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című program

Programvezető: Dr. Ferdinandy Péter, egyetemi tanár
Témavezetők: Dr. Szentesi Andrea, tudományos munkatárs
Dr. Hegyi Péter, egyetemi tanár

NEW INSIGHTS INTO THE DIAGNOSIS AND PROGNOSIS OF ACUTE PANCREATITIS

Ph.D. Thesis

Gefu Cai, MSc

Translational Medicine Program

Pharmaceutical Sciences and Health Technologies Division

SEMMELWEIS UNIVERSITY



Supervisor:

Andrea Szentesi, MSc., Ph.D.

Péter Hegyi, DSc., M.D., Ph.D.

Official reviewers:

Simon Sirtl, DSc., M.D., Ph.D.

Roxana Sirli, DSc., M.D., Ph.D.

Head of the Complex Examination Committee:

Gábor Varga, DSc, M.D., Ph.D.

Members of the Complex Examination Committee: Karl J. Oldhafer, DSc, M.D., Ph.D.

Áron Vincze, M.D., Ph.D.

Emese Mihály, M.D., Ph.D.

Zoltán Zádori, M.D., Ph.D.

Roland Molontay, M.D., Ph.D.

Budapest

2026

***“Research is to see what everybody else has
seen, and to think what nobody else has
thought.”***

Albert Szent-Györgyi

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1. LIST OF ABBREVIATIONS

AP – Acute pancreatitis

APR – Acute Pancreatitis Registry

BMI – Body mass index

CI – Confidence interval

CP – Chronic pancreatitis

DM – Diabetes mellitus

HbA1c – Glycated hemoglobin

HIV – Human immunodeficiency virus

HR – Hazard ratio

HTG – Hypertriglyceridemia

IAP/APA – International Association of Pancreatology / American Pancreatic Association

JB – Joanna Briggs Institute

OR – Odds ratio

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QUIPS – Quality in Prognosis Studies

SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

SHAP – SHapley Additive exPlanations

WBC – White blood cell

RMSE – Root Mean Squared Error

IQR – Interquartile Range

SD – Standard Deviation

CRP – C-Reactive Protein

RCT – Randomized Controlled Trial

ERCP – Endoscopic retrograde cholangiopancreatography

RAP – Recurrent acute pancreatitis

2. STUDENT PROFILE

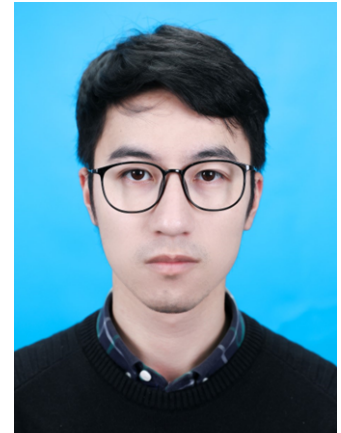
2.1. Vision and mission statement, specific goals

Vision: To advance a more precise understanding of acute pancreatitis through the integration of external and patient-specific factors.

Mission: My aim was to investigate how comorbidities influence diagnostic accuracy and to evaluate the impact of viral infections on acute pancreatitis outcomes, with the goal of improving risk assessment.

Specific Goals:

- 1) To assess the effect of viral infections on AP outcomes
- 2) To evaluate the impact of comorbidities on enzyme levels and diagnosis
- 3) To identify patients at risk of underdiagnosis
- 4) To support more individualized approaches in AP



2.2. Scientometrics

Number of all publications:	7
Cumulative IF:	53
Av IF/publication:	7.57
Ranking (SCImago):	D1; Q1.
Number of publications related to the subject of the thesis:	2
Cumulative IF:	28.5
Av IF/publication:	14.25
Ranking (Sci Mago):	D1; Q1.
Number of citations on Google Scholar:	27
Number of citations on MTMT (independent):	6
H-index:	3

The detailed bibliography of the student can be found on pages 71-72.

2.3. Future plans

I plan to continue my academic development by engaging in both basic and translational research, with the aim of contributing to the generation of clinically relevant

knowledge. In the next phase, I intend to further explore how scientific findings can be effectively translated into practical applications, bridging the gap between experimental research and real-world healthcare challenges.

I aim to maintain a broad scientific perspective and work at the interface of disciplines. In the long term, I hope to contribute to evidence-based approaches by facilitating the translation of research findings into improved diagnostic and therapeutic strategies, ultimately supporting better patient outcomes.

3. SUMMARY OF THE THESIS

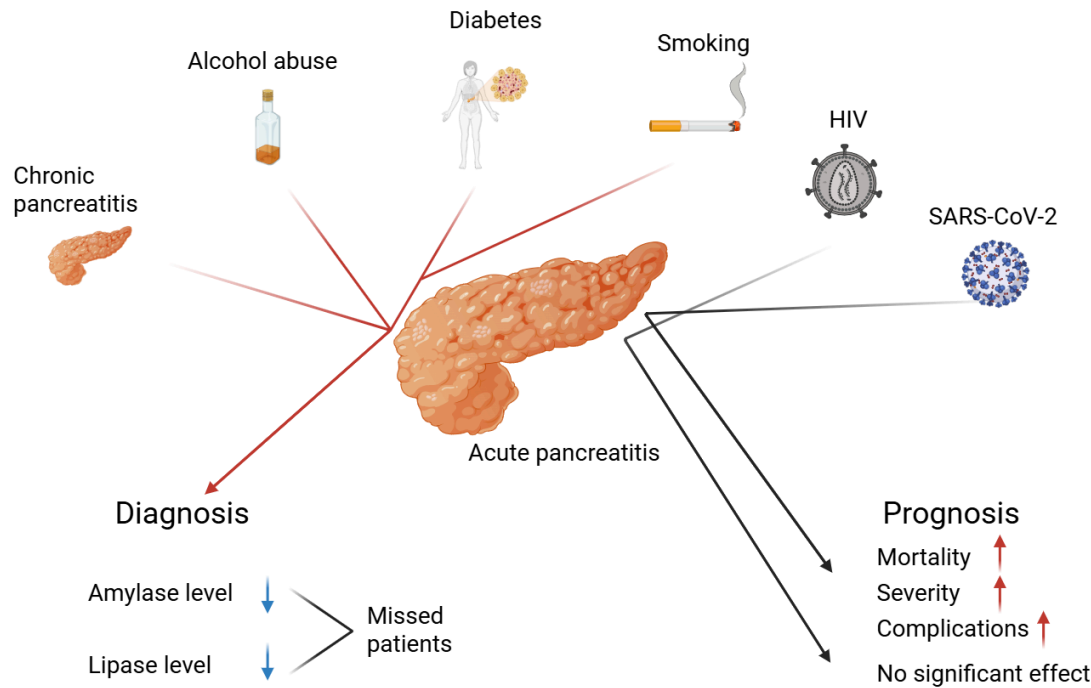
Acute pancreatitis (AP) is a common gastrointestinal emergency with highly variable outcomes. This thesis investigates two critical aspects: (1) the influence of patient-related factors on the reliability of pancreatic enzyme measurements, and (2) the impact of systemic viral infections on AP prognosis. Both studies utilize large, multicenter, international datasets to provide a comprehensive perspective on diagnostic challenges, clinical management, and disease outcome.

