

METABOLIC RISK FACTORS AS DETERMINANTS OF OUTCOME IN ACUTE PANCREATITIS

Ph.D. Thesis

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***“Things may come to those who wait, but only
the things left by those who hustle.”***

Abraham Lincoln

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1. LIST OF ABBREVIATIONS

AP Acute Pancreatitis

APA American Pancreatic Association

APACHE II Acute Physiology and Chronic Health Evaluation II

BISAP Bedside Index for Severity in Acute Pancreatitis

BMI Body-Mass Index

BUN Blood Urea Nitrogen

CCI Charlson Comorbidity Index

CI Confidence Interval

COVID-19 Coronavirus Disease 2019

CRP C-Reactive Protein

CT Computed Tomography

DM Diabetes Mellitus

HDL High-Density Lipoprotein

HR Hazard Ratio

HTG Hypertriglyceridemia

HTN Hypertension

IAP International Association of Pancreatology

ICU Intensive Care Unit

IL-6 Interleukin-6

I² Higgins' Heterogeneity Statistic

LDL Low-Density Lipoprotein

MAP Mild Acute Pancreatitis

MD Mean Difference

MS Metabolic Syndrome

MSAP Moderately Severe Acute Pancreatitis

NOS Newcastle–Ottawa Scale

OR Odds Ratio

PICO Population, Intervention/Exposure, Comparison, Outcome

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO International Prospective Register of Systematic Reviews

QUIPS Quality in Prognostic Studies

RCT Randomized Controlled Trial

RR Relative Risk

SAP Severe Acute Pancreatitis

SD Standard Deviation

SE Standard Error

TNF- α Tumor Necrosis Factor Alpha

VAT Visceral Adipose Tissue

WHO World Health Organization

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve the prevention, risk stratification, and personalized management of patients with acute pancreatitis (AP) through high-quality translational research. By bridging evidence synthesis, clinical epidemiology, and patient-centered research, I aim to contribute to a better understanding of the factors that influence disease development, progression, and outcomes.



My mission is to investigate the role of metabolic and lifestyle-related factors in AP and to translate these findings into clinically applicable strategies that support early identification of high-risk patients and targeted preventive interventions. Particular emphasis is placed on obesity, metabolic syndrome (MS), and other modifiable risk factors that may influence both the occurrence and severity of AP.

My specific goals are to evaluate the prognostic significance of obesity and MS components in AP, to identify modifiable risk factors associated with disease development and adverse outcomes, and to support the development of metabolically informed risk stratification approaches. Furthermore, I aim to explore the broader impact of metabolic health on acute inflammatory diseases and to contribute to the development of personalized prevention and management strategies through international collaborative research.

2.2. Scientometrics

Number of all publications:	11
Cumulative IF:	47.183
Av IF/publication:	4.29
Ranking (SCImago):	D1:1, Q1:7, Q2:3,
Number of publications related to the subject of the thesis:	2
Cumulative IF:	9.365
Av IF/publication:	4.68
Ranking (Sci Mago):	Q1:2
Number of citations on Google Scholar:	683
Number of citations on MTMT (independent):	237
H-index:	8

The detailed bibliography of the student can be found on pages 49-51.

2.3. Future plans

My future plans focus on further developing my expertise in pancreatology, translational medicine, and clinical research. I intend to continue participating in international multicenter collaborations and contribute to studies investigating the role of metabolic and lifestyle-related factors in AP and other inflammatory diseases.

Building on the findings presented in this thesis, I would like to further explore how metabolic abnormalities influence disease development, progression, and outcomes, with the ultimate goal of improving patient care through evidence-based approaches.

A particular professional goal is to gain further experience in the design, conduct, and coordination of clinical trials. I am interested in developing expertise in clinical trial methodology, study management, regulatory aspects of clinical research, while contributing to high-quality investigator-initiated and international clinical studies.

In parallel, I plan to continue supporting the education of medical students and junior researchers, while further developing my skills in clinical research methodology, evidence synthesis, and biostatistics. I am also committed to promoting the broader dissemination and understanding of clinical research methodologies among participants of medical and related PhD training programs, thereby strengthening methodological competence in the next generation of clinician-scientists and researchers. Through these activities, I hope to contribute to the generation of clinically relevant evidence and to the advancement of patient-centered research.

3. SUMMARY OF THE THESIS

AP is a common gastrointestinal disease with a highly variable clinical course, ranging from mild inflammation to severe disease associated with organ failure and death. Despite advances in patient management, early risk stratification remains challenging. At the same time, obesity, MS, and related metabolic disorders have become increasingly prevalent worldwide. The aim of this thesis was to evaluate the impact of obesity and metabolic abnormalities on AP outcomes and their potential role in risk stratification.

This thesis summarizes two systematic reviews and meta-analyses. The first study investigated the association between body-mass index (BMI) and AP outcomes. A meta-analysis of 19 studies involving 9,997 individuals demonstrated that increasing BMI was associated with a higher risk of severe AP, while obesity was associated with increased mortality. Underweight was also identified as a risk factor for death. These findings established BMI as an important prognostic factor in AP.

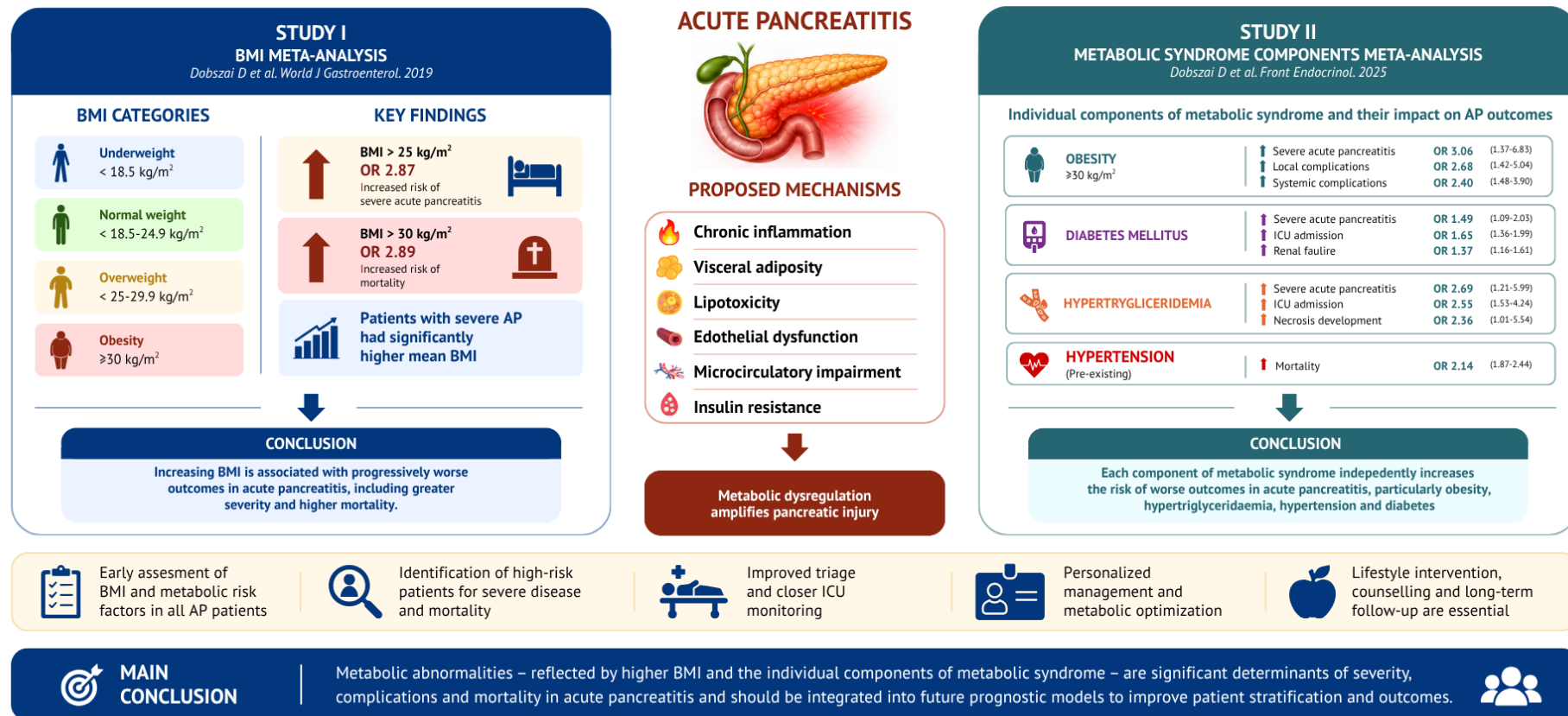
The second study expanded the investigation beyond obesity and evaluated the prognostic significance of other MS components. A systematic review and meta-analysis of 89 studies involving approximately 4.5 million participants demonstrated that obesity, diabetes, hypertension, and hypertriglyceridemia were all associated with adverse outcomes. Hypertriglyceridemia emerged as one of the strongest predictors of severe AP and pancreatic necrosis, diabetes was associated with disease severity and organ dysfunction, and hypertension was associated with mortality. Although MS itself was not significantly associated with severity or mortality, its individual components consistently demonstrated prognostic significance.

Overall, the findings indicate that the prognostic impact of metabolic health in AP extends beyond obesity alone. Metabolic abnormalities represent important determinants of adverse outcomes and should be considered in future risk prediction models. Further research should focus on prospective validation and the development of personalized preventive and therapeutic strategies targeting metabolic risk factors.

4. GRAPHICAL ABSTRACT

METABOLIC RISK FACTORS AS DETERMINANTS OF SEVERITY AND OUTCOME IN ACUTE PANCREATITIS

Evidence from two systematic reviews and meta-analyses



AP: Acute pancreatitis; BMI: Body-mass index; OR: Odds ratio; CI: Confidence interval; ICU: Intensive care unit; MS: Metabolic syndrome

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

AP is an acute inflammatory disease of the pancreas with a highly variable clinical course. According to the revised Atlanta classification, the disease is categorized as mild, moderately severe, or severe based on the presence of local or systemic complications and organ failure, with severe AP being associated with persistent organ failure and substantial mortality (1, 2). The global incidence of AP has continuously increased over recent decades, making it one of the most common gastrointestinal causes of hospitalization worldwide. Although advances in supportive care and intensive care medicine have improved patient management, severe AP still carries considerable morbidity and mortality (3).

