 4).

Patients with NAFLD tended to have longer hospital stay (WMD = 1.41 days, CI: 0.03–2.79 days; Figure S5).

3.5. Additional Analysis

The risk of bias and quality assessment of the individual studies are summarized in Table S4. Details of the risk of bias assessment are included in Appendix S1.

Funnel plots can be found in Figures S6, S7 and S8. According to the results, we did not observe evidence of publication bias when assessing funnel plots visually.

Sensitivity analysis, except for one outcome, showed no significant difference. When we removed the study of Yoon et al. [37] from the forest plot with the odds of pancreatic pseudocyst, the results became non-significant (OR = 2.09; CI: 0.97–4.55).

4. Discussion

As we know, this is the first meta-analysis to analyze the risk of multiple outcomes in AP patients with NAFLD.

Previously, only one meta-analysis that included a limited number of articles reported increased AP severity in FLD patients [39]. In this analysis, they reported on the severity of AP in patients with and without FLD, even though one of the included articles in their analysis reported on the association between severe FLD and AP severity. They did not manage to make a difference between FLD etiologies (alcoholic, non-alcoholic, metabolic etc.), even though it could have an impact on AP severity.

FLD is known to be associated with increased cardiovascular mortality and elevated risk of chronic kidney disease [40]. Fatty liver is common in AP patients because both conditions share contributing factors such as obesity, alcohol abuse, or hyperlipidemia, but its association with the prognosis of AP is still unclear.

Based on pooled data, AP patients with FLD were more likely to die during in-hospital stay than those in the non-FLD group. Eight of the included articles in this meta-analysis found a clear association between FLD and the development of severe AP. The rate of moderately severe/severe AP was also higher in AP patients with NAFLD, with significantly longer in-hospital stay, however the rate of mortality did not reach a significant difference. Overall, AP patients with FLD and NAFLD had a more severe disease course, an increased risk for the development of both local and systemic complications, and also a longer in-hospital stay.

Guidelines recommend performing a contrast-enhanced CT scan within 72 h–96 h after the onset of the AP symptoms [6]. Combined unenhanced and enhanced CT scans may be useful in assessing the status of both AP and FLD [37]. Studies that used CT scan and US or other methods (US elastography, MRI, etc.) have all shown acceptable levels of sensitivity for detecting FLD [3,41]. According to international guidelines, US should be used on the first hand to diagnose FLD since it is more widely available and cheaper than the gold standard MRI. However, US has limited specificity and does not reliably detect steatosis when <20%, compared to the MRI that can detect 5% fat in the liver. Another clinically available imaging technique, the controlled attenuation parameter (CAP) can diagnose FLD which classifies the steatosis in three grades based on the amount of liver with fatty change [3].

Significant heterogeneity could be observed among the cause of AP and FLD. According to Yoon et al. [37], a strong trend between the presence of FLD and AP severity was observed regardless of the cause of pancreatitis (alcoholic vs. non-alcoholic). Xu et al. [18] have found no difference in AP severity when comparing alcoholic FLD with NAFLD. In both cases the course of AP was worse compared to non-FLD patients.

MetS is often seen in patients with FLD. According to Szentesi et al. [13], the presence of two, three, or four MetS factors significantly increased the rate of worse outcome parameters by 9.5, 24.1, and 66.7%, respectively. In this analysis, only hypertriglyceridemia was independently associated with a more severe course of AP (OR = 3.41, 95%CI: 1.39–8.37).

Based on four articles [18,19,32,42], the severity of FLD affects AP outcomes. All these findings imply that the severity of FLD has a negative impact on the course of AP. Wang et al. [43] also reported a higher rate of severe AP in patients with severe FLD. On the other hand, the course of AP was more severe in cirrhotic patients [44]; however, the higher rate of mortality was attributed to complications of cirrhosis.

Results regarding AP severity defined by score systems were also reported in five of the included studies. Significantly higher BISAP scores (mean BISAP 0.813 vs. 0.544, $p < 0.01$) [28] and in two articles significantly higher CTSI scores were reported in FLD patients compared to non-FLD patients (mean CTSI 2.9 vs. 1.1, $p < 0.01$ and 4 vs. 2.2, $p < 0.05$) [30,33]. APACHE-II score was also significantly higher (mean APACHE-II 8.4 vs. 7.2, $p < 0.01$) in one of the included studies [30].

Four of the included articles suggested the incorporation of FLD into prognostic tools, but only Hao et al. [27] analyzed the effect of inclusion of FLD in the APACHE-II score system. They reported increased sensitivity and specificity when predicting severe AP (78.1% vs 85.4% and 86.2% vs 75.5%).

While Ding et al. [45] reported a non-significant effect of FLD on pancreatic necrosis infection (OR = 0.971; 95% CI: 0.45–2.08), another study reported an increased risk of infection in AP patients with FLD (46.5% vs. 38%, $p < 0.05$) [18]. Satapathy et al. [33] reported an increased need for antibiotics in AP patients with FLD (69.6% vs. 30.6%). This data was only represented in a few articles and therefore was not suitable for quantitative analysis.

FLD was also associated with increased hospital readmission of patients with AP (OR = 3.48, 95% CI: 1.70–7.11). However, data were collected retrospectively and admission diagnosis of acute or chronic pancreatitis were screened together regarding later readmission with a pancreatitis-related diagnosis [34].

According to Yuan et al. [38], fatty liver was a risk factor for abnormal fasting blood glucose levels (HR = 1.869, 95% CI = 1.16–3.01) after the first episode of AP. The median follow-up period in the study was three years; however, the definition of FLD was not reported. None of the included studies in the analysis discussed long-term complications.

Strengths and Limitations

Our meta-analysis has several strengths, most importantly, the rigorous methodology. We performed a systematic search followed by reproducible selection and data extraction. The strengths of this study also include the covariate-adjusted for AP severity and the high number of AP cases.

Several limitations should be taken into consideration when interpreting our conclusions. First, we included conference abstracts to reduce the risk of publication bias, but these are often lacking details; therefore, they are subjected to a potential risk of bias. Due to the low number of studies included (<10), we were unable to test if publication bias affects the results. All the included articles were retrospective, single-center cohort studies. Most of the study populations came from Asia, with a potential bias when making general conclusions, and may not be representative of other geographical regions. The diagnosis of AP and FLD was not uniformly used in the included articles. Neither of the included studies confirmed FLD in patients with liver biopsy. Not all the included articles reported the timing of repeated abdominal imaging; therefore, a potential heterogeneity is present in the rate of local complications. Significant heterogeneity could be found in some of the results (severity, independent

risk, and peripancreatic fluid collection). Sensitivity analysis showed significant difference just in the case of one outcome (the odds of pancreatic pseudocyst).

