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Obesity and alcoholic etiology as risk factors for multisystem organ failure in acute pancreatitis: Multinational study

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Abstract

Background: Multisystem organ failure (MSOF) is the most important determinant of mortality in acute pancreatitis (AP). Obesity and alcoholic etiology have been examined as potential risk factors for MSOF, but prior studies have not adequately elucidated their independent effects on the risk of MSOF.

Objective: We aimed to determine the adjusted effects of body mass index (BMI) and alcoholic etiology on the risk of MSOF in subjects with AP.

Methods: A prospective observational study of 22 centers from 10 countries was conducted. Patients admitted to an APPRENTICE consortium center with AP between August 2015 and January 2018 were enrolled. Multivariable logistic regression was used to estimate the adjusted effects of BMI, etiology, and other relevant covariates on the risk of MSOF. Models were stratified by sex.

Results: Among 1544 AP subjects, there was a sex-dependent association between BMI and the risk of MSOF. Increasing BMI was associated with increased odds of MSOF in males (OR 1.10, 95% confidence interval [CI] 1.04–1.15) but not in females (OR 0.98, 95% CI 0.90–1.1). Male subjects with AP, whose BMIs were 30–34 and >35 kg/m^2, had odds ratios of 3.78 (95% CI 1.62–8.83) and 3.44 (95% CI 1.08–9.99), respectively. In females, neither higher grades of obesity nor increasing age increased the risk of MSOF. Alcoholic etiology was independently associated with

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increased odds of MSOF compared with non-alcohol etiologies (OR 4.17, 95% CI 2.16–8.05).

Conclusion: Patients with alcoholic etiology and obese men (but not women) are at substantially increased risk of MSOF in AP.

KEYWORDS
acute pancreatitis, alcoholic pancreatitis, multi-system organ failure, obesity

INTRODUCTION

Acute pancreatitis (AP) is a clinical syndrome that results from inflammation of the exocrine pancreas and is among the leading causes of GI-related hospitalizations in the U.S.[1] While most of patients with AP recover rapidly, 30%–40% experience substantial morbidity and mortality from local and/or systemic complications.[2] While there has been substantial progress in the management of local complications, such as acute fluid and necrotic collections in AP, there is currently no effective treatment to mitigate organ failure, a potentially fatal systemic complication of AP.[3] Specifically, multi-system organ failure ([MSOF]; organ failure involving two or more vital organs) represents the most terminal stage of systemic complications and is the main driver of mortality in AP.[2,4]

Obesity and alcoholic etiology—present in 30%–50% of AP cohorts—have been examined as potential risk factors for MSOF in a few studies.[5,6] However, previous studies have generated conflicting results: some even suggested the "obesity paradox," implying that obesity has protective effects in severe AP,[7] while others found that obesity does not increase the risk of organ failure.[8] Results regarding the impact of alcoholic etiology on AP outcomes have similarly been mixed.[9] This heterogeneity is largely attributable to significant methodologic constraints that plague both prospective observational studies and retrospective cohort studies that use large administrative databases.[10,11] Studies of large administrative databases possess excellent statistical power, but ascertainment and misclassification biases in AP diagnosis, severity grading, and AP etiology challenge the validity of their findings.[12] Prospective cohort studies that obtain patient-level data accurately identified AP and ascertained endpoints precisely, but they suffered from small sample size,[13] selection bias from single-center design,[14] and further loss of statistical power by dichotomizing the body mass index (BMI) variable in small cohorts.[15] Additionally, important effect-modifiers seen in other acute disease models such as age, sex, and BMI have not been simultaneously investigated as risk factors for MSOF in AP.[16]

Objective

The primary aim of this study was to determine the adjusted effects of BMI and AP etiology on the risk of MSOF in AP patients and ascertain whether there is an effect modification by age and/or sex.

Key Summary

Established knowledge on the subject

- Multi-system organ failure (multisystem organ failure) is the most fatal systemic complication of acute pancreatitis (AP).
- Obesity and alcoholic etiology have emerged as potential risk factors for multi-system organ failure in AP, but the results of previous studies have been mixed.

Significant and/or new findings of the study

- Obesity increases the risk of multi-system organ failure only in male patients with AP.
- Alcoholic etiology is an independent risk factor for multi-system organ failure in AP.

Hypothesis

We hypothesized that BMI and alcoholic etiology will increase the risk of MSOF and that age and sex may modify their effects.