In parallel with the increasing incidence of AP, obesity and metabolic disorders have also become major global health concerns. The prevalence of obesity has increased dramatically since the 1970s, and MS currently affects approximately one-quarter of the adult population in Western countries (4).

MS is characterized by the coexistence of abdominal obesity, hypertension, impaired glucose metabolism, and dyslipidemia (5). These conditions are associated with chronic low-grade inflammation, endothelial dysfunction, insulin resistance, and altered immune responses, all of which may influence the course of acute inflammatory diseases (6).

This thesis focuses on the relationship between metabolic abnormalities and AP, with particular emphasis on the prognostic role of obesity and MS components in determining disease severity and clinical outcomes.

5.1.2. What is the problem to solve?

Despite significant advances in the understanding and management of AP, early risk stratification remains insufficient in clinical practice. Current prognostic scoring systems, including APACHE II, BISAP, Ranson, and Glasgow-Imrie scores, have several

limitations, including complexity, delayed applicability, and limited predictive performance (7, 8). Importantly, most currently used prognostic systems do not adequately incorporate metabolic parameters despite the rapidly increasing prevalence of obesity and metabolic diseases among patients with AP (9).

Previous studies investigating the role of obesity, diabetes mellitus (DM), hypertension, and hypertriglyceridemia in AP reported inconsistent and sometimes contradictory findings (10-14). Furthermore, although individual metabolic factors were previously investigated separately, no comprehensive synthesis was available regarding their individual and combined effects on AP outcomes.

Another important limitation of the existing literature is the lack of standardized definitions and harmonized reporting of metabolic parameters. Different studies used varying BMI cut-offs, MS definitions, and outcome measures, making direct comparison difficult. Therefore, there is a critical need for high-quality evidence synthesis evaluating the role of metabolic risk factors in AP and clarifying their prognostic importance.

Collectively, these knowledge gaps suggest that metabolic dysfunction may represent a previously underappreciated determinant of AP outcomes. Therefore, this thesis was designed to evaluate the prognostic significance of obesity and other metabolic abnormalities in a stepwise manner, beginning with BMI and subsequently expanding the investigation to the broader spectrum of MS components.

5.1.3. What is the importance of the topic?

The importance of investigating metabolic risk factors in AP is supported by both epidemiological and clinical considerations.

Obesity and MS have become major public health concerns worldwide. These conditions not only increase the burden of chronic cardiovascular and metabolic diseases but may also worsen the outcome of acute inflammatory disorders (6).

Several pathophysiological mechanisms may explain the connection between metabolic dysregulation and AP severity. Visceral adiposity contributes to chronic low-grade

inflammation and increased production of pro-inflammatory cytokines, while pancreatic fat accumulation may promote lipotoxicity and necrosis formation during AP (15).

Hypertriglyceridemia may directly induce pancreatic injury through the release of free fatty acids (16-18), whereas diabetes and hypertension contribute to endothelial dysfunction, microcirculatory impairment, oxidative stress, and immune dysregulation (19, 20).

Understanding the impact of these metabolic abnormalities on AP outcome is clinically important because metabolic parameters are readily available during the early phase of hospitalization. Identifying high-risk patients earlier may improve monitoring strategies, ICU triage, preventive interventions, and long-term patient management.

5.1.4. What would be the impact of our research results?

The studies included in this thesis provide a comprehensive evaluation of the prognostic role of obesity and other metabolic abnormalities in AP. By quantitatively synthesizing the available evidence, the findings help clarify the magnitude of risk associated with individual metabolic factors and identify those most strongly linked to adverse outcomes. Furthermore, this work follows the principles of translational medicine by transforming epidemiological and clinical evidence into knowledge that may be directly applicable to patient care and outcome prediction (21, 22).

The results may contribute to the development of more accurate and clinically relevant risk stratification approaches that incorporate metabolic parameters alongside established clinical predictors. Such metabolically informed models could improve the early identification of high-risk patients, facilitate clinical decision-making, guide ICU admission and monitoring strategies, and support more personalized management of AP.

Beyond their immediate clinical implications, the findings highlight the broader importance of metabolic health in AP and emphasize that the prognostic impact of metabolic dysfunction extends beyond obesity alone. By identifying potentially modifiable risk factors associated with adverse outcomes, this work also strengthens the rationale for preventive and therapeutic interventions targeting obesity, diabetes,

hypertriglyceridemia, and other metabolic abnormalities. Ultimately, these findings may contribute to improved patient outcomes and support the integration of metabolic health into future clinical practice and research in AP.

5.2. Evidence gaps and rationale for the thesis

Despite the growing body of literature examining metabolic abnormalities in AP, important evidence gaps remained prior to the present work. Most studies investigated individual risk factors separately, and the available findings were often inconsistent because of differences in study populations, definitions, and outcome measures. In addition, previous evidence syntheses primarily focused on obesity and did not comprehensively evaluate the independent prognostic impact of other MS components, including diabetes, hypertension, and hypertriglyceridemia (23-25).

Therefore, the overarching aim of this thesis was to systematically evaluate the prognostic significance of metabolic abnormalities in AP through a stepwise approach. Beginning with BMI and subsequently expanding to the broader spectrum of MS components, the thesis seeks to provide a comprehensive evidence base for metabolically informed risk stratification in AP.

6. OBJECTIVES

6.1. Study I. – Body-mass index correlates with severity and mortality in acute pancreatitis: a meta-analysis

The primary objective of the first study was to evaluate the association between BMI and clinically relevant outcomes in AP. Specifically, the study aimed to investigate the relationship between BMI and disease severity, assess the impact of obesity on mortality, and explore the prognostic significance of different BMI categories. Furthermore, the study sought to identify clinically relevant BMI cut-off values associated with poor outcomes and summarize the available evidence regarding the prognostic role of obesity in AP.

6.2. Study II. – Metabolic syndrome components individually worsen the outcome of acute pancreatitis: a systematic review and meta-analysis

Building upon the findings of the first study, the second study aimed to provide a broader evaluation of the role of metabolic abnormalities in AP by investigating the association between the individual components of MS, including obesity, DM, hypertension, and hypertriglyceridemia, and clinically relevant outcomes. The study sought to assess how these metabolic factors influence disease severity, complications, intensive care unit (ICU) admission, and mortality, while also identifying the factors most strongly associated with adverse outcomes in patients with AP.

7. METHODS

7.1. Study I. - Body-mass index correlates with severity and mortality in acute pancreatitis: a meta-analysis

7.1.1. Methodology and Protocol

The first study was a systematic review and meta-analysis evaluating the association between BMI and clinically relevant outcomes in AP. The study was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (26). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42017077890).

The review focused on the prognostic value of BMI in AP, with particular emphasis on disease severity and mortality. In addition, data on local and systemic complications, length of hospitalization, and ICU stay were collected when available.

7.1.2. Eligibility Criteria

Eligibility criteria were defined according to the PICO (Population, Intervention, Comparison, Outcome) framework. The study population consisted of patients diagnosed with AP, while the intervention and comparison groups were based on different BMI categories. The primary outcomes of interest were disease severity and mortality.

Observational studies reporting original data on BMI and AP outcomes were considered eligible. Studies were included if they enrolled unselected patients with AP regardless of etiology and provided sufficient data for quantitative synthesis. For analyses of disease severity, only studies using either the original or the revised Atlanta Classification (1) were included. Meta-analyses, reviews, case reports, conference abstracts, and studies with insufficient data were excluded.

7.1.3. Information Sources and Search Strategy

A comprehensive literature search was performed in PubMed, EMBASE, and the Cochrane Library from database inception until December 22, 2017. The search strategy combined terms related to AP, BMI, severity, and mortality. Reference lists of relevant

articles were also screened to identify additional eligible studies. All records were imported into EndNote software, and duplicates were removed prior to screening.

7.1.4. Study Selection and Data Extraction

Study selection was performed independently by two reviewers. Titles, abstracts, and subsequently full texts were screened against the predefined eligibility criteria. Disagreements were resolved through discussion and consensus among the investigators.

Data extraction was conducted using a standardized data collection form. Information extracted from eligible studies included publication characteristics, study design, country of origin, sample size, BMI categories, definitions of disease severity, mean BMI values, numbers of severe cases and deaths, as well as additional clinical outcomes such as hospitalization duration, ICU stay, severity scores, and pancreatic necrosis when available.

7.1.5. Risk of Bias and Quality of Evidence Assessment

The methodological quality of the included studies was assessed using a modified version of the Newcastle–Ottawa Scale (NOS). This tool evaluates study quality across several domains, including participant selection, comparability of study groups, and outcome assessment. Publication bias was examined visually using funnel plots and further assessed through the trim-and-fill method.

7.1.6. Data Synthesis and Analysis

Statistical analyses were performed using Stata SE 11. Continuous outcomes were summarized as mean differences (MDs), whereas dichotomous outcomes were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Pooled effect estimates were calculated using random-effects models with the DerSimonian–Laird estimator to account for expected between-study heterogeneity.

Several complementary analyses were conducted to evaluate the prognostic significance of BMI. Mean BMI values were compared between severe and non-severe AP cases, while subgroup analyses assessed the associations between different BMI categories and

the risk of severe disease or mortality. Additional analyses explored clinically relevant BMI cut-off values, including thresholds of 25 kg/m² and 30 kg/m². Statistical heterogeneity was evaluated using the I² statistic and Cochran's Q test, with a p-value below 0.05 considered statistically significant.

7.2. Study II. - Metabolic syndrome components individually worsen the outcome of acute pancreatitis: a systematic review and meta-analysis

7.2.1. Methodology and Protocol

Following the findings of the BMI meta-analysis, a systematic review and meta-analysis was conducted to investigate the association between MS and its individual components and clinically relevant outcomes in AP. The review was designed and reported in accordance with the PRISMA 2020 statement and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. The study protocol was prospectively registered in PROSPERO (registration number CRD42023471092).