The first study is a post hoc analysis of 4,162 AP cases from the international Acute Pancreatitis Registry (APR), examining factors influencing serum pancreatic enzyme levels. Diabetes, chronic pancreatitis (CP), smoking, and alcohol-related etiology were associated with lower amylase and lipase levels, leading to 6.7% of patients being clinical practice diagnosed solely based on imaging and clinical presentation. Multivariable logistic regression and machine learning analyses identified these factors as independent predictors of non-diagnostic enzyme levels, highlighting potential misdiagnosis risks under current diagnostic criteria.

The second study is a systematic review and meta-analysis of 528 studies, including over 2.2 million patients, evaluating the effect of viral infections on AP outcomes. SARS-CoV-2 infection significantly worsens prognosis, with higher in-hospital mortality, increased disease severity, and elevated complication risk, whereas HIV infection shows no significant impact. The analysis followed PRISMA 2020 guidelines, assessed bias using QUIPS and JBI tools, and applied two-level and multi-level random-effects models to account for heterogeneity. Kaplan-Meier survival analysis further confirmed the differential effects of viral infections.

Together, the thesis emphasizes that both host-related factors (comorbidities, lifestyle) and external stressors (viral infections) shape AP detectability and outcomes. Combining prospective registry analysis, machine learning, and high-level evidence synthesis, this work provides clinically relevant insights for individualized diagnosis, risk stratification, and management of AP.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Acute pancreatitis: definition and clinical relevance

AP is one of the most common gastrointestinal emergencies worldwide, characterized by an acute inflammatory process of the pancreas with variable involvement of local and systemic complications. According to the current international consensus, AP is defined clinically by a combination of characteristic abdominal pain, elevated pancreatic enzymes, and/or imaging findings consistent with pancreatic inflammation [1].

The incidence of AP has been increasing globally over the past decades [2], with substantial variation across regions, largely driven by differences in etiological factors such as gallstone disease, alcohol consumption, and metabolic disorders. While the majority of cases follow a mild and self-limiting course, approximately 20% of patients develop moderately severe or severe disease, which may be associated with persistent organ failure, systemic inflammatory response syndrome, and significant mortality [3-5].

Beyond its acute clinical burden, AP represents a complex and heterogeneous condition in which disease expression is influenced not only by the underlying etiology[6] but also by patient-specific factors, including comorbidities and systemic conditions. This heterogeneity poses challenges for both diagnosis and prognostic assessment in routine clinical practice [7].

5.2. Current diagnostic criteria and potential limitations

The diagnosis of AP is currently based on the Revised Atlanta Classification, which requires the presence of at least two of the following three criteria: (1) characteristic abdominal pain, (2) serum amylase and/or lipase levels at least three times the upper limit of normal, and (3) imaging findings consistent with AP [8].

In clinical practice, serum pancreatic enzymes are central to early diagnosis due to their accessibility and rapid turnaround time. However, emerging evidence indicates that reliance on fixed biochemical thresholds may not be universally reliable across all patient populations [9].

5.3. Prognostic assessment and risk stratification

The clinical course of AP is highly variable, necessitating early and accurate risk stratification. According to the Revised Atlanta Classification, disease severity is categorized as mild, moderately severe, or severe based on the presence and duration of organ failure and local or systemic complications [8].

In addition to this classification, several prognostic scoring systems, such as APACHE II [10], BISAP [11], EASY score [12], and Ranson's criteria [13], are widely used to predict disease severity and clinical outcomes. These tools incorporate physiological parameters, laboratory values, and early clinical findings to guide clinical decision-making.

Despite their widespread use, these models have important limitations. Most scoring systems were developed in relatively homogeneous patient populations and may not adequately capture the impact of comorbid conditions or concurrent systemic stressors. As a result, they may underestimate or fail to identify patients at increased risk when additional modifying factors are present.

5.4. Complexity and clinical heterogeneity of acute pancreatitis

AP is a clinically heterogeneous disease with a wide spectrum of etiologies, pathophysiological mechanisms, and clinical outcomes.

The condition may arise from a variety of causes, most commonly gallstone disease and alcohol use, but also includes metabolic factors such as hypertriglyceridemia (HTG), drug-induced injury, and, less frequently, infectious triggers. These diverse etiologies initiate pancreatic inflammation through different biological pathways, contributing to variability in disease onset and progression [14].

In addition to etiological diversity, the clinical course of AP is highly variable. While many patients experience a mild, self-limiting disease, others develop local complications such as pancreatic necrosis[15] and fluid collections, or systemic manifestations including organ failure and systemic inflammatory response syndrome. The interaction between local pancreatic injury and systemic inflammation further amplifies disease complexity [16; 17].

This heterogeneity is further compounded by differences in patient-specific factors, including age, comorbidities, and underlying pancreatic health. As a result, AP should

be considered a dynamic and multifactorial syndrome rather than a single uniform disease entity.

The complexity of AP poses significant challenges for both diagnosis and prognostic assessment. Standardized criteria and scoring systems may not fully capture the variability in disease presentation and progression across different patient populations, highlighting the need for a more individualized and context-aware approach.

5.5. Knowledge gap and study rationale

Despite advances in diagnostic and prognostic frameworks, important gaps remain in understanding how these standardized approaches perform in real-world, heterogeneous patient populations.

In particular, the reliability of enzyme-based diagnostic criteria in patients with altered pancreatic function remains insufficiently characterized. Similarly, the extent to which systemic conditions, such as viral infections, are adequately incorporated into existing prognostic models is unclear.

This potential mismatch between guideline-based frameworks and clinical reality may lead to underdiagnosis, delayed recognition, or misclassification of disease severity in specific patient subgroups.

Therefore, this thesis aims to systematically evaluate the impact of host-related comorbidities and viral co-infections on both diagnostic accuracy and clinical outcomes in AP, using large-scale international data and complementary methodological approaches.

6. OBJECTIVES

6.1. Study I. – Low-enzyme acute pancreatitis: a diagnostic blind spot in current guidelines

The objective of this study was to investigate the impact of patient-related factors on pancreatic enzyme levels in AP and to evaluate their implications for diagnostic accuracy. Specifically, we aimed to identify clinical and demographic characteristics associated with non-diagnostic serum amylase and lipase levels, and to determine the extent to which these factors may contribute to the underdiagnosis of AP within the framework of current diagnostic guidelines.