METHODS

Study design

The APPRENTICE consortium comprises 22 centers from 10 countries (Argentina 2, Greece 1, India 3, Italy 1, Lithuania 1, Mexico 2, Paraguay 1, Romania 2, Spain 1, and USA 8) with a diverse range of hospitals in terms of number of beds (101–1000 beds), the level of care provided (secondary & tertiary referral centers; proportion of referred AP subjects <25%–75%), and AP volume (50–500/year).[17]

We conducted a prospective observational study between November 2015 and January 2018. All participants were hospitalized at the time of enrollment. Subjects fulfilling the entry criteria at the study sites were consecutively invited to participate by the site investigator. Prior to enrollment, study subjects signed an informed consent form based on local IRB requirements. All centers used standardized data collection instruments, which were

developed and finalized before the study was launched. The enrolled subjects were followed for the duration of their hospitalization either until expiration or discharge. The detailed methodology of the APPRENTICE study has been previously described[18] and the study was registered in ClinicalTrials.gov (NCT03075618). See Supporting Information S1 for a detailed outline of study procedures, including the sampling method, data collection, assurance of data quality, and definitions.

Inclusion/exclusion criteria

A patient was eligible for the study when the following inclusion criteria were met: (i) age ≥18 years old, (ii) abdominal pain duration was <7 days, (iii) able to give consent for the study, and (iv) met the predefined diagnostic criteria for AP. The diagnostic criteria were defined in accordance with the published guidelines[19] (See Supporting Information S1 for full definitions).

Exposures

The two main exposures of interest were BMI and etiology. Models were built using BMI as a continuous variable, then stratified analyses were performed with BMI as an ordinal variable using the National Institutes of Health subcategories: underweight: <18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, overweight: 25.0–29.9 kg/m^2, class I obesity: 30.0–34.9 kg/m^2, class II obesity: 35.0–39.9 kg/m^2, and class III obesity: ≥40 kg/m^2. This stratified analysis was performed to evaluate a potentially non-linear association between BMI and risk of MSOF.

Alcohol and smoking history

We collected information via the patient interview on the number of standard drinks/week, years of alcohol consumption, and date of last alcohol consumption. The average number of cigarettes/day and years of smoking were also recorded.

Primary endpoint

MSOF was chosen as the primary endpoint because it precisely captures the most severe stage of systemic complications in AP in contrast to single organ failure[4,20] and is widely accepted as the terminal systemic complication of other acute conditions such as sepsis, COVID-19 and trauma.[4,21] MSOF was defined as organ failure involving more than one of the cardiovascular, respiratory, and renal organ systems, defined according to the Modified Marshall Scoring System[22] (Supporting Information S1 for full justification on the choice of primary endpoint).

Covariates

The following covariates were considered for statistical analysis given their relevance to the outcomes of interest: age, sex, Charlson Comorbidity Index (CCI), congestive heart failure (CHF), chronic kidney disease (CKD), chronic pulmonary disease (CPD), smoking status (current, prior and never), pack-years of tobacco smoking, transfer status, and geographic region of enrollment.

Statistical analyses

Mean and standard deviations were calculated for the age and BMI variables by the MSOF group (yes/no), while the median and interquartile ranges were computed for pack-years of smoking, number of prior AP episodes, and CCI by the MSOF group. Comparisons between group means (medians) were made using independent samples *t*-tests (Mann-Whitney *U* tests). Relative frequencies were computed for each categorial variable by the MSOF group, and chi-squared tests were used to compare groups. Due to collinearity, age was used as a separated covariate and we modified the CCI to exclude age (see Supporting Information S1). Instead of race, geographic region was used, also due to the issue of collinearity (see Supporting Information S1).

Age, sex, BMI, pack years, modified CCI, number of prior AP episodes, geographic region, CHF, CPD, CKD, etiology (dichotomized as alcoholic yes/alcoholic no), and transfer status were entered into a logistic regression model to predict MSOF, and all two-way interactions between the following variables were tested: BMI (continuous), alcohol etiology, age, and sex. Based on the interaction results, stratified analyses were performed by sex. Separate logistic regression models to predict MSOF were fit for males and females using categories of BMI as a predictor along with the significant predictor variables from the unstratified model. After fitting the logistic regression models, the Box-Tidwell test was used to check the assumption of linearity between the continuous variables and the log-odds of MSOF.