The review focused on the prognostic significance of obesity, DM, hypertension, hypertriglyceridemia, and MS in AP. Clinically relevant outcomes included disease severity, local and systemic complications, ICU admission, pancreatic necrosis, organ failure, and mortality.

7.2.2. Eligibility Criteria

Eligibility criteria were established according to the PICO framework. The study population consisted of adult patients diagnosed with AP. The exposures of interest were MS and its individual components (obesity, DM, hypertension, and hypertriglyceridemia). The primary outcomes included disease severity, mortality, ICU admission, local complications, systemic complications, pancreatic necrosis, and organ failure.

Observational studies reporting original data on the association between metabolic abnormalities and AP outcomes were considered eligible. Cohort studies, case-control studies, and cross-sectional studies were included if sufficient data were available for

quantitative synthesis. Reviews, meta-analyses, case reports, conference abstracts, editorials, and studies lacking relevant outcome data were excluded.

7.2.3. Information Sources and Search Strategy

A comprehensive literature search was performed in PubMed, Embase, and the Cochrane Library from database inception until November 1, 2023. Search terms related to AP, MS, obesity, DM, hypertension, hypertriglyceridemia, disease severity, complications, and mortality were combined using Boolean operators.

The search strategy was developed collaboratively by the investigators and adapted to the requirements of each database. To maximize study identification, reference lists of eligible studies and relevant reviews were also manually screened. All retrieved records were imported into EndNote software and duplicates were removed prior to screening.

7.2.4. Study Selection and Data Extraction

Study selection was conducted independently by two reviewers. Following duplicate removal, titles and abstracts were screened for eligibility. Potentially relevant articles underwent full-text assessment according to the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion and consensus with the involvement of a third reviewer when necessary.

Data extraction was performed using a standardized data collection form. Extracted information included study characteristics, publication year, country, study design, sample size, patient demographics, definitions of MS components, outcome definitions, and outcome data. When available, crude event numbers, ORs, CIs, and adjusted effect estimates were collected for quantitative analysis.

7.2.5. Risk of Bias and Quality of Evidence Assessment

The methodological quality of the included studies was assessed using the Quality in Prognostic Studies (QUIPS) tool (27). This instrument evaluates six domains of potential bias, including study participation, study attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting.

Risk of bias assessment was performed independently by two reviewers. Discrepancies were resolved through discussion and consensus. The overall methodological quality of the included studies was considered during the interpretation of the findings and the assessment of the robustness of the pooled estimates.

Potential publication bias was evaluated through visual inspection of funnel plots when an adequate number of studies were available for meta-analysis.

7.2.6. Data Synthesis and Analysis

Quantitative synthesis was performed using random-effects meta-analysis models to account for expected clinical and methodological heterogeneity among studies. ORs with 95% CIs were used as summary effect measures for dichotomous outcomes.

Separate meta-analyses were conducted for obesity, DM, hypertension, hypertriglyceridemia, and MS whenever sufficient data were available. Heterogeneity was assessed using Cochran's Q test and Higgins' I^2 statistic. Leave-one-out sensitivity analyses were performed to evaluate the robustness of pooled estimates and identify influential studies.

All statistical analyses were conducted using R software with the *meta* and *dmetar* packages. Statistical significance was established at a two-sided p-value of less than 0.05.

8. RESULTS

8.1. Study I: Body-mass index correlates with severity and mortality in acute pancreatitis: a meta-analysis

8.1.1. Study Search and Selection

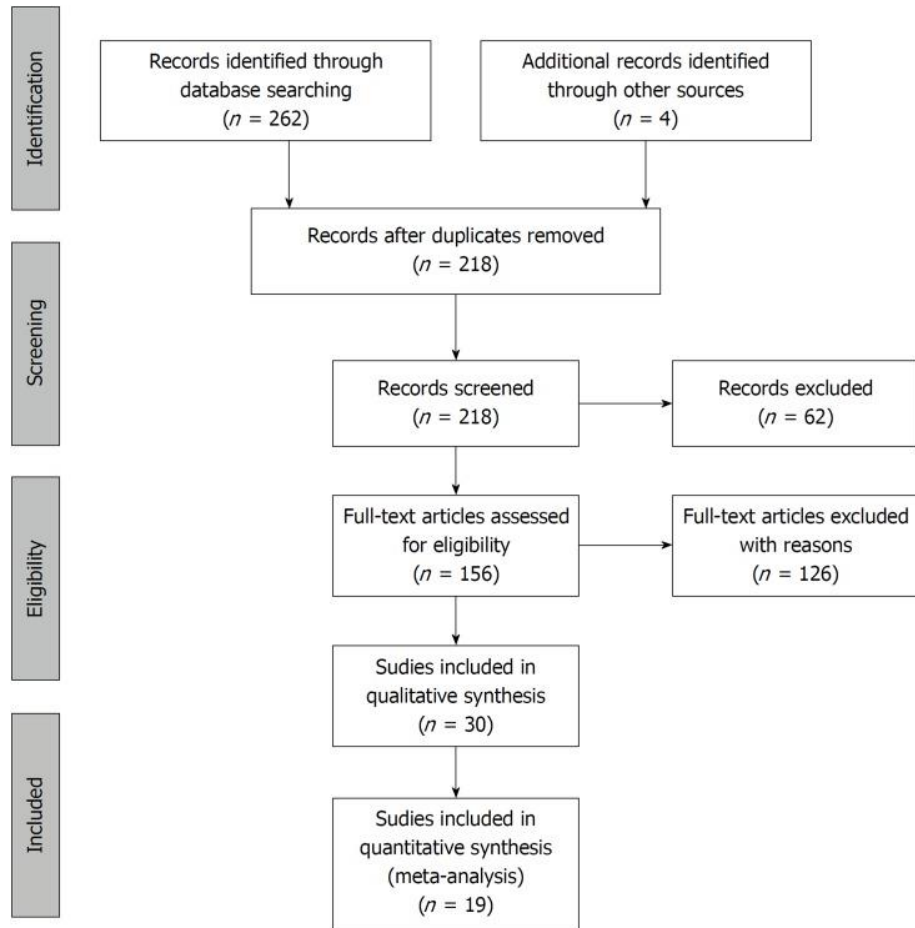


Figure 1. PRISMA flowchart representing the study selection process. (28)

Table 1. Characteristics of studies included in Study I

Study	Country	Design	N	Comparison groups
Bota et al.(29)	Romania	Retrospective	334	Mild vs. Severe AP
Duarte-Rojo et al.(30)	Mexico	Prospective	99	Mild vs. Severe AP
Funnel et al.(31)	South Africa	Prospective	99	<19, 19–25, 26–29, ≥30 kg/m ²
Karpavicius et al.(32)	Lithuania	Prospective	102	Mild/moderate vs Severe AP.
Katuchova et al. (33)	Slovakia	Prospective	384	IEP vs. SAP
Mery et al.(34)	Mexico	Prospective	88	<25, 25–29.9, ≥30 kg/m ²
Papachristou et al.(7)	United States	Prospective	102	<30 vs ≥30 kg/m ²
Párniczky et al.(2)	Hungary	Prospective, multicenter	446	WHO BMI categories
Sharma et al. (35)	United States	Prospective	128	<30 vs ≥30 kg/m ²
Shin et al. (36)	South Korea	Retrospective	374	18.5–22.9, 23–24.9, 25–29.9, ≥30 kg/m ²
Suazo-Barahona et al. (37)	Mexico	Retrospective	150	<25 vs ≥25 kg/m ²
Taguchi et al. (38)	Japan	Retrospective	6002	WHO BMI categories
Thandassery et al. (39)	India	Prospective	280	18.5–22.9, 23–24.9, >25 kg/m ²
Tsai et al. (40)	Taiwan	Prospective	320	<30 vs. ≥30 kg/m ²
Türkoglu et al. (41)	Turkey	Prospective cohort	92	Mild vs. Severe AP
Yang et al. (42)	China	Prospective, multicenter	161	<25 vs. ≥25 kg/m ²
Yashima et al. (43)	Japan	Prospective	124	Mild vs. Severe AP
Yeung et al. (44)	China	Prospective	101	<25 vs. ≥25 kg/m ²
Yoon et al. (45)	South Korea	Retrospective	203	Mild, Moderate, Severe AP

BMI: Body-mass index; WHO: World Health Organization; IEP: Interstitial edematous pancreatitis; SAP: Severe acute pancreatitis

8.1.2. Primary Outcomes

The primary outcomes of the meta-analysis were disease severity and mortality in relation to BMI. A total of 19 studies involving 9,997 participants were included in the quantitative synthesis. Basic characteristics of the included studies are presented in **Table 1**. Nine studies provided data on mean BMI values according to disease severity. Patients who developed severe AP had significantly higher BMI values than those with non-severe disease (MD = 1.79, 95% CI 0.89–2.70, $p < 0.001$) (**Figure 2**).

