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

PhD Thesis

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1. Publications

1.1. Scientific metrics (as of 2023.06.16)

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

1.2. 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. 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, 2020 IF: 4.242**)

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.

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 (5).

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 (6). 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 (7).

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 (7), 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 (8).

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 (9). However, Eslam et al.(10) propose 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**).

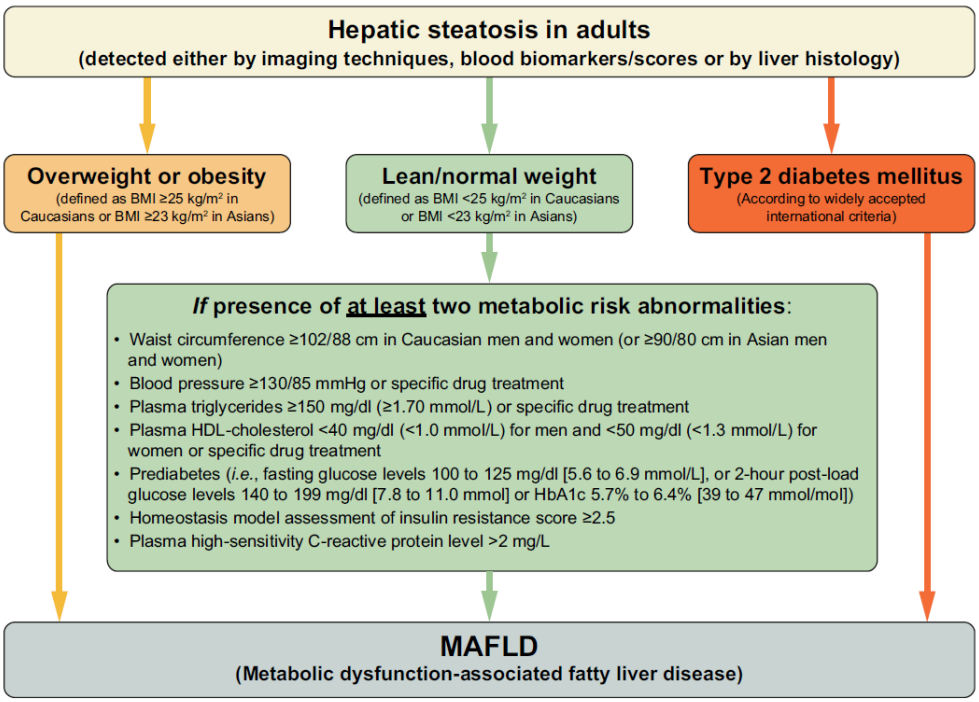

Figure 1. The proposed diagnostic criteria for MAFLD can be represented by a flowchart, outlining the steps required for a positive diagnosis (9).

5.2. 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 (11).

Despite the implications of these findings, NAFLD is not currently included in risk stratification. In 2020, Eslam et al.(10) 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 (12).

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.

5.3.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.

5.4.Objectives and hypotheses

This thesis describes the results of our **(I) systematic review with meta-analysis (11)** and **(II) registry analysis assessing the association between MAFLD and the course of AP (13)** 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 adheres to the PRISMA guidelines for systematic reviews and meta-analyses, ensuring transparency, reproducibility, and accuracy (14). The study protocol was registered in PROSPERO (registration number CRD42019123416).

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

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). 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).

6.1.3. Selection process

In accordance with the guidelines outlined in the Cochrane Handbook,(15, 16) 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).

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.

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 (17).

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. We calculated the pooled odds ratios (OR) and weighted mean difference (WMD) with 95% confidence interval (CI) using the random-effects model with the DerSimonian–Laird method (18).

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.

6.2.2. Characteristics of the studies included in the meta-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 (19) or the Atlanta Classification of 1992 (20) 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) (21) 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.

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

Table 1 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.

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 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).

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). 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). 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).

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).

6.3. 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) (22). 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.

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.