Sensitivity analyses

Sensitivity analyses were planned a priori to build separate models for severe AP outcomes and mortality to test the robustness of our findings.

RESULTS

Baseline characteristics

The characteristics of the study participants are listed in Table 1. A total of 1544 subjects were included in the study. A total of 426 subjects (27.6%) were obese. Male sex, current smoker, pack-years of smoking, enrollment from Europe, CKD, and CPD were associated

TABLE 1 Baseline cohort characteristics and clinical outcomes.

	Full AP cohort (n = 1544)		MSOF (n = 86)	No MSOF (n = 1458)	p-value
Patient characteristics					
Age (mean, SD), years	49.63	18.47	52.14 (16.32)	49.49 (18.56)	0.150
BMI (mean, SD), kg/m^2	27.58	6.40	28.30 (5.96)	27.53 (6.42)	0.278
BMI category (n, %)					
<25	599	38.8	30 (34.9)	569 (39.7)	0.254
25–29	494	32.0	27 (31.4)	467 (32.6)	
30–34	254	16.5	21 (24.4)	233 (16.3)	
35+	172	11.1	8 (9.3)	164 (11.4)	
Male sex (n, %)	808	52.33	69 (80.2)	738 (50.6)	<0.001
Race (n, %)					<0.001
Non-Hispanic White	769	49.81	59 (68.6)	710 (48.7)	
Hispanic	314	20.34	3 (3.5)	311 (21.3)	
Asian	377	24.42	24 (27.9)	353 (24.2)	
Other	84	5.44	0 (0.0)	84 (5.8)	
Current smoking (n, %)	352	23.01	31 (36.0)	321 (22.2)	0.003
Pack years (median, IQR)	0.0	0.0–3.5	1.86 (0.0–23.69)	0.0 (0.0–2.55)	<0.001
Modified Charlson score (median, IQR)	1.0	0.0–3.0	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.034
Congestive heart failure (n, %)	47	3.06	4 (4.7)	43 (3.0)	0.376
Chronic pulmonary disease (n, %)	98	6.38	18 (20.9)	80 (5.5)	<0.001
Chronic kidney disease (n, %)					0.016
No	1452	94.0	78 (90.7)	1374 (94.9)	
Mild	47	3.0	7 (8.1)	40 (2.8)	
Moderate to severe	35	2.3	1 (1.2)	34 (2.3)	
Region (n, %)					<0.001
Europe	396	25.65	41 (47.4)	355 (24.3)	
India	361	23.38	24 (27.9)	337 (23.1)	
Latin America	299	19.37	3 (3.5)	296 (20.3)	
United States	488	31.61	18 (20.9)	470 (32.2)	
AP etiology (n, %)					<0.001
Biliary	697	45.14	21 (24.4)	676 (46.4)	
Alcoholic	332	21.50	43 (50.0)	289 (19.8)	
Hypertriglyceridemia-induced	69	4.47	6 (7.0)	63 (4.3)	
Other	446	28.89	16 (18.6)	430 (29.5)	
Sentinel AP (n, %)	1152	74.61	65 (75.6)	1087 (74.6)	0.832
Outcomes					
Death	39	2.5	32 (37.2)	7 (0.5)	<0.001
ICU admission	257	16.6	81 (94.2)	176 (12.1)	<0.001
Pancreatic necrosis	310	20.1	55 (64.0)	255 (17.6)	<0.001

Note: Mann-Whitney U test and independent samples t-test were used as appropriate for the comparison of continuous variables. Categorical variable comparisons were made using the chi-square test.

Abbreviations: AP, acute pancreatitis; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; MSOF, multisystem organ failure; SD, standard deviation.

with MSOF in the bivariate analysis (Table 1). The primary endpoint, MSOF, occurred in 86 subjects (5.6%). A total of 39 subjects died during the hospitalization (mortality rate 2.5%). As expected, subjects who developed MSOF were associated with worse clinical outcomes than those without MSOF (Table 1).