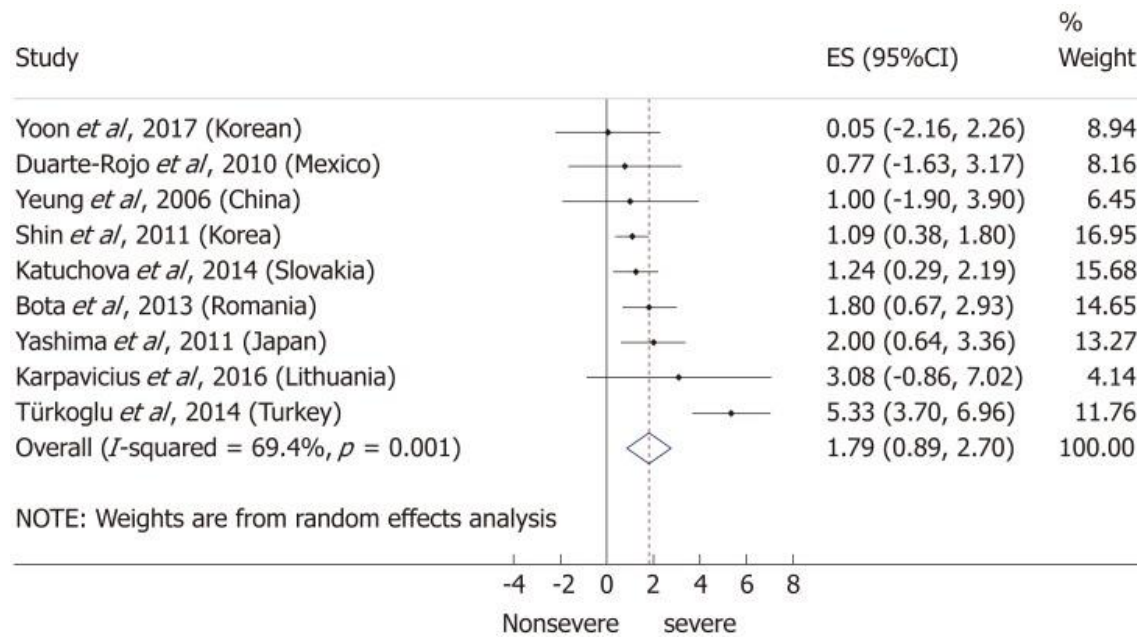


Figure 2. Forest plot of mean BMI in the non-severe and severe patient subgroups. (28)
BMI: Body-Mass Index, CI: Confidence interval.

The risk of severe AP increased progressively with increasing BMI. Patients with a BMI >25 kg/m² had almost threefold higher odds of severe disease compared with individuals with a BMI <25 kg/m² (OR = 2.87, 95% CI 1.90–4.35, $p < 0.001$) (**Figure 3**). Furthermore, those with obesity (BMI >30 kg/m²) had more than threefold higher odds of severe AP compared with patients without obesity (OR = 3.61, 95% CI 1.56–8.36, p = 0.003).

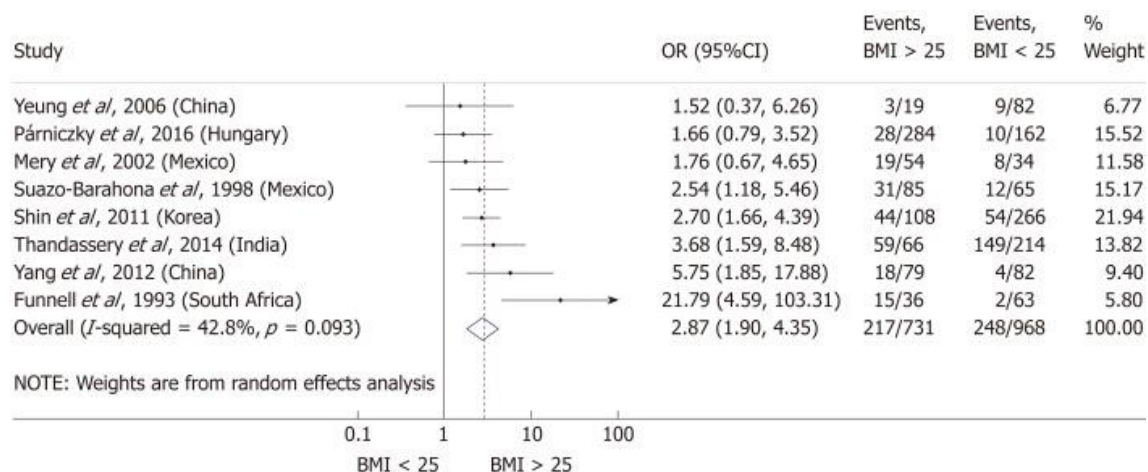


Figure 3. Forest plot of severe AP in the BMI < 25 and BMI > 25 subgroups. (28) BMI: Body-mass index; CI: Confidence interval; OR: Odds ratio.

Analysis according to World Health Organization (WHO) BMI categories demonstrated that those in the overweight category (BMI 25–30 kg/m²) had significantly increased odds of severe disease compared with those in the normal BMI category (OR = 2.53, 95% CI 1.64–3.90, *p* < 0.001). Similarly, individuals with obesity (BMI 30–35 kg/m²) had a significantly increased risk of severe AP (OR = 2.99, 95% CI 1.13–7.92, *p* = 0.028). Although patients with underweight (BMI < 18.5 kg/m²) also showed a tendency toward increased disease severity, the association did not reach statistical significance (OR = 1.89, 95% CI 0.52–6.87, *p* = 0.336).

Mortality analyses included ten studies. While individuals with a BMI > 25 kg/m² did not have significantly higher mortality (OR = 2.46, 95% CI 0.78–7.79, *p* = 0.125), patients with obesity had nearly threefold higher odds of death compared with individuals without obesity (OR = 2.89, 95% CI 1.14–7.36, *p* = 0.026) (**Figure 4**). In addition, those with underweight had significantly increased mortality compared with patients in the normal BMI category (OR = 1.82, 95% CI 1.32–2.50, *p* < 0.001).

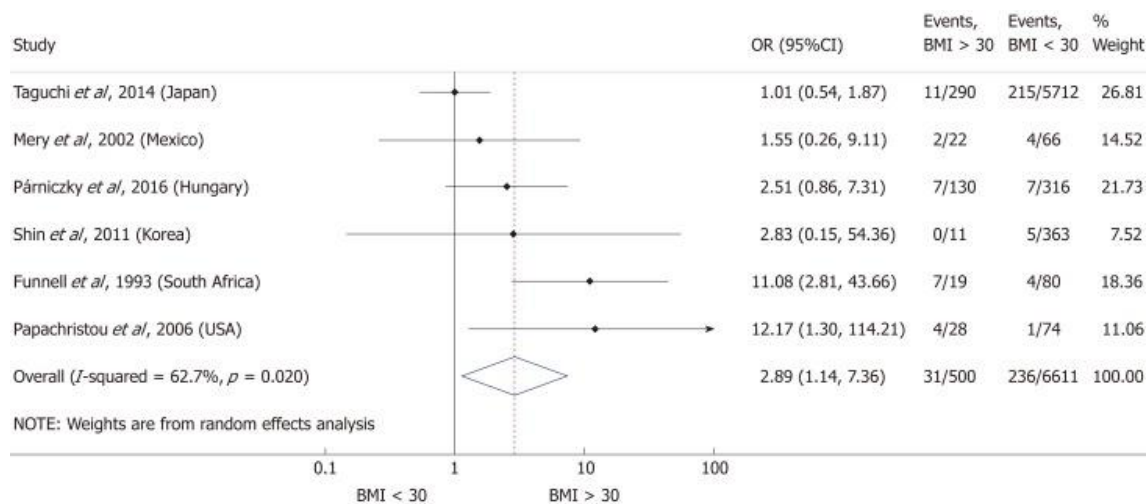


Figure 4. Forest plot of mortality comparing the BMI < 30 and BMI > 30 subgroups. (28)
BMI: Body-mass index; CI: Confidence interval; OR: Odds ratio.

Overall, the findings demonstrated a progressive association between BMI and poor outcomes in AP (**Figure 5**). Higher BMI was associated with an increased risk of severe disease, while both obesity and underweight were associated with increased mortality.

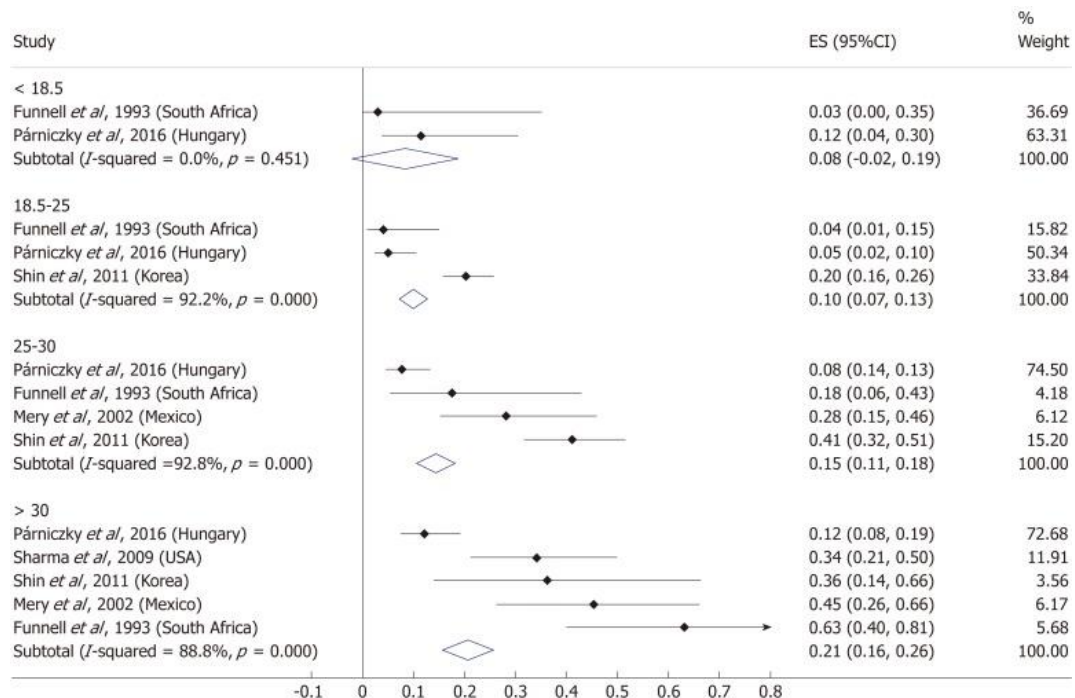


Figure 5. Subgroup analysis of BMI and AP severity displayed on forest plot. (28)
CI: Confidence interval.

8.1.3. Risk of Bias Assessment

Overall, the majority of studies were judged to be of moderate to high methodological quality. Most studies adequately defined the study population and outcome measures; however, variability was observed in patient selection, BMI categorization, and adjustment for potential confounding factors.