Risk factors included in the individual logistic regression analysis were not uniform between the studies (Appendix S1).

5. Conclusions

5.1. Implication for Practice

Our results showed that FLD and NAFLD worsen the course of AP. FLD and NAFLD can be easily diagnosed by abdominal US (affordable, non-invasive investigation) or abdominal CT scan (high sensitivity and specificity). We suggest that, compared to the current practice, a different approach should be taken into consideration in AP patients, and an initial non-invasive assessment of not only the pancreas but also the liver to detect fatty liver may be beneficial for patients with AP and may help to consider more individualized patient care.

5.2. Implication for Research

Since FLD and NAFLD may have an essential impact on AP outcomes, we suggest the incorporation of the assessment of FLD and NAFLD into the prognostic tools applied in the case of AP. Long-term complications were not assessed in the included studies; follow-up results are needed. AP associated with FLD may result in higher health care utilization and costs of medical services. The detailed economic impact of the FLD and NAFLD should be analyzed in patients with AP. Possible treatment options to decrease the increased risks of AP complications should be researched.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/9/2698/s1, **Table S1**: PRISMA checklist, **Table S2**: Inclusion and/or exclusion criteria in each included study in the systematic review and meta-analysis, **Table S3**: Factors included in multivariate logistic regression analyses, **Table S4:** Risk of bias assessment using QUIPS (Quality In Prognosis Studies) tool; **Figure S1**: Odds ratio of severe AP vs mild and moderately severe AP, comparing patients with FLD vs no-FLD, **Figure S2**: Odds ratio of severe AP vs mild AP, comparing patients with FLD vs no-FLD. Acute pancreatitis severity was defined based on the Atlanta Classification (1992) into mild and severe AP, **Figure S3**: Odds ratio of severe AP vs mild and moderately severe AP, comparing patients with NAFLD vs no-NAFLD, **Figure S4**: Forest plot representing the odds of SIRS in FLD and no-FLD patients suffering from AP. SIRS was defined as 2 or more of the included criteria, **Figure S5**: Forest plot representing the differences in length of hospitalization in FLD and no-FLD patients suffering from AP. Subgroup analysis with AP patients with NAFLD was also represented graphically. Data is described as number of patients included in the analysis (n) and mean hospital stay with standard deviation (SD), **Figure S6**: Funnel plot with pseudo 95% confidence intervals with included studies on Figure 2, **Figure S7**: Funnel plot with pseudo 95% confidence intervals with included studies on Figure 3, **Figure S8**: Funnel plot with pseudo 95% confidence intervals with included studies on Figure S1; **Appendix S1**: Results, Risk of bias assessment between studies.

Author Contributions: G.P. and S.V. designed the research and the study concept; S.V. and Z.S. performed the data extraction; D.N. analyzed and interpreted the data; S.V. and Z.S. performed the quality and risk assessment. S.V., Z.S., P.J.H., D.P., A.M., B.E., A.E., and G.P. wrote the article; G.P. supervised the study; G.P. and P.H. conducted a critical revision of the manuscript for important intellectual content. All authors have read and agreed to the published version of the manuscript.

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ORIGINAL ARTICLE

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Metabolic-associated fatty liver disease is associated with acute pancreatitis with more severe course: Post hoc analysis of a prospectively collected international registry

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a proven risk factor for acute pancreatitis (AP). However, NAFLD has recently been redefined as metabolic-associated fatty liver disease (MAFLD). In this post hoc analysis, we quantified the effect of MAFLD on the outcomes of AP.

Methods: We identified our patients from the multicentric, prospective International Acute Pancreatitis Registry of the Hungarian Pancreatic Study Group. Next, we compared AP patients with and without MAFLD and the individual components of MAFLD regarding in-hospital mortality and AP severity based on the revised Atlanta classification. Lastly, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) using multivariate logistic regression analysis.

Results: MAFLD had a high prevalence in AP, 39% (801/2053). MAFLD increased the odds of moderate-to-severe AP (OR = 1.43, CI: 1.09–1.89). However, the odds of in-hospital mortality (OR = 0.89, CI: 0.42–1.89) and severe AP (OR = 1.70, CI: 0.97–3.01) were not higher in the MAFLD group. Out of the three diagnostic criteria of MAFLD, the highest odds of severe AP was in the group based on metabolic risk abnormalities (OR = 2.68, CI: 1.39–5.09). In addition, the presence of one, two, and three diagnostic criteria dose-dependently increased the odds of moderate-to-severe AP (OR = 1.23, CI: 0.88–1.70, OR = 1.38, CI: 0.93–2.04, and OR = 3.04, CI: 1.63–5.70, respectively) and severe AP (OR = 1.13, CI: 0.54–2.27, OR = 2.08, CI: 0.97–4.35, and OR = 4.76, CI: 1.50–15.4, respectively). Furthermore, in patients with alcohol abuse and aged ≥60 years, the effect of MAFLD became insignificant.

Conclusions: MAFLD is associated with AP severity, which varies based on the components of its diagnostic criteria. Furthermore, MAFLD shows a dose-dependent effect on the outcomes of AP.

KEYWORDS
acute pancreatitis, MAFLD, metabolic syndrome, metabolic-associated fatty liver disease, mortality, NAFLD, non-alcoholic fatty liver disease, prognosis, severity, steatosis

INTRODUCTION

Acute pancreatitis (AP) is an acute gastrointestinal disorder affecting 23–49 per 100,000 people annually with significant associated mortality and morbidity.[1] The disease course is mild in 70%–75% of the cases, with mortality below 1%. However, in the remaining 25%–30%, it is moderate-to-severe (MSAP), with mortality reaching 50% in the latter group.[2]

Current guidelines recommend a three-dimensional approach to predict outcomes in AP. Host risk factors, clinical risk scores (e.g., Bedside Index for Severity in Acute Pancreatitis—BISAP score), and response to therapy (e.g., persistent systemic inflammatory response, creatinine) are crucial in risk stratification.[3] For example, age above 65 predicted systemic complications in AP (odds ratio [OR] = 8.93, 95% confidence interval—CI: 1.20–66.80).[4] Furthermore, abnormal body mass indexes (BMI) >30 kg/m^2 (OR = 2.89, 95% CI: 1.10–7.36) and <18.5 kg/m^2 (OR = 1.82, 95% CI: 1.32–2.50) were associated with increased mortality.[5] Components of metabolic syndrome considerably increased each other's harmful effects on the course of AP; the presence of four factors increased the rate of worse outcomes by 66.7%.[6]

Recently non-alcoholic fatty liver disease (NAFLD) and fatty liver disease (FLD) were shown to independently increase the odds of MSAP (OR = 3.39, 95% CI = 1.52–7.56, and OR = 3.68, 95% CI = 2.16–6.29, respectively).[7] However, NAFLD is still not included in risk stratification. In 2020, Eslam et al.[8] proposed new diagnostic criteria for NAFLD and renamed it metabolic-associated fatty liver disease (MAFLD) based on steatosis and metabolic factors. The prognostic role of MAFLD in other acute diseases has been proven,[9] but no studies have investigated its role in AP.