6.2. Study II. – Concomitant virus infection increases mortality and worsens the outcome of acute pancreatitis: a systematic review and meta-analysis

The objective of this study was to systematically evaluate the impact of concomitant viral infections on the clinical outcomes of AP, including mortality, disease severity, and complications.

7. METHODS

7.1. Study I. – Low-enzyme acute pancreatitis: a diagnostic blind spot in current guidelines

7.1.1. *Data collection and ethical permissions*

Clinical data from 4,162 patients with AP were prospectively collected within the international Acute Pancreatitis Registry (APR), coordinated by the Hungarian Pancreatic Study Group between 2014 and 2023, across 29 centers in 14 countries. The present study was designed as a post hoc cross-sectional analysis based on this prospectively gathered registry dataset.

Ethical approval was obtained from the Scientific and Research Ethics Committee of the Medical Research Council and the National Public Health Center (reference numbers: 22254-1/2012/EKU and 17787-8/2020/EÜIG). The study was conducted in accordance with the Declaration of Helsinki (revised in 2024), and all participants provided written informed consent prior to inclusion.

Clinical information was obtained from structured patient interviews conducted by trained clinical research personnel, as well as from electronic and paper-based medical records. Data entry was performed by trained research administrators or study nurses. Data quality was maintained through a four-level monitoring system embedded within the electronic data management platform.

At the first level, a trained local clinical research administrator entered the data and performed an initial quality check. At the second level, a local institutional investigator with a medical degree reviewed and verified the accuracy of the submitted data. The third level consisted of a central data administrator at the HPSG headquarters, who conducted an additional validation step. Finally, the principal investigator performed a comprehensive review and approved the dataset.

Representativeness analyses comparing the full registry cohort with the study population revealed no meaningful differences in baseline characteristics.

7.1.2. *Patients Selection and Definitions*

Patients with AP were enrolled in the APR based on the recommendations of the IAP/APA guidelines[18; 19]. The diagnosis of AP required the presence of at least two of the following three criteria: (1) acute abdominal pain, (2) serum amylase and/or

lipase levels exceeding three times the upper limit of normal, and (3) imaging findings consistent with AP. Disease severity and related complications were classified based on the revised Atlanta classification [8].

Only adult patients (≥ 18 years) were included in the analysis. Individuals with uncertain or alternative diagnoses were excluded. Recurrent acute pancreatitis (RAP) and CP were not considered exclusion criteria and were recorded as baseline variables.

Diabetes mellitus (DM) status was defined based on a prior clinical diagnosis, the use of antidiabetic medication, or laboratory findings during hospitalization, including fasting plasma glucose ≥ 7.0 mmol/L or HbA1c $\geq 6.5\%$. Patients newly diagnosed with diabetes during the index admission were also categorized as having DM. Cases with insufficient data to determine diabetes status were excluded from DM-related analyses.

Patients were classified as having no diagnostic enzyme elevation if, at admission, amylase levels were ≤ 300 U/L and lipase levels were ≤ 180 U/L. These patients were also referred to as the “low amylase” and “low lipase” groups in subgroup analyses.

For analyses related to pancreatic enzyme elevation, patients with missing amylase and/or lipase measurements were excluded.

7.1.3. Study Population

The total study cohort ($n = 4,162$) included patients with AP who had at least one pancreatic enzyme measurement (amylase or lipase) available at hospital admission. This population was used for descriptive analyses.

For subgroup analyses based on enzyme levels ($n = 3,993$), patients were classified into mutually exclusive categories according to admission measurements. Of these, 3,725 patients were identified as having diagnostic enzyme elevation, defined by amylase and/or lipase levels meeting the diagnostic threshold. In contrast, 268 patients were categorized as having no diagnostic enzyme elevation, requiring both amylase and lipase measurements below the threshold at admission.

Patients with incomplete enzyme data ($n = 169$), defined as missing amylase, lipase, or both values such that diagnostic classification was not possible, were excluded from these subgroup analyses.

Multivariable logistic regression analysis ($n = 3,723$) was performed in a reduced cohort restricted to cases with complete data for all variables included in the model. A complete-case approach was applied, excluding patients with missing information on

any covariates, which resulted in a smaller analytic sample compared with the overall cohort.

7.1.4. Variables

The primary outcome of interest was pancreatic enzyme level status, analyzed both as continuous variables (amylase and lipase) and as dichotomous variables reflecting diagnostic versus non-diagnostic enzyme elevation.

All candidate risk factors, including DM, CP, smoking status, etiology, age, sex, and body mass index (BMI), were assessed at the time of hospital admission based on information obtained from patients' medical history, medication records, admission interviews, and initial clinical examinations.

Additional variables included disease severity, local and systemic complications, number of prior AP episodes, inflammatory markers (e.g., C-reactive protein, white blood cell count, procalcitonin), and other laboratory parameters. Data completeness and the Centre distribution are presented in Table 1-2. In total, a broad set of clinical, demographic, and biochemical variables was considered.

Table 1. Data completeness of the analyzed cohort

Variables	Analyzed cohort	Uploaded data	Quality of data
Age	4,162	4,162	100.00%
Sex	4,162	4,162	100.00%
BMI	4,162	3,921	94.21%
Etiology	4,162	4,162	100.00%
Smoking	4,162	4,063	97.62%
Alcohol consumption	4,162	4,075	97.91%
Diabetes	4,162	4,157	99.88%
Diabetes type	1,002	976	97.41%
Insulin treatment before acute pancreatitis	1,002	967	96.51%
Medication taken regularly	4,162	3,058	73.47%
Pancreas morphology	4,162	4,118	98.94%
Recurrent acute pancreatitis	4,162	4,083	98.10%
Chronic pancreatitis	4,162	4,118	98.94%
Systolic blood pressure	4,162	3,794	91.16%
Diastolic blood pressure	4,162	3,791	91.09%
Hemoglobin A1c level	4,162	2,724	65.45%
Glucose	4,162	3,676	88.32%
Cholesterol	4,162	1,285	30.87%
Triglycerides	4,162	2,208	53.05%
C-reactive protein (CRP)	4,162	3,790	91.06%
White blood cell (WBC) count	4,162	3,991	95.89%
Amylase	4,162	4,134	99.33%
Lipase	4,162	3,901	93.73%

