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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.

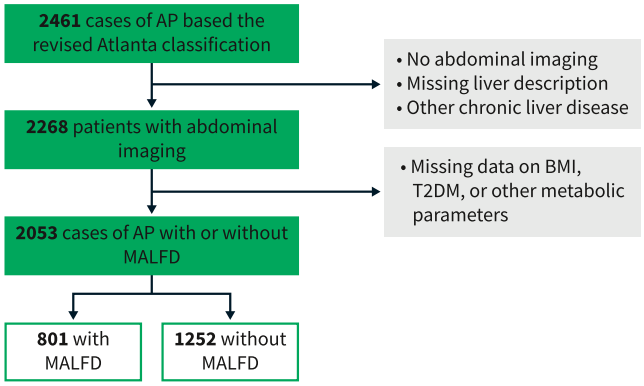

FIGURE 1 Patient selection flowchart.

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

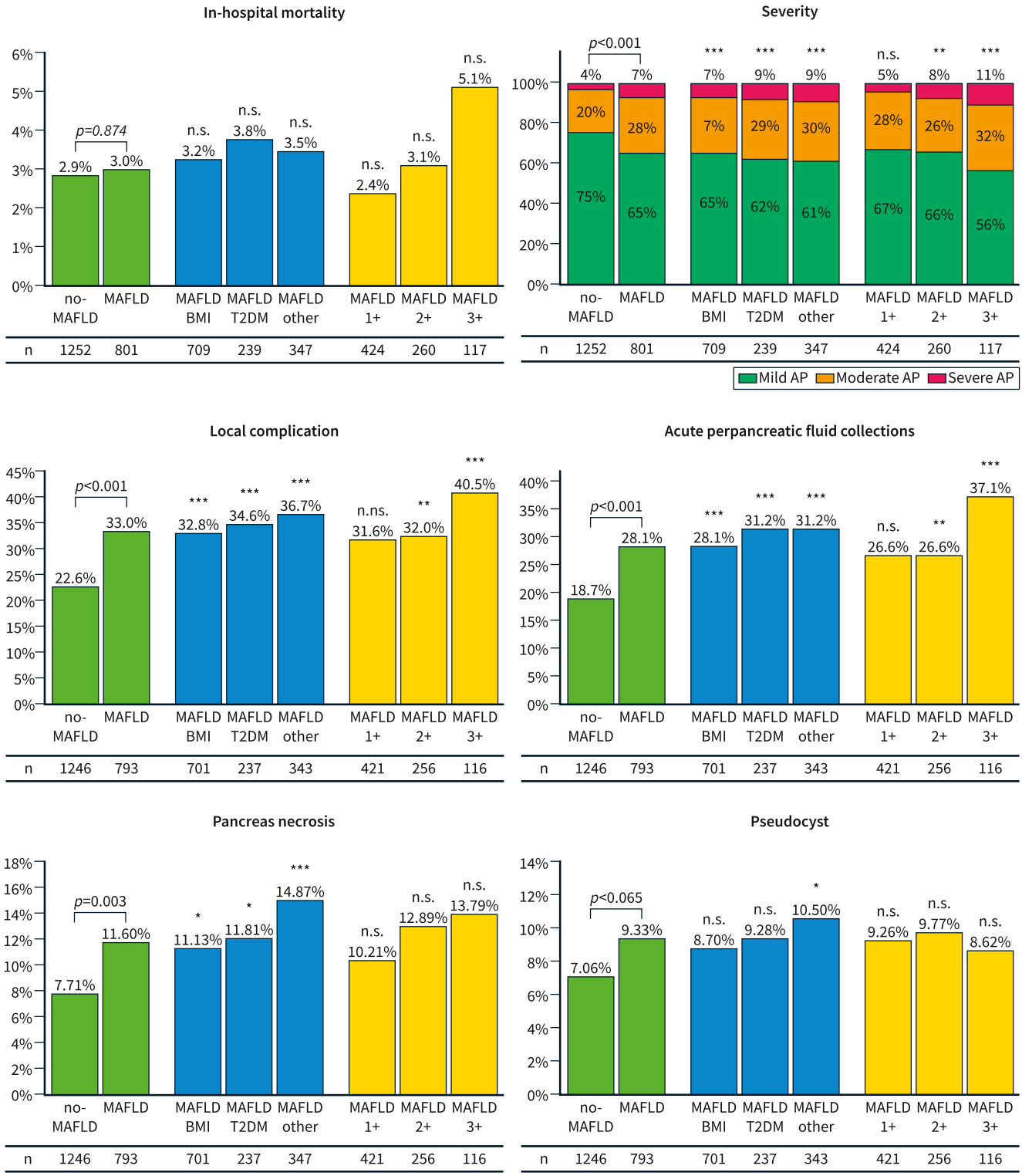

FIGURE 2 Summary figure showing the rate of in-hospital mortality, severity, local complications, acute peripancreatic fluid collection, pancreatic necrosis, and pseudocysts based on the different MAFLD groups. Colors for severity show mild (green), moderate (yellow), and severe (red) acute pancreatitis.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