Therefore, our study aimed to investigate the prognostic role of MAFLD in the course of AP. We hypothesized that the course of AP would be more severe in the presence of MAFLD.

MATERIALS AND METHODS

We report our results following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (see checklist in Table S1).[10]

We performed this post hoc cross-sectional analysis using the data from the international prospective multicenter AP registry of the Hungarian Pancreatic Study Group (HPSG). The registry was approved by the Hungarian Scientific and Research Ethics Committee of the Medical Research Council (22254-1/2012/EKU and 17787-8/2020/EÜIG). In addition, we followed the Declaration of Helsinki revised in 2013, and all participants provided written informed consent.

Patient data were collected from the registry establishment from 2012 until 31 December 2019 using electronic case report forms validated by a four-level data monitoring protocol. Data collection and validation were described by Párniczky et al.[11] We summarized the contributing centers in Table S2. This study overlaps with previous publications by the HPSG.[2,4,6,11–16] However, the analysis in this study and the patient grouping has not been used and published previously.

Key summary

Summarise the established knowledge on this subject

- Metabolic syndrome components are proven risk factors for more severe acute pancreatitis (AP).
- Metabolic-associated fatty liver disease (MAFLD) was recently introduced as a new diagnostic criteria for non-alcoholic fatty liver disease, which was not yet investigated in AP.

What are the significant and/or new findings of this study?

- Our findings provide evidence that MAFLD is highly prevalent in patients with AP, being present in 39% of the patients.
- The MAFLD group based on other metabolic risk abnormalities carried the highest odds of a more severe AP.
- MAFLD dose-dependently increased the odds of in-hospital mortality and the severity of AP.

Definition of MAFLD

MAFLD was retrospectively diagnosed based on the prospectively collected data using the criteria and definition by Eslam et al.[8] MAFLD was diagnosed in the presence of steatosis of the liver on any abdominal imaging and the presence of at least one of the following: (1) overweight/obesity defined by BMI ≥25 and ≥30 kg/m^2, (2) type 2 diabetes mellitus (T2DM),[17] and/or (3) the presence of ≥ two metabolic risk abnormalities. For the third criteria, we included glycated hemoglobin (HbA1c), high blood pressure, hyperlipidemia, and hypercholesterolemia. These were collected based on patient history, drug intake, or in-hospital laboratory analysis. On the other hand, we excluded C-reactive protein (CRP) because of the acute inflammatory state in AP.

As included in the definition, alcohol consumption was not an exclusion factor. Therefore, we created subgroups based on the presence or absence of alcohol abuse (see below).

Patient selection

All the included adult (≥18 years) AP patients were diagnosed using the IAP/APA guidelines.[3]

First, we analyzed the presence of abdominal imaging (ultrasound, computed tomography-CT, magnetic resonance imaging, or endoscopic ultrasound) and the availability of liver descriptions. Steatosis was defined as fat accumulation described in the liver on any imaging during the hospitalization, while non-steatosis was defined if there was an unequivocal description of the liver without steatosis (=non-MAFLD group). We excluded patients with no abdominal imaging, equivocal liver description, or other chronic liver diseases such as cirrhosis or chronic hepatitis B or C in history.

Second, we included patients in the MAFLD group if any of the three criteria were positive, and we included patients in the non-MAFLD group if we could assess all criteria and all of them were negative. Finally, we excluded patients if any criteria for the diagnosis of MAFLD were missing and the others were negative.

Patients were followed from admission to discharge or mortality based on the relief of symptoms, decreasing inflammation, and/or restoration of oral feeding.

Variables

Our primary outcome was all-cause in-hospital mortality. Secondary outcomes were AP severity based on the revised Atlanta 2012 classification,[18] defined as mild AP, moderate AP (MAP), and severe AP (SAP) based on local and systemic complications. In addition, we assessed moderate-to-severe AP as a separate outcome (MSAP), a combination of the moderate and severe groups. Furthermore, we analyzed overall and individual local[18] (acute peripancreatic fluid collections, pancreas necrosis defined as acute necrotic collection or walled of necrosis, and pseudocyst) and systematic[18] (renal, respiratory, and cardiovascular failure) complications, diabetes as a complication (abnormal fasting glucose at discharge),[19] length of hospital stay (LOH), and maximum CRP level.

A list of the included variables is included in Table S3 with the definition of the given parameter. Alcohol abuse was defined as ≥20 g/day for females and ≥30 g/day for males.[20]

Data quality and representativeness

Table S3 shows the proportion of available data for each parameter. Figure 1 shows the selection process of our cohort. Comparing the original cohort (n = 2461) with our analyzed cohort (n = 2053), we did not find differences in gender, age, severity distribution, and LOH (Figure S1).

Statistical analysis

Our study is a post hoc cross-sectional analysis of a prospective AP registry. We conducted our analysis using the R statistical software version 4.0.2 (R Core Team, 2020).

Descriptive statistics were presented as median with 25% and 75% percentiles (interquartile range) or mean with standard deviation for continuous variables and as frequencies and relative frequencies (%) for categorical variables.

We used the Chi^2 test or Fisher's exact test for categorical variables. On the other hand, we used Welch's two-sample t-test or Kruskal-Wallis test, followed by Dunn's post hoc test for continuous variables.

Multivariate binary logistic regression analysis was performed to identify the risk factors independently associated with in-hospital mortality, MSAP, and SAP. We calculated adjusted OR with 95% CIs. We included MAFLD, age ≥60, gender, smoking, alcohol abuse, T2DM, and overweight/obesity. The selected variables were chosen based on the univariate analysis. On the other hand, we also performed analyses excluding T2DM or overweight/obesity due to the level in the variance inflation factor.

A $p < 0.05$ was considered statistically significant, except for the Kruskal-Wallis test, followed by Dunnett's post hoc test, where $p < 0.025$ was considered statistically significant.

We performed subgroup analyses based on the diagnostic criteria of MAFLD (MAFLD BMI, MAFLD T2DM, and MAFLD other), the number of positive criteria in MAFLD (1, 2, or 3), age < and ≥60 years, abdominal imaging with CT and ultrasound, and patients with and without alcohol abuse.