Table 2. Centre distribution

Institute	City	Country	Number of cases
First Department of Medicine, University of Pécs	Pécs	Hungary	1,351
Institute of Pancreatic Diseases, Semmelweis University	Budapest	Hungary	1,309
Szent György University Teaching Hospital of County Fejér	Székesfehérvár	Hungary	464
Department of Medicine, University of Szeged	Szeged	Hungary	460
Division of Gastroenterology, Department of Internal Medicine, University of Debrecen	Debrecen	Hungary	164
Bajcsy-Zsilinszky Hospital	Budapest	Hungary	78
County Emergency Clinical Hospital of Târgu Mures - Gastroenterology Clinic and University of Medicine, Pharmacy, Sciences and Technology "George Emil Palade"	Targu Mures	Romania	72
Dr. Bugyi István Hospital	Szentes	Hungary	38
Saint Luke Clinical Hospital	St. Petersburg	Russia	30
Békés County Central Hospital, Dr. Réthy Pál Hospital, 2nd Ward of Gastroenterology	Békéscsaba	Hungary	28
Vilnius University Hospital Santariskiu Klinikos	Vilnius	Lithuania	28
Markusovszky University Teaching Hospital	Szombathely	Hungary	24
General Surgery, Consorci Sanitari del Garraf	Sant Pere de Ribes	Spain	23
Helsinki University Central Hospital	Helsinki	Finland	15
Digestive Tract Care Center, Vítkovická hospital a.s.	Ostrava	Czech Republic	13
Hospital of Bezmialem Vakif University, School of Medicine	Istanbul	Turkey	12
Gomel Regional Clinical Hospital	Gomel	Belarus	8
Gastroenterology, Hepatology and Nutritional Centre, Pauls Stradins Clinical University Hospital	Riga	Latvia	7
Békés County Pándy Kálmán Hospital, 3rd Department of Internal Medicine and Gastroenterology	Gyula	Hungary	6
S. Andrea Hospital University "Sapienza"	Rome	Italy	6
Bogomolets National Medical University	Kiev	Ukraine	6
Second Department of Internal Medicine, Semmelweis University	Budapest	Hungary	5
Medical Academy named after SI Georgievsky	Simferopol	Russia	5
Clinical Hospital Center Rijeka	Rijeka	Croatia	4
Keio University	Tokyo	Japan	2
Jahn Ferenc Dél-Pest Hospital and Clinic	Budapest	Hungary	1
Uzsoki Street Hospital	Budapest	Hungary	1
Veszprém County Csolnoky Ferenc Hospital	Veszprém	Hungary	1
Central Military Emergency Hospital "Dr Carol Davila"	Bucharest	Romania	1

Total	4,162
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7.1.5. *Statistical Analysis*

Descriptive statistics were calculated using mean, standard deviation (SD), as well as median, range, and interquartile range (IQR) for continuous variables, and counts with relative frequencies for categorical variables.

To compare continuous variables between patients group we used Welch two-sample t-test, while Pearson's Chi-square test was applied for categorical variables.

We conducted univariate and multivariate logistic regression analysis to examine the associations between the independent patient characteristics and diagnostic enzyme elevation. In the final univariate model, Amylase and lipase values, treated as continuous response variables, were log10-transformed. Furthermore, both enzymes were analyzed as dichotomous variables as well. In the multivariate logistic regression model, we included no diagnostic enzyme elevation as a dependent binary variable and sex, age, diabetes, CP and etiology as independent explanatory variables.

In all statistical analyses, a threshold of $p < 0.05$ was deemed statistically significant.

The t-test, Chi-square test, and logistic regressions were conducted in R version 4.1.3 (R Core Team, 2025). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. (<<https://www.R-project.org/>>.)

7.1.6. *Predictors and Machine Learning Models*

The machine learning analysis was conducted as an exploratory, hypothesis-generating approach to identify variables associated with pancreatic enzyme levels in either direction. In contrast to the hypothesis-driven multivariable logistic regression presented in the main manuscript, which focused on patient-related factors associated with non-diagnostic enzyme levels, the machine learning model aimed to capture overall predictive contributions and complex interactions among clinical variables. Feature importance rankings derived from this approach, therefore, reflect predictive relevance rather than independent causal or mechanistic effects.

We trained an extreme gradient boosting (XGBoost) model to predict the clinical outcome of interest, using a 70:30 train-test split. The analysis was performed in R (version 4.4.2) using the xgboost, SHAPforxgboost, and shapviz packages. To identify

the most influential predictors and understand their contributions to individual predictions, we applied SHapley Additive exPlanations (SHAP) [20], a modern tool for model-agnostic interpretability.

Predictor variables were entered simultaneously into the XGBoost model without prior feature selection. Model hyperparameters were optimized using grid search combined with 5-fold cross-validation on the training set. For each hyperparameter configuration, the optimal number of boosting iterations was determined via early stopping based on cross-validated root mean squared error (RMSE). The final model was trained on the full training set using the hyperparameter combination that minimized cross-validated RMSE and was subsequently evaluated on the held-out test set to assess out-of-sample performance.

SHAP values quantify the marginal contribution of each feature to the model's prediction for each patient. Formally, the SHAP value of a feature represents the difference between the predicted outcome with that feature included and the expected prediction over the dataset, averaged across all possible combinations of features. This decomposition allows both global interpretability (assessing which predictors are generally most important across all patients) and local interpretability (explaining the prediction for an individual patient).

SHAP summary plots visualize these contributions:

Each row represents a predictor, ordered by its mean absolute SHAP value (overall importance).

Each dot represents an individual patient, positioned along the x-axis according to that feature's SHAP value (positive: pushes prediction upward, negative: pushes prediction downward).

The color indicates the feature value (low: yellow, high: purple), providing insight into the direction of association.

The spread of points shows the heterogeneity of the feature's effect across patients.

Acute inflammatory markers such as C-reactive protein (CRP) and WBC ranked highly in the machine learning feature importance analysis, reflecting their strong predictive contribution in the acute inflammatory setting. As feature importance is influenced by variable scale, variability, and correlation structure, these findings should be interpreted

as indicators of short-term inflammatory burden rather than chronic patient-related risk factors.

Predictor variables were entered simultaneously into the XGBoost model without prior feature selection. Model hyperparameters were optimized using grid search combined with 5-fold cross-validation on the training set. For each hyperparameter configuration, the optimal number of boosting iterations was determined via early stopping based on cross-validated root mean squared error (RMSE). The final model was trained on the full training set using the hyperparameter combination that minimized cross-validated RMSE and was subsequently evaluated on the held-out test set to assess out-of-sample performance. While the primary interpretation is based on the original-scale models for clinical interpretability, the log-transformed models were retained due to their slightly improved predictive performance. Importantly, the SHAP results were qualitatively consistent across the original and log-transformed specifications, indicating robust predictor–outcome relationships that are not sensitive to outcome scaling. SHAP values quantify the marginal contribution of each feature to the model’s prediction for each patient. Formally, the SHAP value of a feature represents the difference between the marginal contribution of the model prediction when the feature is included and when the feature is not included.