Potential sources of bias included the predominantly observational study designs, differences in severity classification systems, and heterogeneity in the reporting of clinical outcomes. Despite these limitations, the overall risk of bias was considered acceptable, supporting the reliability of the pooled estimates.

8.2. Study II: Metabolic syndrome components individually worsen the outcome of acute pancreatitis: a systematic review and meta-analysis

8.2.1. Study Search and Selection

The systematic literature search identified 19,766 records across the selected databases. Following automatic and manual duplicate removal, 15,904 records underwent title and abstract screening. A total of 392 full-text articles were assessed for eligibility according to the predefined inclusion and exclusion criteria. Ultimately, 106 studies were included in the qualitative synthesis, of which 89 studies provided sufficient data for quantitative meta-analysis. The study selection process is summarized in the PRISMA flowchart presented in **Figure 6**.

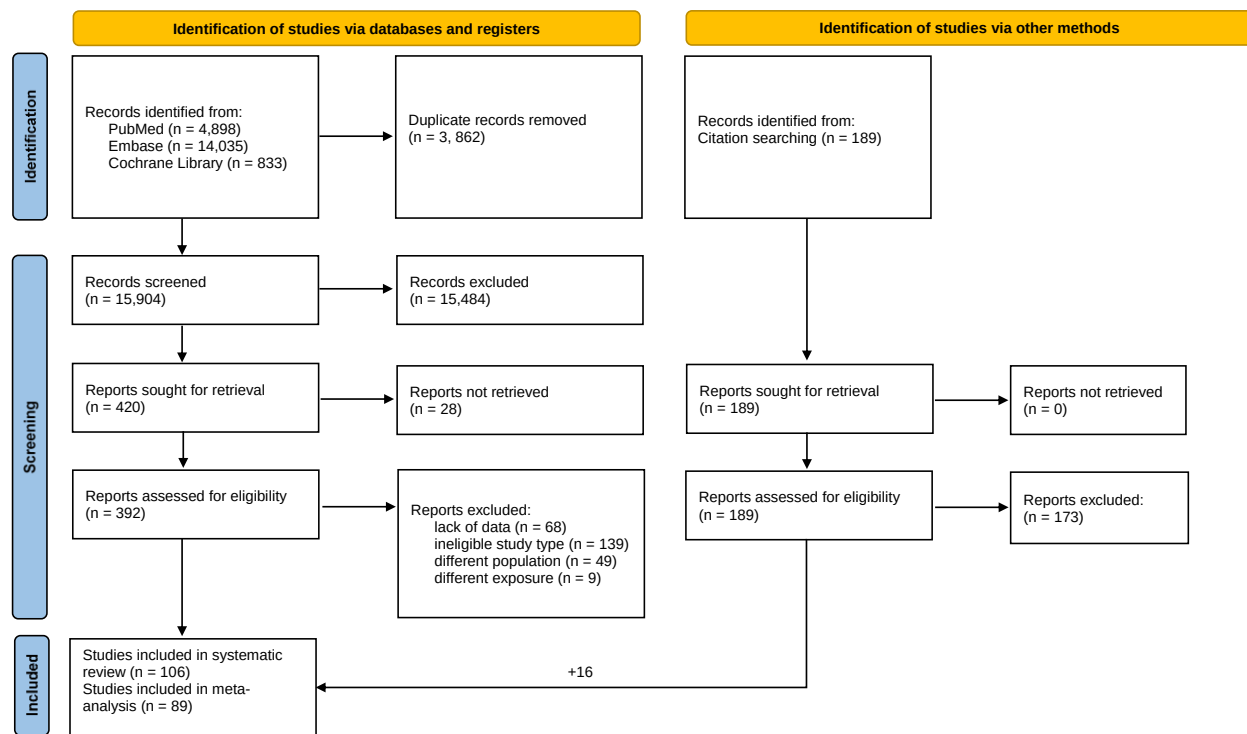


Figure 6. PRISMA flowchart of the selection process. (46, 47)

8.2.2. Study characteristics

A total of 89 studies published between 1993 and 2023 were included in the meta-analysis. The studies originated from Europe, Asia, North America, and the Middle East and comprised approximately 4.5 million patients. Most studies were retrospective or prospective cohort studies. Sample sizes ranged from 38 to more than 1.3 million patients, with mean ages generally between 40 and 65 years (**Table 2**).

Table 2. Summary characteristics of studies included in Study II

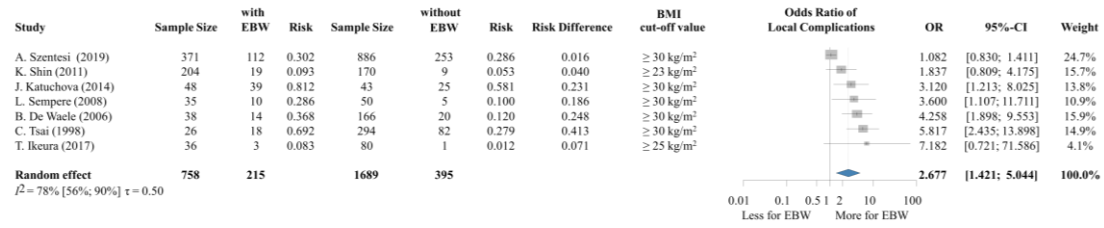
Characteristic	Value
Number of included studies	89
Total number of patients	approximately 4.5 million*
Publication years	1993–2023
Countries represented	25+
Study design	Predominantly retrospective and prospective cohort studies
Main prognostic factors investigated	Obesity, hypertriglyceridemia, diabetes mellitus, hypertension, metabolic syndrome
Most frequently assessed factor	Obesity
Geographic distribution	Europe, Asia, North America, Middle East
Sample size range	38–1,330,302 patients
Mean/median age range	Approximately 35–75 years
Female proportion	Approximately 20–76%

8.2.3. Primary Outcomes

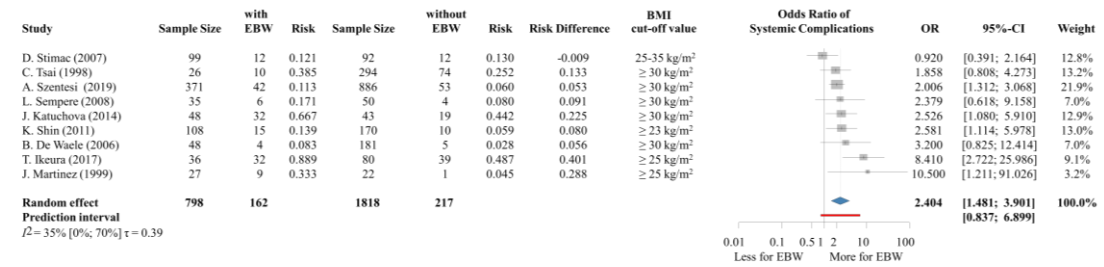
The primary outcomes of interest were disease severity and mortality. Excess body weight (overweight and obesity) was associated with significantly worse clinical outcomes in AP. Seven studies (11, 33, 36, 40, 48-50), including 1,814 patients, reported data on the association between EBW and the development of local complications, while nine studies (11, 33, 36, 40, 48-52) with a sample size of 2,616 reported on systemic complications. Patients with excess body weight had a higher risk of developing both local complications (OR=2.677, 95% CI 1.421–5.044) (**Figure 7A**) and systemic complications (OR=2.404, 95% CI 1.481–3.901) (**Figure 7B**). Among systemic complications, renal failure (OR=4.757, 95% CI 2.073–10.915) and respiratory failure (OR=1.769, 95% CI 1.562–2.003) occurred significantly more frequently in patients with excess body weight.

To further evaluate the impact of obesity on disease severity, a subgroup analysis was performed including studies that defined obesity according to the WHO criterion of BMI ≥ 30 kg/m². This analysis included 16 studies (7, 11, 31, 33, 34, 36, 40, 48, 49, 52-57) with a total of 4,449 patients. Obesity emerged as one of the strongest predictors of severe AP, with patients with obesity having more than a threefold increased risk of developing severe disease compared with non-obese patients (OR=3.058, 95% CI 1.369–6.829) (**Figure 7C**). Furthermore, excess body weight was significantly associated with an increased risk of both moderately severe and severe AP.

A) Local complications



B) Systemic complications



C) Severe pancreatitis

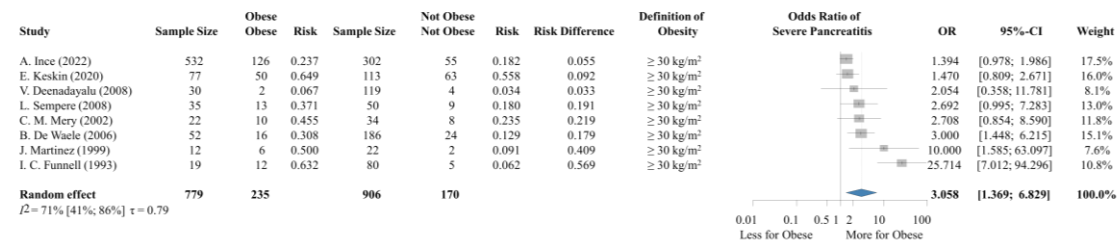


Figure 7. A) The odds of local and B) systemic complications are significantly increased in the group of patients with overweight or obesity. C) The odds of developing severe AP is significantly increased among patients with obesity. (47) EBW: excess body weight, BMI: body-mass index, OR: odds ratio, CI: confidence interval.

Additional analyses comparing body composition parameters across severity categories showed that patients with moderately severe and severe AP had higher BMI values and greater visceral adipose tissue accumulation than patients with mild disease (**Figure 8**), whereas subcutaneous adipose tissue did not differ significantly between severity groups.