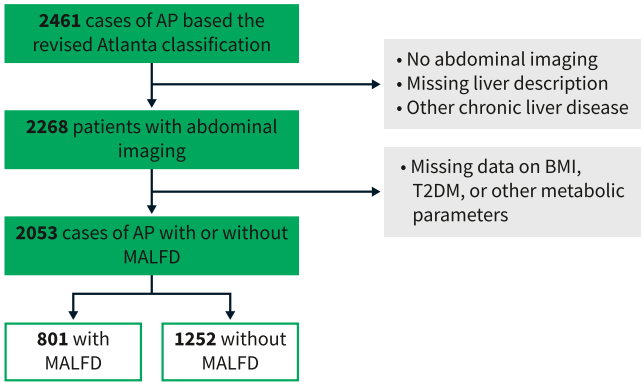

FIGURE 1 Patient selection flowchart.

RESULTS

One in three patients suffering from AP has MAFLD

Based on our selection criteria, we included 801 patients (39%, CI: 37%–41.1%) in the MAFLD group and 1252 (61%) in the non-MAFLD group (Figure 1). We summarized the descriptive statistics of the included AP patients in Table 1.

In our study, 1818 (89%) patients had at least one abdominal ultrasound, of which 1624 were performed during the first 2 days, and 1099 had only ultrasound as imaging. On the other hand, 952 (46%) had at least one CT, with 606 performed on the first 2 days and 233 had only CT as abdominal imaging. Furthermore, 23 (1%) patients had at least one magnetic resonance imaging, and 36 (2%) had at least an endoscopic ultrasound.

Patients in the MAFLD group have more comorbidities

Comparing AP patients with MAFLD to those without, we found a significantly lower rate of females (34% vs. 50%, $p < 0.001$) and higher rate of patients aged <60 years (59% vs. 52%, $p < 0.001$). Regarding comorbidities, AP patients with MAFLD had higher rates of comorbidities, alcohol abuse, and higher mean BMI (Table 1). Density plots for continuous variables in the MAFLD and non-MAFLD groups can be found in Figure S2.

Furthermore, MAFLD increased the rate of the analyzed outcomes (severity, local and systemic complications, and diabetes as a complication). However, the rates of in-hospital mortality, cardiovascular failure, and pseudocysts were not significantly higher (p = 0.874, p = 0.214, and p = 0.065, respectively) (Table 1 and Figures 2 and 3). Furthermore, Figures 2 and 3 represent the rate of different outcomes in the analyzed MAFLD groups. Further details of the analyzed parameters based on the subgroups can be found in Tables S4–S13.

MAFLD is an independent risk factor of AP severity but not for in-hospital mortality

Based on multivariate-adjusted logistic regression analysis (Table 2, see details in Supporting Information S1), MAFLD independently increased the odds of MSAP (OR = 1.39, CI: 1.05–1.84). However, the odds of in-hospital mortality (OR = 0.87, CI: 0.40–1.83) and SAP (OR = 1.63, CI: 0.93–2.89) were not higher in the MAFLD group.

Regarding the diagnostic criteria of MAFLD, we found significant differences. MAFLD based on overweight/obesity increased the odds of SAP (OR = 1.71, CI: 1.03–2.83) and MSAP (OR = 1.50, CI: 1.17–1.92) only if we exclude overweight/obesity from the multivariate model. On the other hand, in the case of MAFLD based on T2DM, the odds of MSAP became insignificant if we excluded T2DM from the multivariate model (Model 1 OR = 2.37, CI: 1.33–4.33; Model 2

TABLE 1 Basic characteristics of the included patients and comparison between MAFLD and non-MAFLD groups.

Parameter	All patients	MAFLD	Non-MAFLD	*p*-value
Age	57 (±17) (2053)	56 (±14) (801)	57 (±18) (1252)	0.162[a]
Age ≥60 years	932/2053 (45%)	332/801 (41%)	600/1252 (48%)	<0.001[b]
Female	902/2053 (44%)	276/801 (34%)	626/1252 (50%)	<0.001[b]
Comorbidities				
Steatosis	853/2053 (42%)	801/801 (100%)	52/1252 (4%)	<0.001[b]
Hypertension	1196/1563 (77%)	537/647 (83%)	659/916 (72%)	<0.001[b]
Type 2 diabetes mellitus	426/2039 (21%)	239/797 (30%)	187/1242 (15%)	<0.001[b]
Obesity/overweight	1349/1898 (71%)	709/765 (93%)	640/1133 (56%)	<0.001[b]
Body mass index	28.4 (±5.9) (1898)	31.10 (±5.53) (765)	26.57 (±5.41) (1133)	<0.001[a]
Hypertriglyceridemia	440/1393 (32%)	273/592 (46%)	167/801 (21%)	<0.001[b]
Hypercholesterinemia	410/1285 (32%)	223/527 (42%)	187/758 (25%)	<0.001[b]
CCI 0	578/1850 (31%)	0/716 (0%)	578/1134 (51%)	<0.001[b]
CCI 1–2	918/1850 (50%)	533/716 (74%)	385/1134 (34%)	<0.001[b]
CCI 3–4	253/1850 (14%)	126/716 (18%)	127/1134 (11%)	<0.001[b]
CCI ≥5	101/1850 (5.5%)	57/716 (8%)	44/1134 (4%)	<0.001[b]
Smoking	596/2041 (29%)	246/798 (31%)	350/1243 (28%)	0.195[b]
Alcohol consumption	236/1457 (16%)	125/548 (23%)	111/909 (12%)	<0.001[b]
Laboratory values				
Admission amylase (U/L)	722 (300-1518) (1910)	595 (228-1305) (748)	773 (346-1643) (1162)	<0.001[a]
Admission lipase (U/L)	1448 (573-3387) (1512)	1324 (471-3322) (596)	1499 (635-3429) (916)	0.593[a]
Max CRP (U/L)	139 (51–237) (2027)	184 (88–286) (792)	109 (38–200) (1235)	<0.001[a]
Max CRP day	3 (2–4) (2027)	3 (2–4) (792)	3 (2–4) (1235)	0.218[a]
Admission HbA1C (%)	5.60 (5.30–6.20) (685)	5.90 (5.50–7.00) (269)	5.50 (5.20–5.80) (416)	<0.001[a]
Admission glucose (mmol/L)	7.5 (6.1–9.6) (1799)	8.39 (6.70–10.79) (702)	7.00 (5.83–8.93) (1097)	<0.001[a]
Etiology				
Biliary	913/2053 (44%)	297/801 (37%)	616/1252 (49%)	<0.001[b]
Alcohol	432/2053 (21%)	226/801 (28%)	206/1252 (17%)	<0.001[b]
Hypertrigliceridaemia	140/2053 (7%)	108/801 (14%)	32/1252 (3%)	<0.001[b]
Other	568/2053 (28%)	170/801 (21%)	398/1252 (31%)	<0.001[b]
Outcomes				
In-hospital mortality	60/2053 (2.9%)	24/801 (3%)	36/1252 (2.9%)	0.874[b]
Mild AP	1465/2053 (71.4%)	520/801 (65%)	945/1252 (75.5%)	<0.001[b]
Moderate AP	481/2053 (23.4%)	225/801 (28%)	256/1252 (20.5%)	
Severe AP	107/2053 (5.2%)	56/801 (7%)	51/1252 (4%)	
Local complications	543/2039 (26.6%)	262/793 (33%)	281/1246 (22.5)	<0.001[b]
Peripancreatic fluid collection	456/2039 (22.4%)	223/793 (28.1%)	233/1246 (18.7%)	<0.001[b]
Pancreas necrosis	188/2038 (9.2%)	92/793 (11.6%)	96/1245 (7.7%)	0.003[b]
Pseudocyst	162/2039 (7.9%)	74/793 (9.3%)	88/1246 (7.1%)	0.065[b]
Systemic complications	172/2049 (8.4%)	82/799 (10.3%)	90/1250 (7.2%)	0.015[b]
Renal failure	79/2049 (3.9%)	46/799 (5.8%)	33/1250 (2.6%)	<0.001[b]