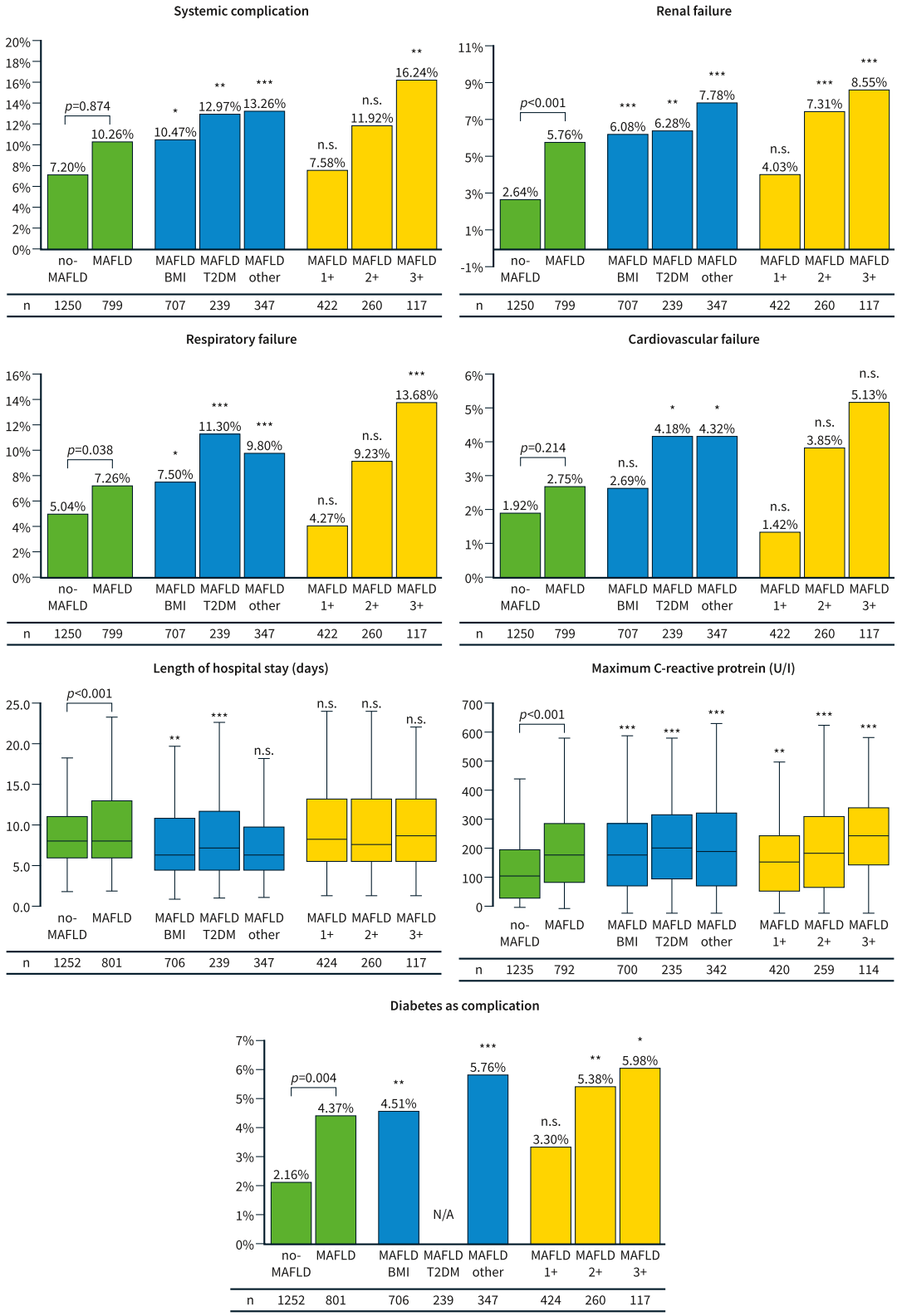

FIGURE 3 Summary figure showing the rate of systemic complications, renal failure, respiratory failure, cardiovascular failure, and diabetes as a complication, and the boxplots for the length of hospital stay and maximum C-reactive protein based on the different MAFLD groups. MAFLD, metabolic-associated 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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