6.4. Implication for practice, research, and policy makers

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.

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.

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.

Table 1. 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;

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 (23).

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.(24) describe the data collection and validation processes in detail.

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.(10)

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 (19), which categorizes AP as mild, moderate (MAP), or severe (SAP).

7.1.4. 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.

We conducted a multivariate binary logistic regression analysis to identify the risk factors that are independently associated with in-hospital mortality, MSAP, and SAP.

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.

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. We conducted a thorough analysis of the data collected and reported the descriptive statistics of the included AP patients.

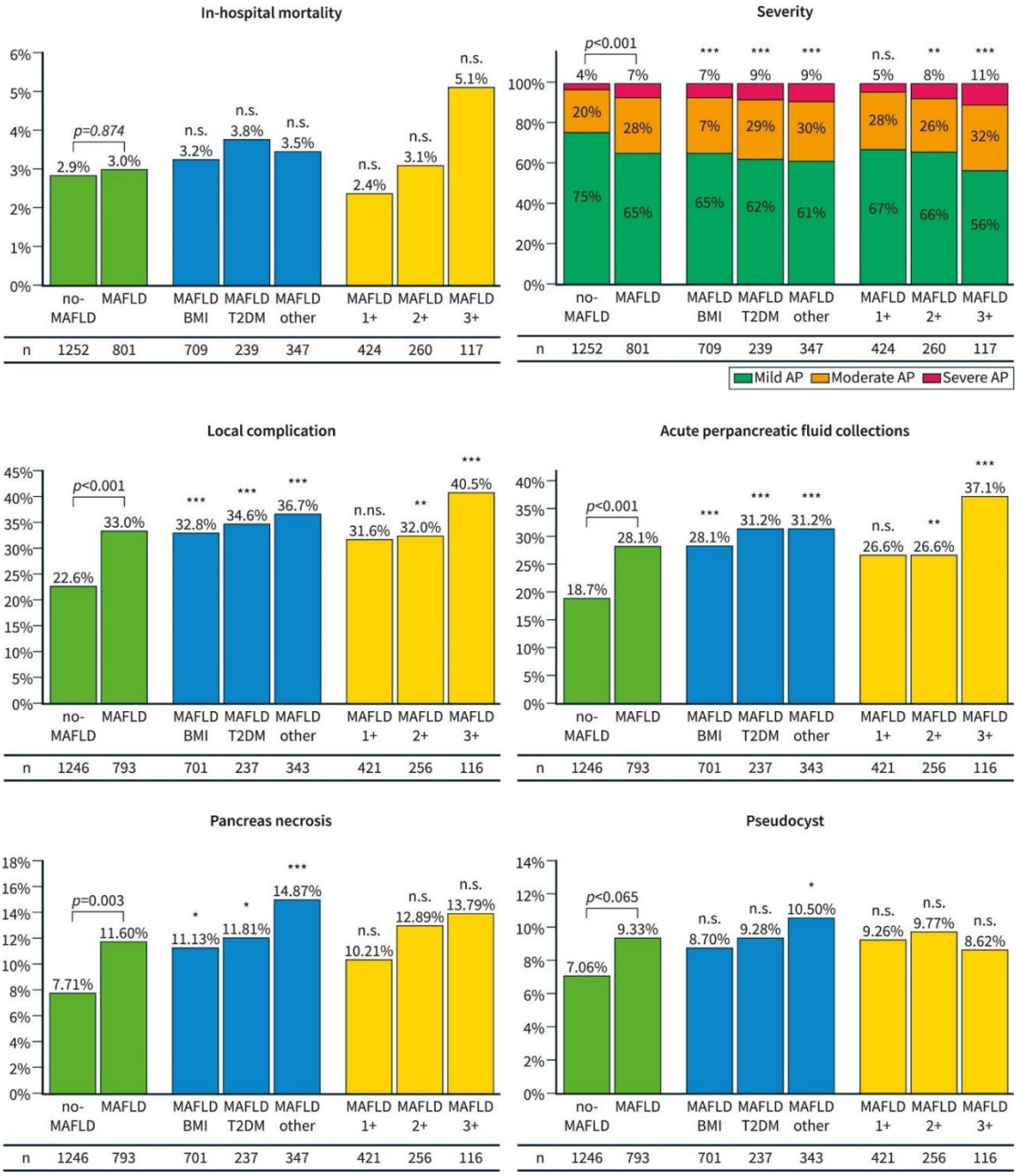

Figure 2. Summary figure showing the rate of in-hospital mortality, severity, local complications, acute peripancreatic fluid collection, pancreas necrosis, and pseudocysts based on the different MAFLD groups. Colors for severity show mild (green), moderate (yellow), and severe (red) acute pancreatitis. 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.'