7.2. Study II. – Concomitant virus infection increases mortality and worsens the outcome of acute pancreatitis: a systematic review and meta-analysis

7.2.1. Methodology and Protocol

This study was designed as a systematic review and meta-analysis to assess the impact of viral infections on clinical outcomes in patients with AP. Established international methodological standards were followed to ensure transparency, reproducibility, and scientific rigor.

The reporting of this study adhered to the PRISMA 2020 guideline [21]. In addition, the methodological approach was based on the recommendations of the Cochrane Handbook, and the study protocol was prospectively registered in PROSPERO (registration number CRD42023400683) [22].

7.2.2. Eligibility Criteria

Studies were eligible for inclusion if they reported patients with AP and concomitant viral infection, regardless of virus type, and provided data on at least one of the following outcomes: mortality, disease severity, or AP-related complications.

Studies focusing on CP or pancreatic cancer populations were excluded, as were reviews, in vitro studies, animal experiments, and clinical guidelines. No restrictions were applied regarding age, sex, language, or publication period.

A broad inclusion strategy was applied to capture the full spectrum of viral infections potentially associated with AP and to reduce the risk of selection bias.

7.2.3. Information Sources and Search Strategy

A systematic literature search was performed in PubMed, Embase, and the Cochrane Library on 18 February 2023. In addition, a search for Chinese-language publications was conducted on 28 April 2023 using the China Science and Technology Journal Database (VIP), China National Knowledge Infrastructure (CNKI), and Wanfang databases.

The search strategy was developed in both English and Chinese and consisted of three conceptual domains.

English search terms for PubMed, Embase, and Cochrane Library

((acute) OR (Biliary))

AND

(Pancreatitis)

AND

((Virus) OR (Viral) OR (Mumps) OR (Coxsackie B) OR (Epstein-Barr) OR (EBV) OR (rubella) OR

(rubeola) OR (measles) OR (influenza) OR (hepatitis) OR (HAV) OR (HBV) OR (HCV) OR (HDV)

OR (HEV) OR (COVID-19) OR (SARS-CoV-2) OR (coronavirus) OR (“human immunodeficiency virus”) OR (HIV) OR (AIDS) OR (herpes simplex) OR (HSV) OR (varicella) OR (VZV) OR (chickenpox) OR (West Nile) OR (WNV) OR (Cytomegalo*) OR (CMV) OR (“Hemorrhagic fever virus”))

Wanfang Data Knowledge Service Platform

全部:("急性胰腺炎" or "胆源性胰腺炎")AND 全部:("病毒" OR "腮腺炎" OR "疱疹" OR "麻疹" OR "流感" OR "甲肝" OR "乙肝" OR "丙肝" OR "丁肝" OR "戊肝" OR "甲型肝炎" OR "乙型肝炎" OR "丙型肝炎" OR "丁型肝炎" OR "戊型肝炎" OR "新冠" OR "SARS" OR "人类免疫缺陷" OR "艾滋" OR "HIV" OR "水痘" OR "出血热" OR "登革热")

China Science and Technology Journal Database (VIP database)

U=("急性胰腺炎" OR "胆源性胰腺炎") AND U= ("病毒" OR "腮腺炎" OR "疱疹" OR "麻疹" OR "流感" OR "甲肝" OR "乙肝" OR "丙肝" OR "丁肝" OR "戊肝" OR "甲型肝炎" OR "乙型肝炎" OR "丙型肝炎" OR "丁型肝炎" OR "戊型肝炎" OR "新冠" OR "SARS" OR "人类免疫缺陷" OR "HIV" OR "艾滋" OR "水痘" OR "出血热" OR "登革热")

China National Knowledge Infrastructure (CNKI)

TKA=('急性胰腺炎'+ '胆源性胰腺炎') AND TKA=('病毒'+ '腮腺炎'+ '疱疹'+ '麻疹'+ '流感'+ '甲肝'+ '乙肝'+ '丙肝'+ '丁肝'+ '戊肝'+ '甲型肝炎'+ '乙型肝炎'+ '丙型肝炎'+ '丁型肝炎'+ '戊型肝炎'+ '新冠'+ 'SARS'+ '人类免疫缺陷'+ '艾滋'+ '水痘'+ '出血热'+ '登革热')

The reference search was conducted after full-text selection with Rayyan [23].

7.2.4. Study Selection and Data Extraction

Study selection was performed independently by four reviewers (G.C., P.M., J.B., and X.L.) following removal of duplicate records. Titles and abstracts were first screened, followed by full-text assessment according to predefined eligibility criteria. Any disagreements were resolved through discussion with a third independent reviewer (A.S.).

Data extraction was conducted independently by three authors (G.C., P.M., and X.L.) using a standardized data collection form.

The following information was extracted from each eligible study: title, first author, year of publication, country, study design, key findings, patient characteristics, type of viral infection (exposure), and outcomes. Primary outcomes included in-hospital mortality and 30-day mortality. Secondary outcomes included disease severity and AP-related complications, such as pancreatic necrosis, organ failure, and sepsis.

7.2.5. Risk of Bias and Quality of Evidence Assessment

Risk of bias was assessed using the Quality in Prognostic Studies (QUIPS) tool for cohort studies and the Joanna Briggs Institute (JBI) checklist for case reports.

The assessment was independently performed by three reviewers (G.C., P.M., and X.L.), with disagreements resolved through consultation with a fourth investigator (A.S.).

7.2.6. Data Synthesis and Analysis

As we assumed considerable between-study heterogeneity in all cases, a random-effects model was used to pool effect sizes using the frequentist framework. (a priori, given expected clinical and methodological heterogeneity across studies)

The proportion of presence or absence of virus infection and odds ratio (OR) with 95% confidence interval (CI) were used for the main effect size measure. We report proportion difference (risk difference, RD) at the study level. To calculate study proportions, pooled proportions, and OR, the total number of patients and those with the event of interest in each group was separately extracted from the studies. For OR (and RD), we reported the results as the odds (or risk probability) for virus infection present versus (minus for RD) the odds for no virus infection.

We performed two types of analyses. "Classical 2-level" random-effects meta-analyses were performed to pool OR of different two-arm studies and compare the presence and absence of virus infection using the Mantel–Haenszel method, with the exact Mantel–Haenszel approach (without continuity correction) applied to handle zero cell

counts. To include one-arm studies too, for pooling proportions, we conducted an additional analysis using the "3-level" model, accounting for the dependency of multiple observations within the same study and thereby allowing inclusion of single-arm data.

In the 3-level model, observed proportions were logit-transformed, and a continuity correction (adding 0.5 to zero-event cells and corresponding totals) was applied where necessary. Pooled estimates were calculated using inverse variance weighting with restricted maximum likelihood estimation.