Overall adjusted analysis

The final adjusted model included sex, (continuous) BMI, the interaction between sex and BMI, and the additional covariates (Table S2). Alcoholic etiology conferred an increased risk for developing MSOF (OR 4.17, 95% confidence interval [CI] 2.16–8.05, $p < 0.001$). Among other covariates, CPD (OR 2.69, 95% CI 1.20–6.02, $p = 0.016$), subjects enrolled in Europe (OR 5.64, 95% CI 3.74–22.65, $p < 0.001$ [ref: U.S.]) and transferred subjects (OR 5.30, 95% CI 3.79–17.37, $p < 0.001$) were also associated with MSOF (Figure 1). In addition, the interaction term between BMI and sex was statistically significant ($p = 0.019$). Given this statistically significant interaction between BMI and sex, the odds ratios corresponding to sex and BMI in the final adjusted model are uninterpretable without stratifying the analysis by sex (Table S2). To address the impact of the sex-BMI interaction on the model interpretation, adjusted analyses stratified by sex are presented next.

Sex-stratified analyses

In the stratified analysis (Figure 2), BMI was associated with increased odds of MSOF for males (OR 1.10, 95% CI 1.04–1.15) but not for females (OR 0.98, 95% CI 0.90–1.05). Obesity conferred increased risk of MSOF in males (OR 3.93 for the obese group [ref: underweight/normal weight], 95% CI 1.65–9.37, $p = 0.002$) but not in the female cohort. To determine whether the female sex's protection against BMI's risk of MSOF was age-dependent, we tested for an interaction between age and sex within the female cohort; the result was not statistically significant. Finally, there were no significant interactions between BMI and different regions within either cohort, indicating that the association between BMI and MSOF did not depend on the geographic region of study enrollment for either males or females.

Post-hoc power calculations

The observed power to detect the main effect of alcoholic etiology (OR = 4.17) was 1.00, while the observed power for the main effect of BMI in the male-only model (OR = 3.93) was 0.87. In female subjects, there was 86% power to detect an odds ratio of 1.05 when treating BMI as a continuous variable.

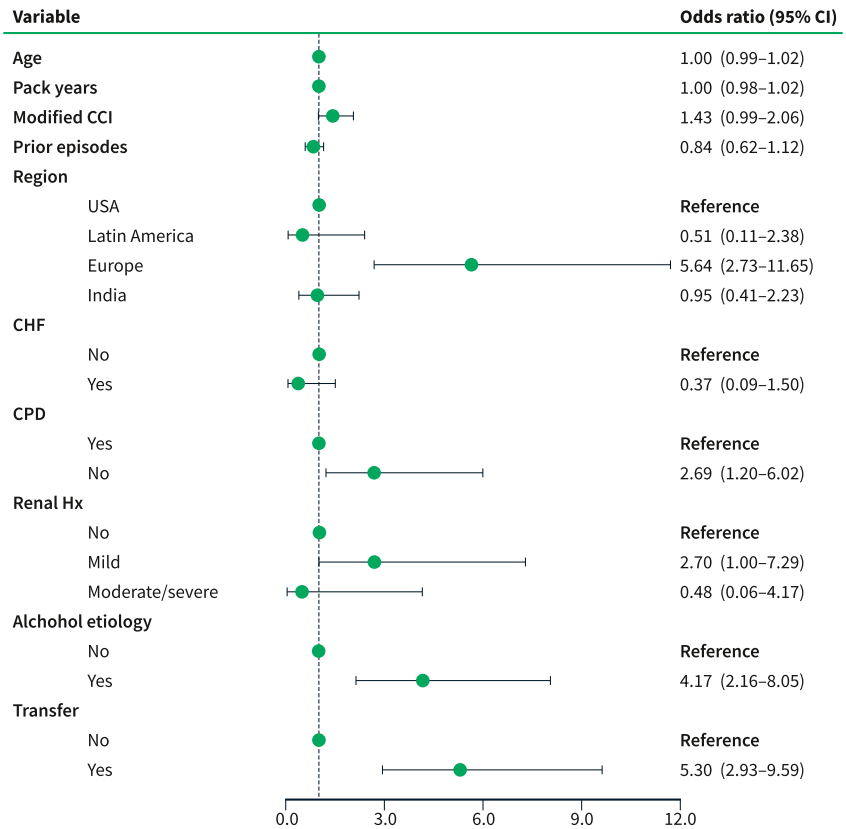

FIGURE 1 Forest plot of odds ratios for selected variables' association with multisystem organ failure in acute pancreatitis. CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CI, confidence interval; CPD, chronic pulmonary disease; Transfer, subjects who were transferred from a secondary care hospital.