(Continues)

TABLE 1 (Continued)

Parameter	All patients	MAFLD	Non-MAFLD	*p*-value
Respiratory failure	121/2048 (5.9%)	58/799 (7.3%)	63/1249 (5%)	0.038[b]
Cardiovascular failure	46/2049 (2.2%)	22/799 (2.8%)	24/1250 (1.9%)	0.214[b]
Diabetes as complication	62/2053 (3%)	35/801 (4.4%)	27/1252 (2.2%)	0.004[b]
Length of hospital stay	10.62 (±9.9) (2053)	11.54 (±11.24) (801)	10.03 (±8.91) (1252)	<0.001[a]

Note: Categorical variables were described as event/total (%), continuous variables as mean or median with standard deviation or 25% and 75% percentiles (IQR).

Abbreviations: AP, acute pancreatitis; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; IQR, interquartile range; MAFLD, metabolic-associated fatty liver disease.

[a]Welch two sample *t*-test.

[b]Pearson's Chi-squared test.

OR = 1.36, CI: 0.93–1.96). Lastly, MAFLD based on metabolic risk abnormalities is an independent predictor of SAP (OR = 2.53, CI: 1.31–4.82) and MSAP (OR = 1.72, CI: 1.21–2.44) (Table 2). Details of the analysis are included in Tables S14–S16.

MAFLD dose-dependently increases the odds of SAP

We further analyzed the effect of multiple positive MAFLD criteria compared with non-MAFLD AP patients. The presence of one, two, and three diagnostic criteria dose-dependently increased the odds of MSAP (OR = 1.23, CI: 0.88–1.70, OR = 1.38, CI: 0.93–2.04, and OR = 3.04, CI: 1.63–5.70, respectively) and SAP (OR = 1.13, CI: 0.54–2.27, OR = 2.08, CI: 0.97–4.35, and OR = 4.76, CI: 1.50–15.4, respectively) (Table 2). Further details of the analyses are included in Tables S14–S16.

The effect of MAFLD is more substantial in patients without alcohol abuse, age <60 years, and with steatosis diagnosed based on abdominal ultrasound

In the subgroup of patients below and above 60 years, the effect of MAFLD differed significantly. MAFLD in patients below 60 years significantly increased the odds of MSAP (OR = 1.53, CI: 1.03–2.28) and SAP (OR = 3.16, CI: 1.17–9.41) but not in patients above 60 years (OR = 1.17, CI: 0.78–1.74, OR = 1.09, CI: 0.52–2.24, respectively).

Similarly, in the subgroup of patients without and with alcohol abuse, the odds of MSAP (OR = 1.51, CI: 1.11–2.03) and SAP (OR = 1.89, CI: 1.03–3.54) were higher in MAFLD patients without alcohol abuse but not in MAFLD patients with alcohol abuse (OR = 0.87, CI: 0.42–1.79, OR = 0.82, CI: 0.22–3.27, respectively).

Lastly, according to our data, MAFLD diagnosed based on abdominal CT was not associated with a worse outcome. However, MAFLD based on abdominal ultrasound increased the odds of MSAP and SAP (OR = 1.61, CI: 1.19–2.18, OR = 1.97, CI: 1.04–3.82, respectively).

Details of the analyses are included in Tables S14–S16.

DISCUSSION

To date, the number of studies investigating the effect of MAFLD on other diseases is limited, and the number of studies is increasing yearly. This is the first study to investigate the association between MAFLD and the severity of AP.

Our study found that MAFLD is present in 39% of AP patients and increases the severity of AP but not the odds of in-hospital mortality. We investigated the AP severity based on the different criteria for diagnosing MAFLD. We found that the group based on other metabolic risk abnormalities carried the highest odds of a more SAP. Furthermore, we found that the number of positive MAFLD criteria dose-dependently increased the odds of in-hospital mortality, MSAP, and SAP. On the other hand, the effect of MAFLD was more prominent in patients aged <60 years and without alcohol abuse. Lastly, we found that the effect of MAFLD may depend on the used abdominal imaging method.

Our results align with the most comprehensive meta-analysis, including 13 articles.[7] Based on pooled results of this meta-analysis, NAFLD/FLD increased the odds of more SAP but not the odds of in-hospital mortality. However, this could be because mortality in AP increases rapidly only after 59, and most of our patients with MAFLD were below 60.[21] The average age in our database is in accordance with other European cohorts.[22]

In a study investigating all-cause mortality due to MAFLD in a general population, the prevalence of MAFLD was lower, 25.9% (95% CI 23.6–28.3), compared to our cohort, where it was 39% (CI: 37%–41.1%).[23] This may be due to the common etiology of the two diseases, or MAFLD may increase the incidence of AP. Based on our results, alcohol- and hypertriglyceridemia-induced AP was more frequent in patients with MAFLD than in non-MAFLD. Based on the current definition of MAFLD, alcohol consumption is not an exclusion criterion.[8] This is because of the heterogeneity of NAFLD and there has been increasing evidence against a safe limit of alcohol consumption in the setting of NAFLD.[24] Furthermore, the prevalence of MAFLD in Eastern Europe is considered high, which may also explain the high MAFLD rate in our study.[25]

Previously, the prediction of SAP was thoroughly investigated. Recently, our study group involving a high number of AP cases