Results were considered statistically significant if the pooled CI did not contain the null value, with Hartung–Knapp adjustment applied where it provided more conservative estimates. We summarized the findings of the meta-analysis in forest plots. Between-study heterogeneity was described by the estimated between-study variance (τ^2) using the Paule–Mandel method with Q-profile CIs and the I^2 statistic (for 3-level models, I^2 was decomposed across levels and reported as total heterogeneity). We reported the prediction interval when meaningful.

Subgroup differences were assessed using the Cochran Q test (omnibus test), with a significance level of 5%.

Small study publication bias was assessed by visual inspection of funnel plots and by modified Egger's test (Harbord method for 2-level models and Begg and Mazumdar rank correlation for 3-level models), acknowledging the limited power of these approaches in analyses with a small number of studies (approximately <10 studies or <25 study records).

For case reports, we estimated survival curves and survival probabilities using the Kaplan-Meier method [24], noting that potential dependence between patients from the same study was not accounted for.

Potential outliers and influential studies were identified using influence diagnostics, including *dfbetas*, Cook's distances, and hat values, in a leave-one-out framework. No substantial evidence of publication bias or influential outliers was identified; therefore, these results are not presented in detail, except for the primary outcome (in-hospital mortality).

All statistical analyses were calculated by R software (v4.3.2) [25] using the *meta* (v6.5.0) [26] package for basic meta-analysis calculations and plots, *metafor* (v4.4.0) [27] for 3-level models, and *dmetar* (v0.1.0) [28] package for additional influential analysis calculations and plots. For survival, the *survival* (v3.5.8) [29] package was used.

8. RESULTS

8.1. Study I. – Low-enzyme acute pancreatitis: a diagnostic blind spot in current guidelines

8.1.1. Basic characteristics of the cohort

The median age of the cohort was 57 (IQR: 44-70) and 56.7% of patients was male. The most common etiology was biliary (44.1%, followed by alcohol-induced (25.1%) and hypertriglyceridemia-induced (6.6%). Altogether, 32.2% of the patients had moderately severe and severe AP. The baseline characteristics of the study cohort, including demographic, clinical, and etiological variables, are summarized in Table 3.

Table 3. Characteristics of the analyzed cohort

Variable	N = 4,162
Age in years, median (IQR)	57 (44-70)
Mean (SD)	56.9 (17.2)
Min; max	18; 96
Male, n (%)	2,361 (56.7%)
Etiology, n (%)	
Biliary	1,835 (44.1%)
Alcoholic	1,046 (25.1%)
Hypertriglyceridemia	275 (6.6%)
Alcoholic and hypertriglyceridemia	261 (6.3%)
Post-ERCP	104 (2.5%)
Idiopathic	915 (22.0%)
Severity	
Mild, n (%)	2,822 (67.8%)
Moderate, n (%)	1,032 (24.8%)
Severe, n (%)	308 (7.4%)
Mortality, n (%)	127 (3.1%)
Length of stay in days, median (IQR)	7 (5-10)
Mean (SD)	8.9 (8.6)
Min; max	1; 244
Patients with local complication, n (%)	1,082 (26.0%)
Acute pancreatic fluid collection, n (%)	774 (18.6%)
Pseudocyst, n (%)	255 (6.1%)
Acute necrotic collection, n (%)	457 (11.0%)
Patients with systemic complication, n (%)	572 (13.7%)
Respiratory failure, n (%)	427 (10.3%)
Heart failure, n (%)	142 (3.4%)
Renal failure, n (%)	253 (6.1%)
Diabetes, n (%)	1,002 (24.1%)

N, n: number of cases, SD: standard deviation, ERCP: endoscopic retrograde cholangiopancreatography, IQR: interquartile range

8.1.2. Diabetes is associated with lower pancreatic enzyme levels

Diabetic patients exhibited significantly lower pancreatic enzyme levels compared to non-diabetic patients. Mean serum amylase levels were 834 (± 921) U/L in patients with diabetes versus 1,018 ($\pm 1,145$) U/L in those without diabetes ($p < 0.0001$). Similarly, mean lipase levels were reduced in diabetic patients ($2,161 \pm 2,944$ U/L vs $2,415 \pm 3,134$ U/L, $p = 0.0239$) (Figure 1).

In line with these findings, diabetes was significantly associated with an increased likelihood of non-diagnostic enzyme levels at admission. The OR for non-diagnostic amylase levels was 1.34 (95% CI: 1.12–1.60, $p = 0.001$), while for lipase it was 1.35 (95% CI: 1.03–1.77, $p = 0.029$).

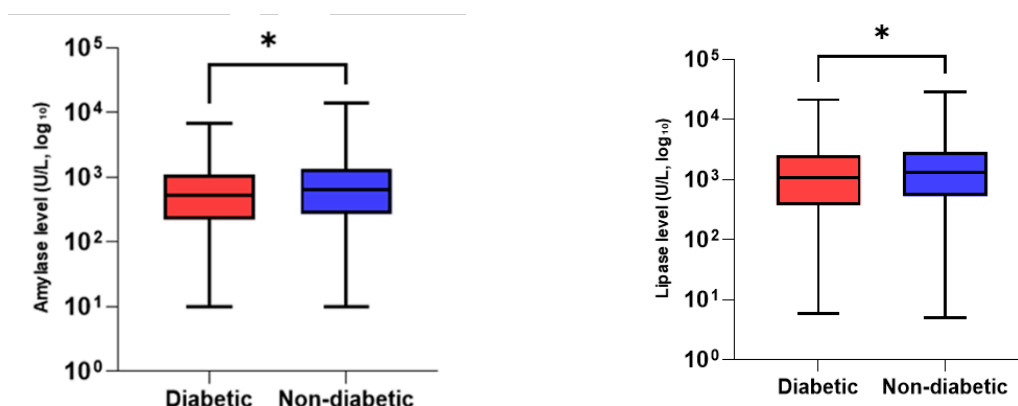


Figure 1. Comparison of log-transformed admission amylase and lipase levels between diabetic and non-diabetic patients [30] (Welch Two Sample t-test, *significant difference)

8.1.3. Multiple patient-related factors contribute to reduced enzyme levels

Beyond diabetes, several clinical factors were identified as being associated with lower pancreatic enzyme levels.

Using a machine learning-based exploratory analysis, smoking, alcohol-related etiology, diabetes, and (CP) emerged as important predictors of reduced enzyme levels (Figure 2). For completeness, the outcome variables were additionally log-transformed

to account for skewness and improve predictive performance; the corresponding SHAP results are shown in Figure 3. These findings suggest that both chronic pancreatic damage and metabolic factors contribute to attenuated biochemical responses during AP.