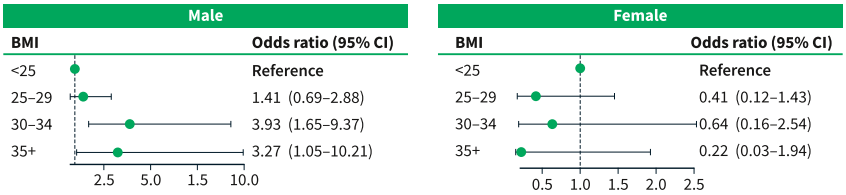

FIGURE 2 Forest plots showing adjusted BMI's association with multisystem organ failure in acute pancreatitis in gender-stratified analyses.

Results of the sensitivity analyses

To test the robustness of our results, we built two separate multivariate logistic regression models for severe AP and death. There was a similar sex-dependent association between BMI and severe AP outcome and between BMI and death. Other variables associated with these outcomes were consistent with the results observed for the MSOF outcome (data not shown).

DISCUSSION

This is the largest prospective observational study in AP that provides a robust sample size to ascertain individual effects of BMI and alcohol etiology on the risk of MSOF with scientific rigor. For the first time, we were able to disentangle BMI's and alcoholic etiology's effects on the systemic complications of AP using MSOF as the primary endpoint with sufficient power, validity, and generalizability. Our findings provide novel insights into the complex association between obesity and MSOF in AP. More specifically, we report for the first time that obesity does not increase the risk of MSOF in all AP subjects, but only in males. Furthermore, we confirmed that the alcoholic etiology represents an independent and significant risk of MSOF in AP. These findings can inform future mechanistic studies to identify pathways unique to alcoholic etiology and obesity that explain their association with MSOF.

Although obesity has emerged as an important prognostic factor in several acute inflammatory illnesses, including sepsis and COVID-19,[5,16] AP literature has shown mixed results on whether obesity increases the risk of MSOF.[8,11] Most studies analyzed BMI as a dichotomized variable, which simplifies the interpretation of results but also increases the vulnerability to potential confounders and bias.[15,23] By analyzing BMI as a continuous variable and multiple categories in our large cohort, we found that the increased risk was confined to male obese subjects. To our knowledge, this effect-modifying impact of sex on MSOF has never been reported in the AP literature. Similar interactions between BMI and sex have, however, been reported in subjects with COVID-19 infection, which shares a similar acute inflammatory phenotype and course as AP.[24,25] Specifically, Tartof et al. found that the increased risk of death among obese COVID-19-positive subjects was seen exclusively among male subjects.[16] In both COVID-19 and AP, mechanistic studies implicate the systemic release of toxic unsaturated free fatty acids from intra- and peripancreatic adipose tissue to be an important driver of systemic organ injury in obese subjects.[26] However, the mechanism by which sex may modify these effects has never been studied. One potential explanation relates to sex hormone-mediated differential adipose tissue distribution among males and females. Centrally located adipose tissue in males (in contrast to peripherally located adipose tissue in females) may provide more substrate for lipolysis and release of toxic unsaturated fatty acids during AP.[6] However, such sex-based differences in fat distribution significantly diminish after menopause.[27] This being the case, one would have expected to still see increased odds of MSOF among obese female AP subjects who are >60 years of age, which was not the case in our stratified analysis. The above findings suggest that the differences in fat distribution alone do not fully explain the effect-modification by the female sex. Some posit that females, owing to the two X-chromosomes, may have important immunologic differences to males that lead to more favorable outcomes in acute inflammatory diseases, but exact mechanisms remain elusive.[28]

Our study also confirmed the importance of alcoholic etiology as a risk factor for MSOF in AP. We postulate that inconsistent results from prior studies may be attributable to smaller sample sizes, heterogeneous study designs, and methodologic challenges.[14,29] Easler et al. showed that the development of organ failure was more common in alcoholic pancreatitis when controlling for BMI, sex, and age in a dual-center cohort of 588 subjects.[14] However, due to the low event-rates of MSOF, its association with alcoholic etiology could not be determined with adequate statistical power. A small sample size has similarly limited statistical power to ascertain a true association in other single-center studies.[30] Selection bias arising from enrolling patients solely from tertiary referral centers is another common methodologic limitation and has undermined the validity of AP prognostic factor studies.[30] As an example, Samanta et al. conducted a single-center study at a tertiary referral center comparing alcoholic versus biliary etiology for severity outcomes and found no differences in the incidence of necrosis, MSOF, and mortality.[29] In their cohort, 97% of alcoholic AP subjects were male, and mild AP accounted for only 10% in the overall cohort suggesting the presence of a strong selection bias. These risks of bias resulting from methodologic limitations and heterogeneity in the study design of prior studies make it difficult to draw meaningful inferences even through meta-analysis of published studies. The validity of our findings is further strengthened by mechanistic studies in severe AP of alcoholic etiology.[31] In animal model pancreata, non-oxidative metabolic products of alcohol mediate acinar cell necrosis via cytosolic calcium dysregulation and