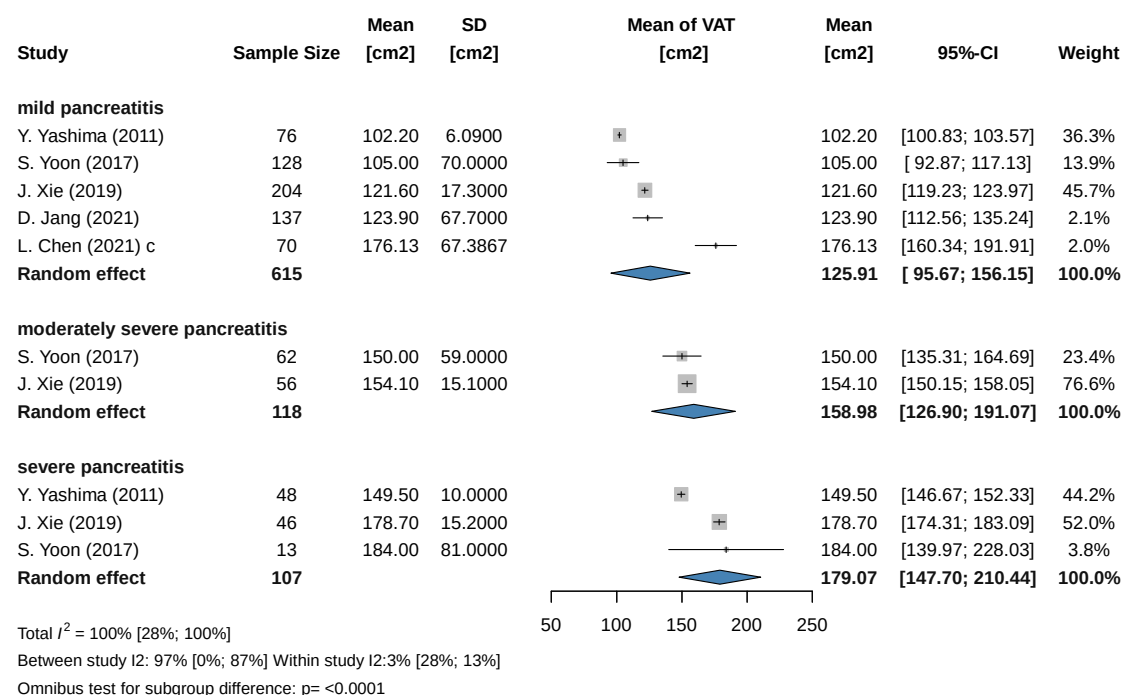
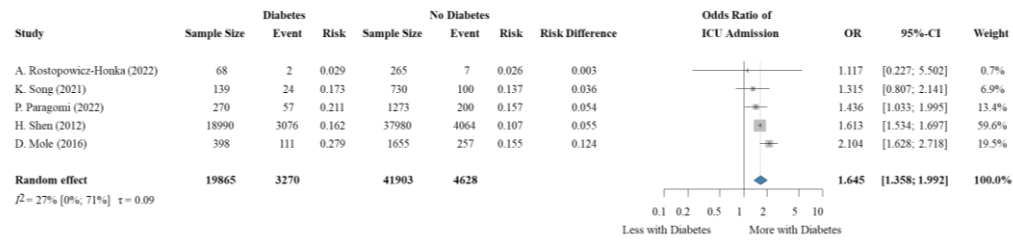


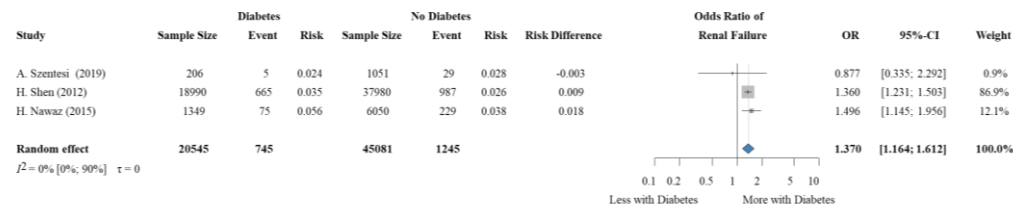
Figure 8. The mean volume of visceral adipose tissue (VAT) in the different AP severity groups. VAT: visceral adipose tissue, CI: confidence interval.

In total, 11 studies (11, 58-67) comprising 71,876 patients reported outcomes according to diabetes status. Pre-existing DM was associated with significantly worse outcomes in AP. Patients with diabetes had a higher likelihood of requiring ICU admission (OR=1.645, 95% CI 1.358–1.992) (**Figure 9A**) and developing renal failure (OR=1.370, 95% CI 1.164–1.612) (**Figure 9B**). DM was also associated with disease severity, increasing the odds of severe AP by approximately 50% (OR=1.490, 95% CI 1.090–2.030) (**Figure 9C**).

A) ICU admission



B) Renal failure



C) Severe pancreatitis

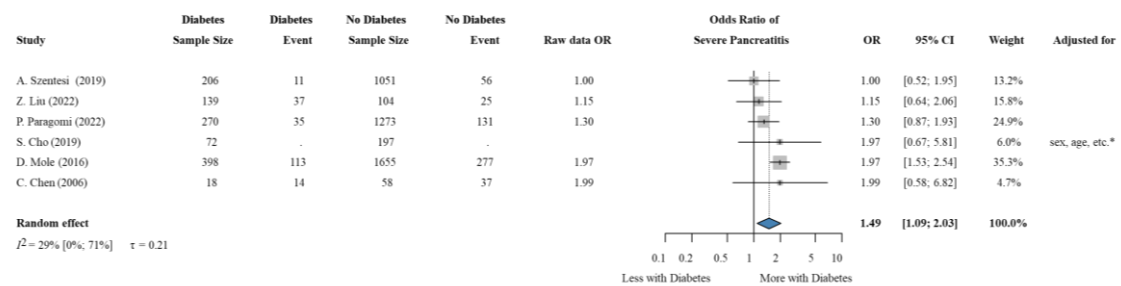
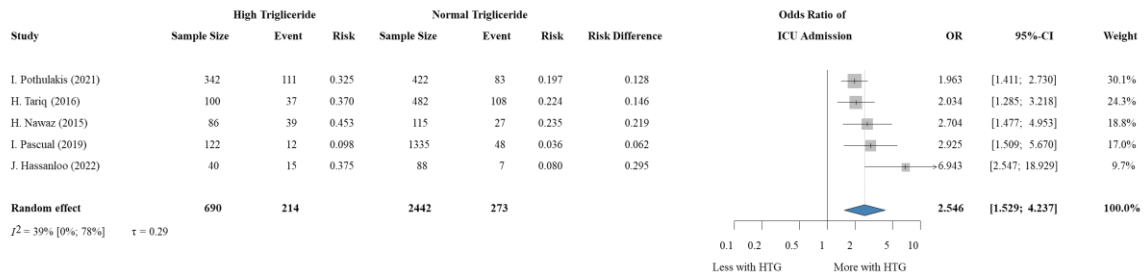


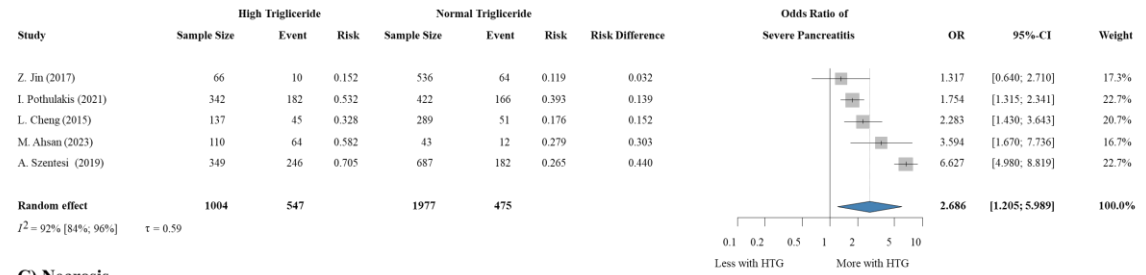
Figure 9. Diabetes is a statistically significant predictor of the need for A) ICU admission, B) renal failure and C) severe pancreatitis. (47) ICU: Intensive Care Unit, OR: odds ratio, CI: confidence interval.

Based on 12 studies (11, 12, 66, 68-76) involving 291,733 patients, we could conclude that patients with elevated triglyceride levels on admission have significantly increased odds for being admitted to the ICU (OR: 2.546, 95%CI 1.529-4.237) (**Figure 10A**), progressing to the severe form of the disease (OR: 2.686, 95%CI 1.205-5.989) (**Figure 10B**) and developing necrosis (OR: 2.364, 95%CI 1.01-5.535) (**Figure 10C**).

A) ICU admission



B) Severe pancreatitis



C) Necrosis

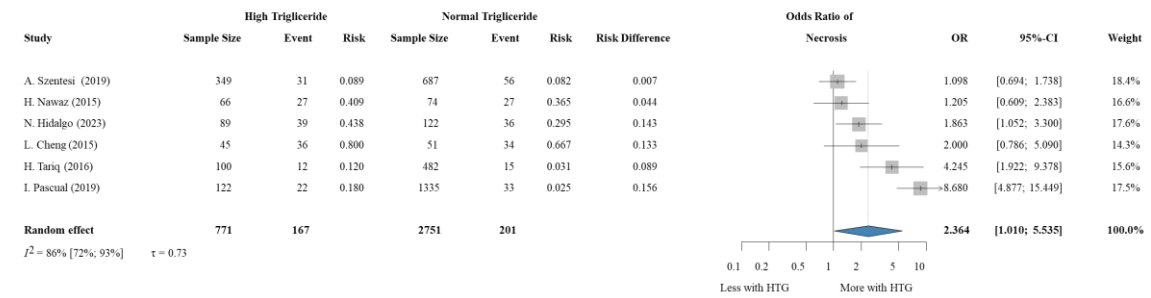
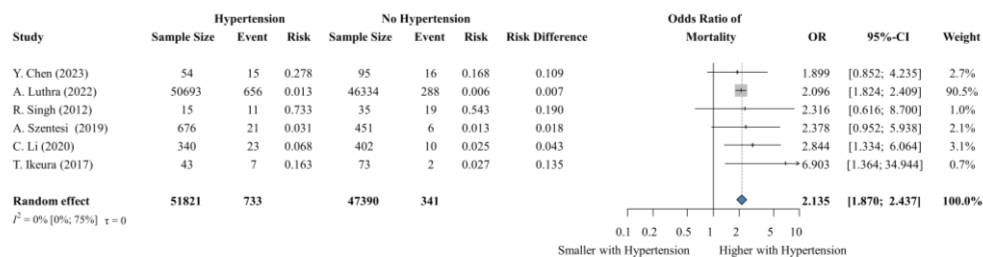


Figure 10. HTG is a predictor of A) requiring ICU admission, B) severity, and C) necrosis development in AP. (47) HTG: hypertriglyceridemia, OR: odds ratio, CI: confidence interval.