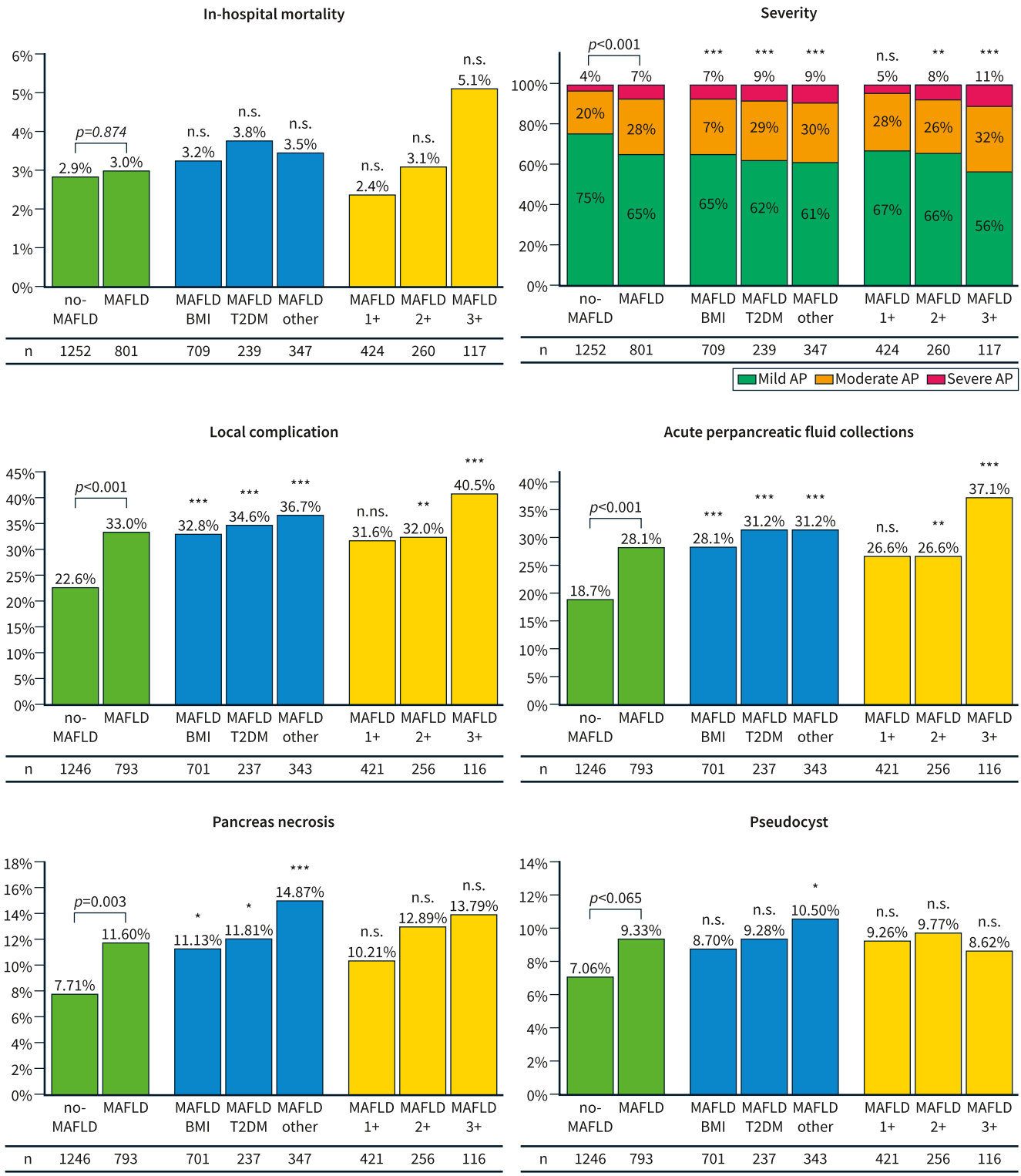

FIGURE 2 Summary figure showing the rate of in-hospital mortality, severity, local complications, acute peripancreatic fluid collection, pancreatic necrosis, and pseudocysts based on the different MAFLD groups. Colors for severity show mild (green), moderate (yellow), and severe (red) acute pancreatitis. MAFLD, metabolic-associated fatty liver disease. *, **, *** represents $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively.

developed an early prediction tool using machine learning that can predict SAP with an area under the curve (AUC) of 0.81 ± 0.03.[26] Several other prognostic tools with similar AUC could predict a more severe course in AP.[27–30] However, none assessed or included NAFLD/MAFLD as a possible factor.

Compared with other metabolic risk factors, MAFLD increased the odds of a more SAP dose-dependently (OR = 1.13, OR = 2.08, OR = 4.76, based on one, two, or three positive MAFLD criteria). Dobszai et al.[5] found that BMI>25 compared to normal weight increased the odds of SAP almost three-fold (OR = 2.87, 95% CI:

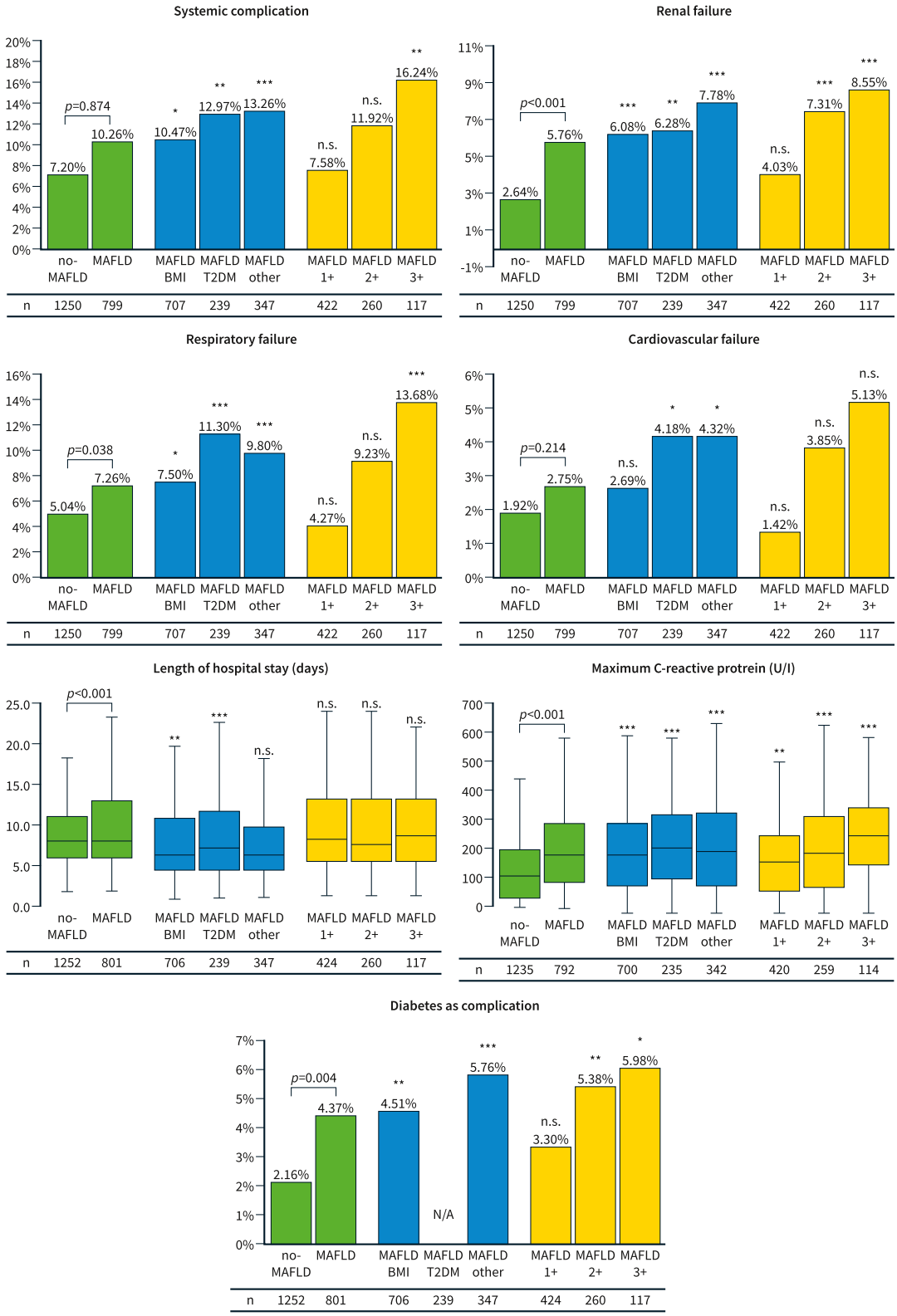

FIGURE 3 Summary figure showing the rate of systemic complications, renal failure, respiratory failure, cardiovascular failure, and diabetes as a complication, and the boxplots for the length of hospital stay and maximum C-reactive protein based on the different MAFLD groups. MAFLD, metabolic-associated fatty liver disease. *, **, *** represents $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively.

1.90–4.35), and this effect of BMI increased with the grade of obesity. Another study by our research group found that T2DM, which is a factor included in the diagnosis of MAFLD, increased the odds of intensive care unit admission (OR = 1.80, 95% CI: 1.44–2.24), renal failure (OR = 1.59, 95% CI: 1.28–1.97), and overall complications (OR = 1.55, 95% CI: 1.27–1.90).[31] Lastly, hypertriglyceridemia,

TABLE 2 Multivariable adjusted logistic regression analysis for MAFLD versus non-MAFLD comparison and different MAFLD groups compared to non-MAFLD in patients with AP.

Comparison	In-hospital mortality	Moderate-to-severe AP	Severe AP
MAFLD versus non-MAFLD	0.87 (0.40–1.83)	**1.39 (1.05-1.84)**	1.63 (0.93–2.89)
MAFLD based on obesity or overweight model 1	0.95 (0.43–2.10)	**1.35 (1.01-1.81)**	1.56 (0.87–2.87)
MAFLD based on obesity or overweight model 2	0.96 (0.47–1.86)	**1.50 (1.17-1.92)**	**1.71 (1.03-2.83)**
MAFLD based on T2DM model 1	3.52 (0.50–70.2)	**2.37 (1.33-4.33)**	2.49 (0.82–9.26)
MAFLD based on T2DM model 2	0.78 (0.23–2.07)	1.36 (0.93–1.96)	1.53 (0.75–2.92)
MAFLD based on metabolic risk abnormalities	1.69 (0.66–3.99)	**1.72 (1.21-2.44)**	**2.53 (1.31-4.82)**
MAFLD meets one criteria[a]	0.50 (0.16–1.31)	1.23 (0.88–1.70)	1.13 (0.54–2.27)
MAFLD meets two criteria[a]	1.29 (0.43–3.39)	1.38 (0.93–2.04)	2.08 (0.97–4.35)
MAFLD meets three criteria[a]	6.00 (0.88–50.9)	**3.04 (1.63-5.70)**	**4.76 (1.50-15.4)**
MAFLD alcohol consumption excluded	0.97 (0.42–2.16)	**1.51 (1.11-2.03)**	**1.89 (1.03-3.54)**
MAFLD alcohol consumers	0.61 (0.09–4.04)	0.87 (0.42–1.79)	0.82 (0.22–3.27)
MAFLD below <60 years	3.03 (0.73–15.0)	**1.53 (1.03-2.28)**	**3.16 (1.17-9.41)**
MAFLD above ≥60 years	0.46 (0.16–1.21)	1.17 (0.78–1.74)	1.09 (0.52–2.24)
MAFLD based on abdominal CT	0.75 (0.33–1.69)	1.12 (0.78–1.63)	1.26 (0.67–2.36)
MAFLD based on abdominal ultrasound	1.17 (0.46–2.98)	**1.61 (1.19-2.18)**	**1.97 (1.04, 3.82)**

Note: Complete multivariate analyses can be found in Supporting Information S1. All the bold values highlight those with $p < 0.05$. Data are expressed as ORs with 95% CIs tested by multivariable logistic regression analyses. Multivariate analyses were adjusted for MAFLD, age ≥60, gender, smoking, alcohol abuse, T2DM, and overweight/obesity. Model 1: obesity/overweight and T2DM are included in the models. Model 2: obesity/overweight or T2DM are excluded from the models.

Abbreviations: AP, acute pancreatitis; CIs, confidence intervals; CT, computed tomography; MAFLD, metabolic associated fatty liver disease; ORs, odds ratios; T2DM, type 2 diabetes mellitus.

[a]Overweight/obesity, T2DM or/and ≥ two metabolic risk abnormalities.

another component of the metabolic syndrome, dose-dependently increased the odds of local complications and organ failure.[12]

We investigated the different types of MAFLD groups that may affect the course of AP differently. Non-obese, non-T2DM MAFLD patients should be highlighted. These patients are called metabolically unhealthy lean (non-obese) patients.[8] Metabolically unhealthy lean MAFLD patients have greater ectopic fat accumulation, especially in visceral fat format. Visceral fat may contribute to peripancreatic fat infiltration in AP. Furthermore, in this group, hypertriglyceridemia may lead to the formation of toxic unsaturated fatty acids while the chylomicron concentration increases elevating the blood viscosity and leading to complications.[32] In obese MAFLD patients, obesity was associated with increased intrapancreatic fat and visceral fat around the pancreas.[33] In T2DM MAFLD, hyperglycemic states were previously linked with direct pancreatotoxic effect, mainly through the intracellular increase in reactive oxygen species.[13]

The underlying mechanism behind the effect of MAFLD on the course of AP needs further clarification. Few studies have examined how MAFLD aggravates the course of AP. The first study by Wang et al.[34] found several dysregulated genes in AP rat fatty liver models. They found that the inhibition of the peroxisome proliferator-activated receptor alpha signaling pathway and the fatty acid degradation pathway may lead to the aggravation of AP. Furthermore, in another study, they found lower alpha-1-antitrypsin levels in both human and rat AP models.[35] Lastly, in the most recent study by Lin et al.,[36] authors found increased bacterial translocation in the liver and pancreas in the FLD rat model.