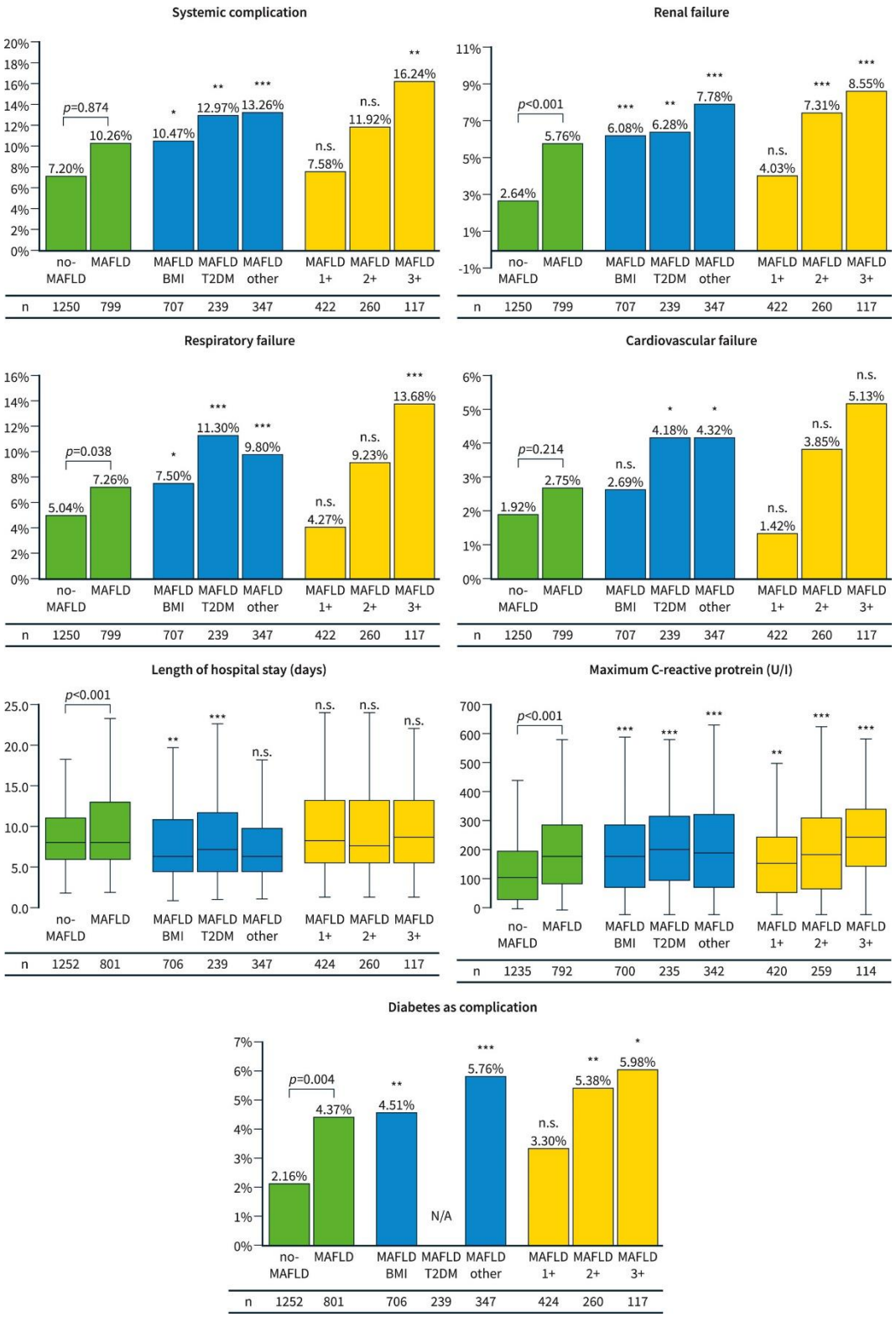

Figure 3. Summary figure showing the rate of multi-organ failure, renal failure, respiratory failure, cardiovascular failure, and diabetes as a complication, and the boxplots for the length of hospital stay and maximum C-reactive protein based on the different MAFLD groups. In the subgroup of MAFLD T2DM 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).

7.2.2. 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 2**, 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.

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).

7.2.3. 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 2**).

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.

7.2.4. 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.

Table 2. 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.

7.3. 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.

7.3.1. Strengths and limitations

Our study's strengths include: (1) being among the first to analyze the usability of the MAFLD definition, as most centers still rely on negative diagnostic criteria for NAFLD; (2) conducting the largest analysis of prospectively collected patient data in acute pancreatitis registries, including information from admission to hospitalization; (3) ensuring high-quality data for the outcomes, with nearly 100% data completeness; (4) performing multiple subgroup analyses using multivariate logistic regression to demonstrate the independent impact of MAFLD on acute pancreatitis progression; (5) adhering to international reporting recommendations when presenting our results.

Our study has some limitations: (1) The presence of MAFLD was determined retrospectively based on collected data since the MAFLD definition was introduced after the start of the registry; (2) In some cases, detailed information (e.g., liver imaging) necessary to determine the presence of MAFLD was lacking, potentially introducing selection bias. However, our representativeness analysis showed no difference between the analyzed and original patient groups; (3) Long-term outcomes such as 30-day or 1-year mortality or readmission were not analyzed; (4) While the overall patient count was high, certain subgroups