Among the investigated metabolic factors, hypertension showed the strongest association with mortality. We investigated the effect of pre-existing chronic hypertension on the outcome of AP using data from 102,496 patients across 13 articles (9, 11, 50, 58, 60, 62, 63, 77-82). Hypertension was not significantly associated with severe AP (OR: 1.243, 95%CI 0.745-2.076), but was a significant predictor of mortality (OR: 2.135, 95%CI 1.870-2.437) (**Figure 11**).

A) Mortality



B) Severity

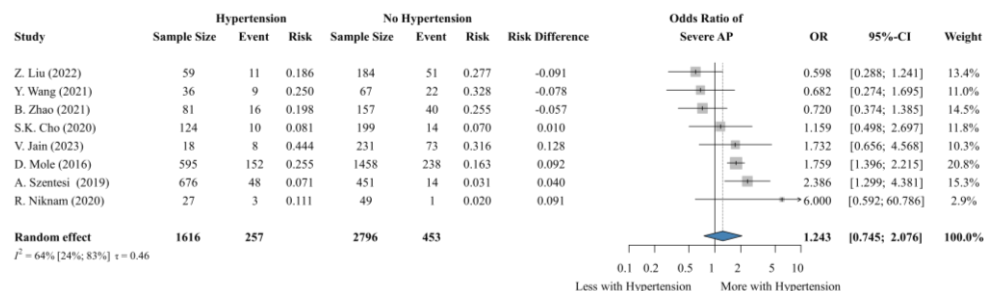


Figure 11. Hypertension significantly increases the risk of A) mortality, but not severity (B). (47) AP: acute pancreatitis, OR: odds ratio, CI: confidence interval.

Five articles (11, 80, 83-85) involving 137,111 patients reported data on MS and AP severity (**Figure 12**). Although individual MS components were consistently associated with adverse outcomes, the pooled analysis did not demonstrate a statistically significant association between MS as a composite condition and severe AP (OR: 1.398, 95%CI 0.918–2.129). Four studies (11, 80, 84, 85) assessed the risk of mortality in the MS patient group. The available evidence was inconsistent, with only two of the studies reporting increased mortality among individuals with MS. Accordingly, the pooled analysis did not identify MS as a significant predictor of mortality (OR: 1.307, 95% CI 0.240–7.102), and considerable between-study heterogeneity was observed.

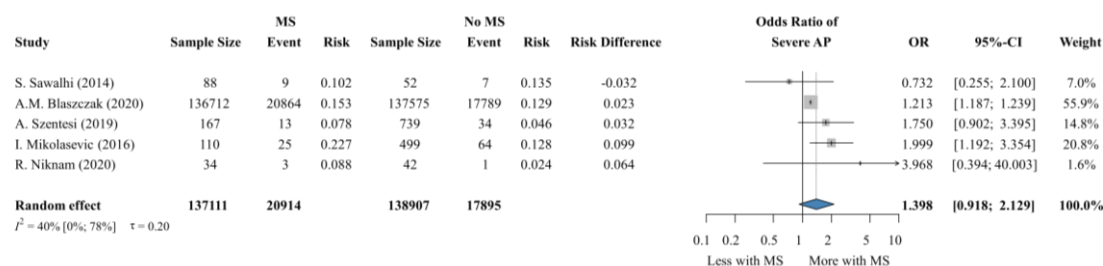


Figure 12. The risk of developing severe AP with and without MS. (47)

MS: metabolic syndrome, AP: acute pancreatitis, OR: odds ratio, CI: confidence interval.

8.2.4. Risk of Bias Assessment

Overall, the risk of bias was considered low for study attrition, prognostic factor measurement, outcome assessment, and confounding domains. Potential concerns were identified primarily in the domains of study participation and statistical analysis reporting.

Sensitivity analyses demonstrated that the pooled results were generally robust. Leave-one-out analyses showed that no individual study substantially influenced the overall conclusions. Although one study investigating obesity exerted a moderate influence on some pooled estimates, its exclusion did not materially alter the findings.

8.2.5. Quality of Evidence

The overall quality of evidence was considered moderate. The consistency of findings across multiple studies and diverse patient populations supports the reliability of the observed associations between metabolic abnormalities and AP outcomes. Obesity, DM, hypertriglyceridemia, and hypertension consistently demonstrated detrimental effects on clinically relevant outcomes across the included studies.

Nevertheless, the evidence base was limited by the observational design of all included studies, heterogeneity in the definitions of MS and its individual components, and differences in outcome reporting. Variability in study design, patient characteristics, and regional healthcare settings also contributed to between-study heterogeneity. Despite

these limitations, the available evidence strongly supports the prognostic importance of metabolic abnormalities in patients with AP.

9. DISCUSSION

9.1. Summary of Findings, International Comparisons

A central finding of this thesis is that metabolic dysfunction represents an important determinant of AP outcomes, with obesity being only one component of a broader metabolic risk profile. Although elevated BMI was consistently associated with increased disease severity and mortality, the second meta-analysis demonstrated that other metabolic abnormalities, including DM, hypertension, and hypertriglyceridemia, also independently contribute to adverse outcomes. These results suggest that focusing exclusively on obesity may underestimate the prognostic importance of metabolic dysfunction and support a more comprehensive metabolic approach to risk stratification in AP.

The association between obesity and severe AP has been recognized for more than two decades. Early observational studies reported that increased body weight was associated with a higher risk of organ failure, pancreatic necrosis, and mortality (7, 25, 86). Our BMI meta-analysis confirmed and strengthened these observations by demonstrating a clear relationship between increasing BMI and adverse clinical outcomes, with obesity being associated with both severe disease and mortality. These findings are consistent with previous reports suggesting that excess adipose tissue contributes to pancreatic injury through lipotoxicity, chronic low-grade inflammation, and increased production of pro-inflammatory cytokines (87, 88).

The second study extended this concept beyond obesity alone. Hypertriglyceridemia emerged as one of the strongest predictors of severe disease, ICU admission, and pancreatic necrosis. These findings are in agreement with previous cohort studies and international registry analyses demonstrating that elevated triglyceride levels contribute directly to pancreatic injury through the generation of toxic free fatty acids. Furthermore, hypertriglyceridemia-induced AP is increasingly recognized as a distinct clinical entity characterized by a more severe disease course (89-91).

Diabetes was also associated with severe AP, renal failure, and ICU admission. These results support previous meta-analyses and cohort studies indicating that chronic hyperglycemia and insulin resistance may impair immune function, promote systemic

inflammation, and increase susceptibility to organ dysfunction during acute illness (10, 67, 92-94). The observed association between diabetes and adverse outcomes is particularly relevant given the increasing global prevalence of type 2 DM (95).

Interestingly, hypertension was not significantly associated with disease severity but emerged as a strong predictor of mortality. This finding differs somewhat from earlier reports that linked hypertension primarily to systemic complications and severe disease (96, 97). The observed increase in mortality may reflect the cumulative effect of vascular dysfunction, endothelial injury, and cardiovascular comorbidities commonly present in hypertensive patients (98). These results further highlight the importance of considering chronic comorbid conditions when evaluating the prognosis of AP.

Although the individual components of MS consistently demonstrated adverse prognostic effects, the pooled analysis did not reveal a statistically significant association between MS as a composite diagnosis and AP outcomes (83, 85). This apparent discrepancy likely reflects the considerable heterogeneity in MS definitions across studies, differences in patient populations, and the unequal prognostic contribution of individual metabolic abnormalities. Consequently, evaluating individual components may provide more clinically meaningful information than treating MS as a single entity.

Taken together, the findings of this thesis suggest that metabolic abnormalities should be considered important determinants of disease severity, complications, and mortality in AP. The results support the growing body of international evidence emphasizing the role of metabolic health in the prognosis of acute inflammatory diseases.

9.2. Strengths

Several strengths increase the validity and clinical relevance of the present thesis. First, both studies were conducted according to prospectively registered protocols and followed internationally accepted methodological standards, including PRISMA guidelines and Cochrane recommendations. This minimized the risk of selective reporting and enhanced methodological transparency.

Second, the thesis provides a comprehensive assessment of metabolic risk factors in AP. While previous studies typically focused on individual exposures, the present work systematically evaluated obesity, DM, hypertension, hypertriglyceridemia, and MS within a unified conceptual framework. This approach allowed the identification of common patterns linking metabolic dysfunction to adverse clinical outcomes.

Third, the included studies collectively represented hundreds of thousands of patients from multiple countries and healthcare systems, substantially increasing the statistical power and generalizability of the findings. The large sample sizes enabled the detection of clinically meaningful associations that may not have been apparent in individual studies.

A major strength of this thesis is that it approached AP from a metabolic perspective and integrated findings across multiple related risk factors rather than evaluating them in isolation.

Finally, our work has important translational value. The findings directly address a clinically relevant question and provide evidence that can be applied to patient risk stratification, prognostic model development, and personalized management strategies in AP.

9.3. Limitations

A number of limitations should also be considered when interpreting the findings. First, all pooled analyses were based on observational studies. Consequently, causal relationships cannot be definitively established, and residual confounding cannot be excluded. Factors such as age, comorbidity burden, lifestyle characteristics, and treatment differences may have influenced the observed associations.