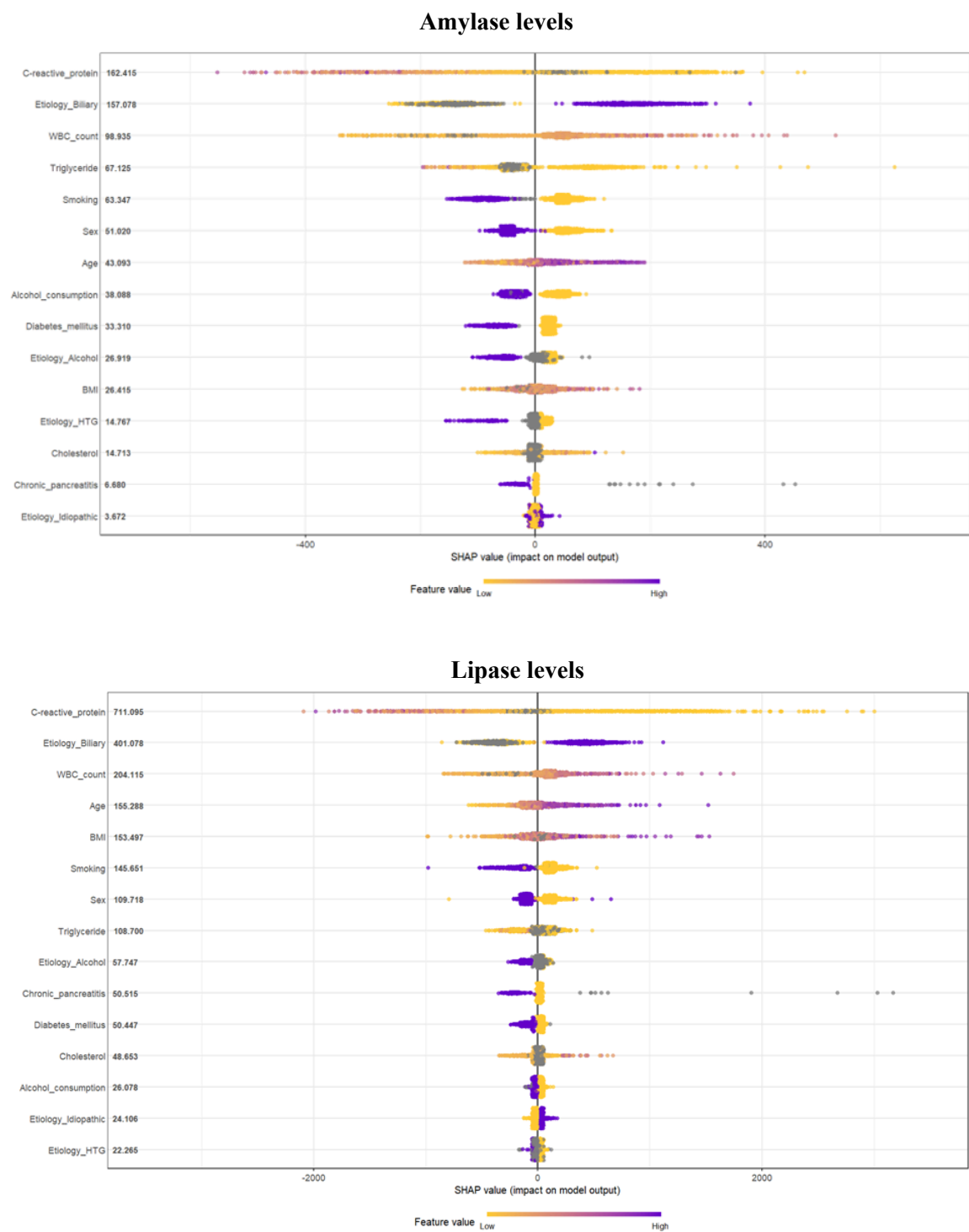


Figure 2. Variables associated with amylase and lipase levels [30](SHAP values)

WBC: white blood cell, BMI: body mass index, HTG: hypertriglyceridemia

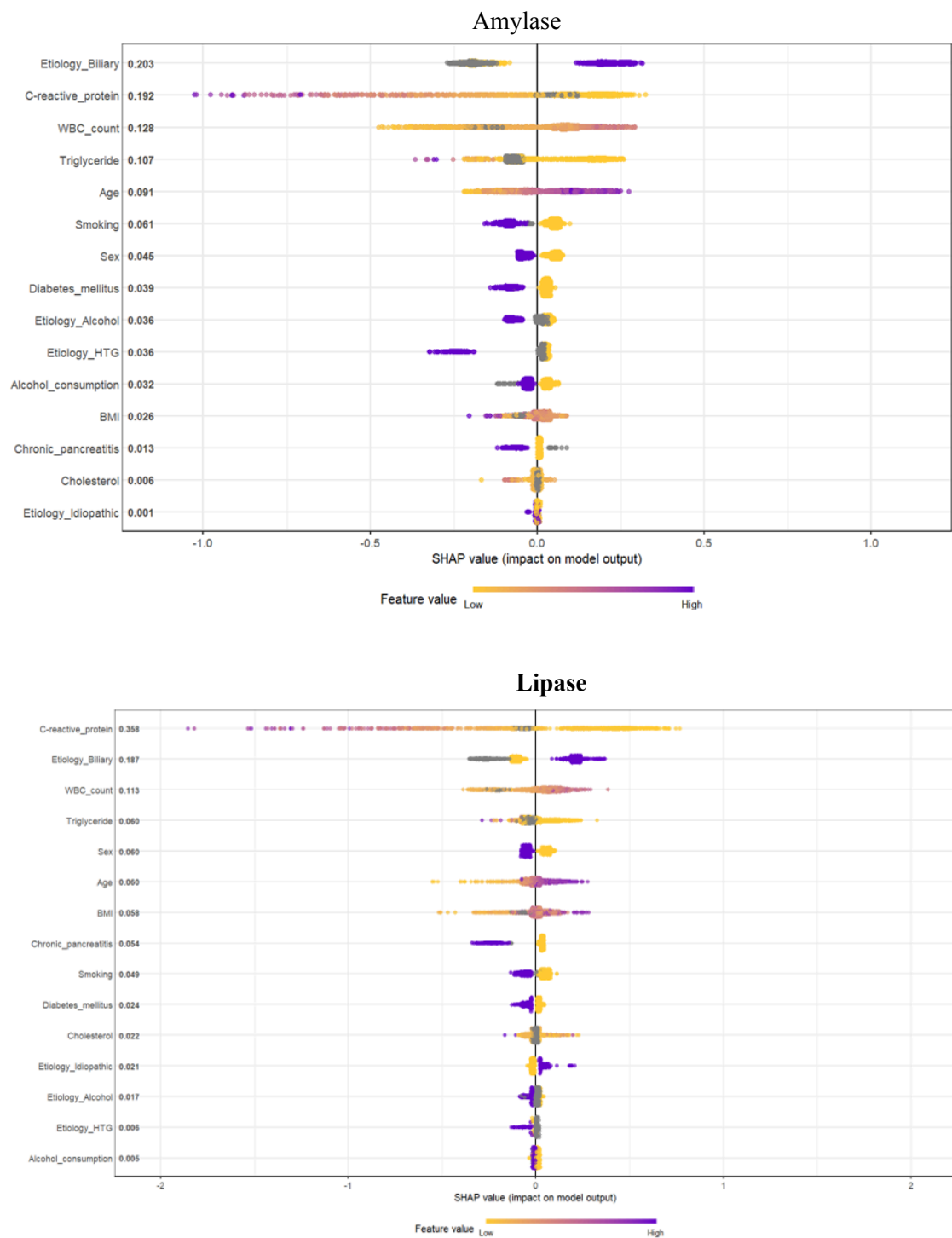


Figure 3. Variables associated with log amylase and log lipase levels [30](SHAP values)