had a smaller number of patients included; (5) Liver biopsy, the gold standard for measuring liver steatosis, was not performed in any acute pancreatitis cases, although the MAFLD definition does not require biopsy; (6) The effectiveness of acute pancreatitis therapy based on the presence of MAFLD was not analyzed. It should be noted that there is currently no specific therapy for acute illnesses related to MAFLD.

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. As such, it is crucial to consider these variables when assessing patients with AP for the presence of MAFLD and determining appropriate treatment approaches.

7.5.Implication for practice, research and policymakers

Assessing AP patients for MAFLD is crucial in clinical practice. It is important to incorporate this evaluation during acute care and after discharge to improve severity predictions on admission and educate patients about reducing or eliminating MAFLD. Our findings highlight the significance of including MAFLD screening in routine care for AP patients, which can lead to better outcomes by identifying high-risk individuals and enabling early interventions to manage MAFLD and prevent AP progression.

The long-term effects of MAFLD in AP patients require further investigation to understand its impact on the development and progression of the disease. Additionally, more research is needed to uncover the molecular and cellular mechanisms linking MAFLD and acute pancreatitis, specifically exploring the role of gut-liver axis dysfunction, inflammation, and metabolic dysregulation. Such studies could contribute to the development of improved treatments and prevention strategies for this condition.

Policymakers should prioritize using MAFLD instead of NAFLD to improve accurate detection of liver steatosis and enable early diagnosis in AP patients. However, the healthcare cost associated with AP treatment in the presence of MAFLD remains poorly understood, highlighting the importance of analyzing its financial impact. Previous studies have shown the necessity of promptly implementing scientific findings in patient care for AP (26, 27).

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.

9. References

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