Second, considerable heterogeneity was present across studies. Differences in study design, patient populations, severity classifications, outcome definitions, and diagnostic criteria for MS may have contributed to variability in the pooled estimates. Although random-effects models were used to account for this heterogeneity, some uncertainty remains.

Third, obesity was primarily assessed using BMI. Although BMI is widely used in clinical practice, it does not adequately distinguish between fat and lean body mass, nor does it capture differences in fat distribution. Emerging evidence suggests that visceral adiposity may be a more accurate predictor of AP outcomes than BMI alone.

Fourth, the number of studies available for some outcomes was limited, reducing the precision of certain estimates and restricting the ability to perform detailed subgroup analyses. Similarly, publication bias could not be thoroughly evaluated for all outcomes because of the limited number of eligible studies. In addition, the relatively limited number of studies evaluating MS as a composite diagnosis may have reduced statistical power to detect associations with clinical outcomes.

Finally, the analyses focused primarily on in-hospital outcomes. Long-term consequences of AP, including recurrent disease, chronic pancreatitis, diabetes development, cardiovascular complications, and post-discharge mortality, remain insufficiently studied and warrant further investigation.

10. CONCLUSIONS

The findings of this thesis demonstrate that metabolic abnormalities are important determinants of disease severity and clinical outcomes in AP. Through two complementary systematic reviews and meta-analyses, the present work provides comprehensive evidence supporting the prognostic significance of obesity and other components of MS in patients with AP.

The first study showed that increasing BMI is associated with a progressively higher risk of severe AP, while obesity is also linked to increased mortality. These findings confirm that excess body weight represents a clinically relevant risk factor that should be considered during the early assessment of patients presenting with AP.

Building upon these results, the second study demonstrated that obesity, DM, hypertension, and hypertriglyceridemia are independently associated with adverse clinical outcomes. Obesity and hypertriglyceridemia were among the strongest predictors of severe disease, whereas hypertension was associated with increased mortality. DM was linked to a higher risk of severe AP, ICU admission, and organ dysfunction.

Taken together, these findings suggest that metabolic dysfunction contributes substantially to the progression and severity of AP. The observed associations are biologically plausible and are supported by current knowledge regarding chronic inflammation, lipotoxicity, endothelial dysfunction, and metabolic dysregulation.

The results of this thesis also highlight important limitations of currently used prognostic systems, which only partially account for metabolic risk factors despite their significant impact on patient outcomes. Incorporating metabolic parameters into future prognostic models may improve risk stratification and facilitate more personalized management strategies.

In conclusion, obesity and other metabolic abnormalities should be recognized as major prognostic factors in AP. Their routine assessment may contribute to the early identification of high-risk patients and support the development of more accurate, metabolically informed approaches to patient care.

11. IMPLICATIONS FOR PRACTICE

The findings of this thesis have several important implications for clinical practice. First, metabolic abnormalities should be routinely considered during the initial assessment of patients presenting with AP. Readily available parameters such as BMI, history of DM, hypertension, and serum triglyceride levels may provide valuable prognostic information early in the course of the disease.

The results indicate that patients with obesity and other metabolic abnormalities represent a higher-risk population and may require closer clinical monitoring, more frequent reassessment, and earlier consideration of ICU admission. Identifying these patients at an early stage could facilitate timely interventions and improve patient outcomes.

The observed associations between metabolic abnormalities and poor outcomes also emphasize the importance of multidisciplinary patient management. Collaboration between gastroenterologists, endocrinologists, nutrition specialists, and primary care physicians may contribute to improved acute management and long-term prevention strategies.

Finally, the findings support the incorporation of metabolic risk factors into future prognostic models and clinical decision-making tools, potentially enabling more accurate risk stratification and personalized management of patients with AP.

12. IMPLICATIONS FOR RESEARCH

12.1. Methodology and Study Design

The findings of this thesis highlight several methodological considerations for future research. Standardized definitions of MS are needed to improve comparability across studies. Similarly, harmonized reporting of clinically relevant outcomes would facilitate future evidence synthesis and reduce methodological heterogeneity.

Future investigations should prioritize large prospective multicenter studies with standardized data collection protocols. Such studies would allow more accurate assessment of the independent effects of metabolic abnormalities while minimizing the influence of residual confounding. In addition, future prognostic studies should incorporate detailed body composition measurements, including visceral adipose tissue assessment or measuring waist circumference, rather than relying exclusively on BMI.

Another important direction is the development and validation of prognostic models integrating metabolic factors alongside established clinical, laboratory, and imaging parameters. Such approaches may improve predictive accuracy and support personalized risk stratification in AP. Prospective validation studies are required to determine whether metabolic factors can be reliably incorporated into routine prognostic scoring systems and clinical decision-making algorithms.

12.2. New Areas

The results of this thesis identify several promising areas for future investigation. Given the strong association between metabolic abnormalities and AP outcomes, further research is needed to better understand the underlying biological mechanisms linking metabolic dysfunction to pancreatic injury and systemic inflammation.

Future studies should explore the role of body composition, visceral adiposity, metabolic biomarkers, and inflammatory mediators in determining disease severity. Advanced imaging techniques, metabolomics, and biomarker-driven patient phenotyping may provide additional insights into the heterogeneity of AP and help identify novel therapeutic targets.

Another promising research direction is the investigation of the gut microbiome as a potential mediator between metabolic abnormalities and AP outcomes (99). Given the well-established links between obesity, DM, MS, and gut dysbiosis, future studies should explore whether microbiome alterations contribute to the increased severity observed in metabolically compromised patients. Integrating microbiome profiling with clinical, metabolic, and inflammatory data may facilitate the identification of novel biomarkers and therapeutic targets, ultimately supporting the development of personalized approaches in AP.

In parallel, advances in artificial intelligence and machine learning offer new opportunities for improving outcome prediction in AP. Future AI-based prediction models integrating clinical, laboratory, imaging, and metabolic data may enhance early risk stratification and support the implementation of personalized treatment strategies.

Finally, the long-term consequences of metabolic abnormalities following AP remain incompletely understood. Future research should investigate the impact of metabolic risk factors on recurrent AP, chronic pancreatitis, post-pancreatitis diabetes, cardiovascular outcomes, and long-term mortality. These studies may ultimately contribute to the development of comprehensive preventive and therapeutic strategies for patients with AP.

13. IMPLICATIONS FOR POLICY MAKERS

The findings of this thesis have important implications not only for clinical practice but also for public health policy and healthcare planning. The increasing prevalence of obesity and metabolic dysregulation represents a growing global health challenge, with consequences extending beyond chronic cardiometabolic diseases to acute conditions such as AP.

The results demonstrate that metabolic abnormalities are associated with increased disease severity, higher rates of complications, greater ICU utilization, and increased mortality in patients with AP. Consequently, the rising burden of metabolic diseases may contribute to increased healthcare expenditures, prolonged hospitalizations, and greater demand for specialized and intensive care services.

From a public health perspective, these findings further support the implementation of effective prevention strategies targeting obesity and MS. Population-level interventions promoting healthy nutrition, physical activity, weight management, and early detection of metabolic disorders may not only reduce the incidence of chronic diseases but also decrease the burden of severe AP.

Healthcare systems may also benefit from incorporating metabolic risk assessment into clinical pathways and quality improvement initiatives. The identification of high-risk patient populations could facilitate more efficient resource allocation, improve patient outcomes, and reduce healthcare costs associated with severe disease and its complications.

Finally, the growing recognition of the interaction between metabolic health, inflammation, and acute disease outcomes highlights the importance of integrated healthcare policies that address metabolic disorders as systemic conditions with wide-ranging clinical consequences. Supporting multidisciplinary prevention and management programs may therefore provide substantial long-term benefits for both patients and healthcare systems.

14. FUTURE PERSPECTIVES

The findings of this thesis have also generated new research questions regarding the broader prognostic significance of metabolic abnormalities beyond AP. Given the consistent association observed between metabolic abnormalities and adverse outcomes in AP, we sought to determine whether similar prognostic relationships could be identified in other acute inflammatory diseases characterized by overlapping pathophysiological mechanisms. Increasing evidence suggests that several acute inflammatory diseases share common biological pathways, including dysregulated immune responses, systemic inflammation, endothelial injury, and metabolic dysfunction. Previous studies have also highlighted mechanistic similarities between AP and COVID-19 (100), suggesting that metabolic abnormalities may influence disease outcomes through partially overlapping pathways. One such project involved the analysis of a multicentre COVID-19 cohort comprising 1,034 patients with confirmed SARS-CoV-2 infection. The study investigated the prognostic impact of individual and cumulative MS components on disease severity and clinical outcomes. Preliminary results demonstrated that obesity and the coexistence of multiple MS components were independently associated with severe or critical COVID-19, supporting the hypothesis that metabolic dysfunction may represent a common determinant of poor outcomes across different acute inflammatory conditions. The manuscript has been completed and is currently under revision.

The observations of the present thesis also contributed to a growing interest in the role of modifiable lifestyle factors in AP. This concept is currently being investigated in the ongoing international LIFESPAN case-control study, which evaluates lifestyle-related risk factors associated with the development of AP. Interim analyses have identified significant associations between AP and several potentially modifiable factors, including obesity, smoking, alcohol consumption, diabetes, lipid metabolism disorders, sleep disturbances, and impaired stress management. These findings suggest that the influence of metabolic health extends beyond disease progression and may also contribute to disease development.

Together, these ongoing projects broaden the scope of the present thesis by extending the investigation of metabolic and lifestyle-related risk factors from AP outcomes to disease susceptibility and to other acute inflammatory disorders. Future studies integrating epidemiological, metabolic, microbiome, and artificial intelligence-based approaches may further improve our understanding of individual disease vulnerability and support the development of personalized preventive and therapeutic strategies.

The increasing availability of large-scale clinical datasets, advanced biostatistical methods, and artificial intelligence-based prediction models will require close collaboration between clinicians, researchers, biostatisticians, and data scientists. The successful implementation of such approaches highlights the importance of integrated translational medicine training and multidisciplinary scientific education for future healthcare professionals (101).

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