mitochondrial dysfunction, which can lead to cytokine storm and organ dysfunction.[31,32] Extra-pancreatic mechanisms of alcohol resulting in organ failure have also been described, mainly via alveolar epithelial barrier disruption, oxidative stress, macrophage dysfunction and decreased fluid clearance in the pulmonary system.[33,34]

Among the measured covariates, we found that CPD is also a risk factor for MSOF in AP. One previous study investigated the impact of CPD as a risk factor for the development of systemic complications in AP.[35] Szakacs et al. conducted an international multi-center study comprising 1203 patients and found age and CPD to increase the risk of mortality. However, BMI was not recorded, and its effects were not adjusted for.[35] A possible mechanistic hypothesis for the above risk is that patients with CPD are vulnerable towards developing pulmonary failure due to the poor pulmonary reserve. Based on our findings, CPD represents an important variable to consider when determining the AP prognosis. We also found a significant association between subjects enrolled from Europe and the risk of MSOF. There is likely a multifactorial explanation for this association, including differences in patient characteristics, region-specific disease management approaches, and environmental factors (e.g., lifestyle factors).

This study has several noteworthy strengths. The distribution of key characteristics of the cohort in terms of demographics, etiology and outcomes were remarkably similar to the large epidemiologic studies in AP with consecutive patients.[10,36] This is likely because our cohort was sampled from 22 centers of different hospital sizes, types (i.e., secondary and tertiary care) and AP volumes in nine countries.[17] Additionally, our data monitoring method ensured that the ascertainment and misclassification biases in AP diagnosis and MSOF—two most important biases that undermine the rigor of administrative database-derived studies—were minimized, while retaining adequate statistical power attested by our post-hoc power analysis.

Several limitations need to be noted. First, BMI is understandably not a perfect representation of adiposity; however, it is readily available clinically and widely used as a surrogate measure in epidemiological research. Next, there is a risk of under-ascertainment of an alcoholic AP etiology as this is contingent on self-reporting. We were unable to keep an exhaustive list of all subjects who were screened for eligibility. AP subjects enter the hospital systems via transfer, emergency department, and direct admissions and are managed by many different service providers. Due to resource constraints, especially in community-hospital size centers, and given the acuity of the disease, this was practically impossible. This practical limitation is conceded even by large government-funded studies in AP (NCT05197920). Additionally, any differences in AP management between countries and individual sites were not quantified and adjusted for. Nevertheless, we believe that management variations were best adjusted by categorizing centers into different regions. Lastly, the purpose of our analysis was to analyze associations while controlling for relevant clinical variables, and as such, the final adjusted model explained only 28% of the variability in the MSOF outcome (Table S2). This is not surprising due to the exclusive use of clinical variables; however, future studies are needed to further examine the role of body composition and free fatty acid metabolism and explore differences in genomics, proteomics, and transcriptomics. Hidden confounders not measured during the study could have also influenced the results. For example, genetic susceptibilities to organ dysfunction and dietary differences were not captured but could have influenced the results as sources of confusion. Taken together, the exclusive use of clinical variables was a limitation in the study.

In conclusion, we found that obesity is a risk factor for the development of MSOF exclusively in men, but not women, with AP. Alcoholic etiology and CPD also increase the risk of developing MSOF. Our results will inform mechanistic studies to characterize how sex modulates the effect of obesity on the risk of MSOF in AP and to identify potential therapeutic targets within obesity and alcohol-mediated pathways.

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CONFLICT OF INTEREST STATEMENT

All authors of this article declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

AVAILABILITY OF DATA, ANALYTICAL METHODS, AND STUDY MATERIALS

As above.

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