In our study, MAFLD was diagnosed with multiple types of abdominal imaging. Interestingly, MAFLD diagnosed with abdominal ultrasound resulted in increased AP severity but not in MAFLD based on abdominal CT. This can be due to the level of steatosis that the imaging modality can detect. One of the AP diagnostic criteria is based on abdominal imaging. However, current guidelines do not require imaging to confirm the diagnosis of AP.[3] ultrasound is currently the most widely available tool for diagnosing steatosis. However, with a fat percentage <20%, ultrasound becomes unreliable. Furthermore, high abdominal fat can decrease diagnostic performance.[8] On the other hand, abdominal CT or MRI can detect lower levels of steatosis. However, AP guidelines recommend CT or MRI at least 72 h after the start of the disease.[3]

Diabetes as a complication occurred higher in the MAFLD group (4.4% vs. 2.2%, $p = 0.004$). Diabetes in our study was diagnosed as abnormal fasting glucose at discharge. Compared to this, Petrov MS et al.[19] in a review recommend following the diagnostic criteria for diabetes by the American Diabetes Association.[17] Similarly, in the study by Yuan et al.,[37] fatty liver was a risk factor for abnormal

fasting blood glucose levels (HR = 1.87, 95% CI = 1.16–3.01) after the first episode of AP. Based on a recent meta-analysis,[7] only Yuan et al. evaluated long-term complications with a median follow-up of 3 years.

Lastly, it must be highlighted that the diagnostic criteria of MAFLD need further validation. However, it was already endorsed by multiple expert boards.[38,39]

Strengths and limitations

Our study has several strengths and limitations. This is the first study to investigate the effect of MAFLD on the disease course of AP in a multivariate model. Furthermore, we included a high number of AP patients from a registry with precise data collection and created subgroups based on multiple criteria. Lastly, we used a rigorous methodology and followed the STROBE recommendations while reporting our results.

On the other hand, our study has several limitations. First, although we included the patients prospectively in our registry, the diagnosis of MAFLD was made retrospectively while we could not reassess the pictures of abdominal imaging. This may have resulted in selection bias. Second, the diagnosis of MAFLD still needs further validation, and it is not yet included in the guidelines. Third, despite the high number of AP patients, the event rate in some of the analyzed groups was low. For steatosis measurement, we used multiple imaging methods, but not biopsy. Furthermore, for the diagnosis of MAFLD, we could not include all the parameters based on the diagnosing criteria. Lastly, although we found an increased severity in AP patients with MAFLD, there is no specific therapy for MAFLD in acute cases, nor in the long term.

CONCLUSION

Based on our results, MAFLD is prevalent in AP and is associated with increased severity but not in-hospital mortality. The effect of MALFD varies based on the diagnostic criteria, age, alcohol consumption, and the abdominal imaging used.

Implications for practice and research

The benefit of implementing research results into practice is unquestionable, and it brings significant health and economic benefits.[40,41]

From a clinical point of view, MAFLD should be included in assessing patients with AP in acute care and after discharge. Our results not only provide an opportunity for better severity predictions on admission but also help to educate patients on the importance of reducing or eliminating the extent of MAFLD after AP.

The long-term effects of MAFLD in patients with AP should be further investigated. In addition, further research is needed to understand the pathophysiological effect of MAFLD in the course and development of AP.

AUTHOR CONTRIBUTIONS

Szilárd Váncsa, **Péter Hegyi**, **Gabriella Pár**, **Bálint Erőss**, **Andrea Párniczky**, **Andrea Szentesi**: Conceptualization. **Szilárd Váncsa**, **Brigitta Teutsch**: Methodology. **Zoltán Sipos**, **Alex Váradi**: Formal analysis. **Szilárd Váncsa**, **Rita Nagy**, **Katalin Márta**, **Alexandra Mikó**, **Péter Jenő Hegyi**, **Áron Vincze**, **Ferenc Izbéki**, **László Czakó**, **Mária Papp**, **József Hamvas**, **Márta Varga**, **Imola Török**, **Artautas Mickevicius**, **Bálint Erőss**, **Andrea Párniczky**, **Andrea Szentesi**, **Gabriella Pár**, **Péter Hegyi**, HPSG contributors: Resources. **Szilárd Váncsa**, **Zoltán Sipos**, **Alex Váradi**, **Rita Nagy**, **Brigitta Teutsch**, **Klementina Ocskay**, **Félix Márk Juhász**: Data Curation. **Szilárd Váncsa**, **Péter Hegyi**: Writing - Original Draft. **Szilárd Váncsa**, **Rita Nagy**, **Brigitta Teutsch**, **Klementina Ocskay**, **Félix Márk Juhász**, **Katalin Márta**, **Alexandra Mikó**, **Péter Jenő Hegyi**, **Áron Vincze**, **Ferenc Izbéki**, **László Czakó**, **Mária Papp**, **József Hamvas**, **Márta Varga**, **Imola Török**, **Artautas Mickevicius**, **Bálint Erőss**, **Andrea Párniczky**, **Andrea Szentesi**, **Gabriella Pár**, **Péter Hegyi**, HPSG contributors: Writing - Review & Editing. **Szilárd Váncsa**, **Zoltán Sipos**, **Alex Váradi**: Visualization. **Péter Hegyi**: Supervision. **Péter Hegyi**, **Szilárd Váncsa**: Project administration. **Péter Hegyi**, **Szilárd Váncsa**: Funding acquisition. All co-authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets used in this study can be found completely in this publication.

ETHICS APPROVAL

Ethics approval was obtained from the Scientific and Research Ethics Committee of the Medical Research Council of Hungary (22254-1/2012/EKU and 17787-8/2020/EÜIG). The study was conducted following the Helsinki Declaration. The datasets used in this study can be found completely in this publication.

CONSENT FOR PUBLICATION

The corresponding author accepts responsibility for releasing this material on behalf of all co-authors.

CONSENT TO PARTICIPATE

Written informed consent was obtained from all participants before enrollment.

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