WBC: white blood cell, BMI: body mass index, HTG: hypertriglyceridemia

8.1.4. A substantial proportion of acute pancreatitis cases present without diagnostic enzyme elevation

Among the study population, 268 patients (6.7%) were diagnosed with AP despite not meeting the biochemical diagnostic criterion of elevated pancreatic enzymes. These diagnoses were established based on abdominal pain and imaging findings.

Compared with patients who had diagnostic enzyme elevation, those without diagnostic enzyme levels had a significantly higher prevalence of several risk factors. Diabetes was present in 33.2% versus 23.7% ($p < 0.001$), smoking in 44.1% versus 35.0% ($p = 0.003$), and CP in 18.3% versus 10.0% ($p < 0.001$) (Table 4).

Table 4. Descriptive statistics of groups of patients with and without diagnostic pancreatic enzyme elevation in the acute pancreatitis cohort

		Overall	No	Yes	p-value*
Characteristic	N	N = 3,993 (100%)	N = 3,725 (93%)	N = 268 (6.7%)	
Age	3,993 (100%)				0.003
N non-missing		3,993	3,725	268	
Mean (SD)		57.0 (17.3)	57.2 (17.3)	54.2 (16.3)	
Median (IQR)		57.0 (44.0, 71.0)	57.0 (44.0, 71.0)	55.0 (42.0, 66.0)	
Min; Max		18.0; 96.0	18.0; 96.0	18.0; 89.0	
Sex	3,993 (100%)				<0.001
Female		1,738 (44%)	1,649 (44%)	89 (33%)	
Male		2,255 (56%)	2,076 (56%)	179 (67%)	
BMI	3,993 (94%)				0.846
N Non-missing		3,758	3,511	247	
Mean (SD)		28.3 (6.2)	28.3 (6.2)	28.4 (6.6)	
Median (IQR)		27.5 (24.1, 31.8)	27.5 (24.1, 31.7)	27.6 (23.9, 32.3)	
Min; Max		13.2; 62.4	13.2; 62.4	14.5; 47.4	
Missing data		235	214	21	
Diabetes mellitus	3,993 (100%)				<0.001
No		3,017 (76%)	2,838 (76%)	179 (67%)	
Yes		971 (24%)	882 (24%)	89 (33%)	
Missing data		5	5	0	
Chronic pancreatitis	3,993 (99%)				<0.001
No		3,538 (89%)	3,323 (90%)	215 (82%)	
Yes		416 (11%)	368 (10.0%)	48 (18%)	
Missing data		39	34	5	
C-reactive protein	3,993 (91%)				<0.001
N Non-missing		3,637	3,402	235	

Mean (SD)		56.6 (79.8)	51.7 (73.7)	127.2 (120.3)	
Median (IQR)		21.2 (6.5, 73.4)	19.2 (6.1, 66.0)	91.3 (25.8, 205.1)	
Min; Max		0.1; 590.9	0.1; 590.9	0.5; 587.0	
Missing data		356	323	33	
Smoking	3,993 (98%)				0.003
No		2,510 (64%)	2,364 (65%)	146 (56%)	
Yes		1,389 (36%)	1,274 (35%)	115 (44%)	
Missing data		94	87	7	
Etiology	3,993 (100%)				<0.001
Idiopathic		884 (22%)	812 (22%)	72 (27%)	
Alcohol		801 (20%)	737 (20%)	64 (24%)	
Alcohol-HTG		98 (2.5%)	85 (2.3%)	13 (4.9%)	
Biliary		1,702 (43%)	1,639 (44%)	63 (24%)	
HTG		141 (3.5%)	123 (3.3%)	18 (6.7%)	
Other		367 (9.2%)	329 (8.8%)	38 (14%)	

*Welch Two Sample t-test; Pearson's Chi-squared test. N: case number, SD: standard deviation, IQR: interquartile range

8.1.5. Independent predictors of non-diagnostic enzyme elevation

In multivariable logistic regression analysis, DM and CP remained independently associated with non-diagnostic pancreatic enzyme levels (Table 5).

Table 5. Independent risk factors of pancreatic enzyme levels not reaching the diagnostic criterion.

Variable	N	Event N	OR	95% CI	p-value
Sex	3,723	243			
Female	1,619	79	1.000	—	
Male	2,104	164	1.220	0.902, 1.650	0.201
Age	3,723	243	0.996	0.987, 1.000	0.341
BMI	3,723	243	1.010	0.991, 1.040	0.235
Diabetes mellitus	3,723	243			
No	2,822	160	1.000	—	
Yes	901	83	1.500	1.100, 2.040	0.011
Chronic pancreatitis	3,723	243			
No	3,323	197	1.000	—	
Yes	400	46	1.640	1.120, 2.350	0.009
Etiology	3,723	243			
Idiopathic	817	63	1.000	—	
Alcohol	751	59	0.944	0.636, 1.400	0.776
Alcohol-HTG	91	11	1.500	0.712, 2.910	0.256
Biliary	1,590	58	0.499	0.340, 0.730	<0.001
HTG	130	18	1.450	0.782, 2.580	0.221
Other	344	34	1.230	0.781, 1.900	0.363

Dependent variable: No diagnostic enzyme elevation (amylase <300 U/L, lipase <180 U/L), Reference: diagnostic enzyme elevation. Odds ratios were derived from a

multivariable logistic regression model mutually adjusted for all variables listed. N: number of patients with available data for each variable, Event N: the number of patients whose outcome was the absence of diagnostic enzyme elevation. OR: odds ratio, CI: confidence interval, HTG: hypertriglyceridemia

To assess the potential influence of acute inflammatory burden on the primary multivariable model, a sensitivity analysis was performed including CRP and WBC as additional covariates. CRP was entered as a continuous variable without rescaling. The outcome remained non-diagnostic pancreatic enzyme elevation. The results of this sensitivity analysis are presented in Table 6.

Table 6. Sensitivity analysis of factors associated with non-diagnostic pancreatic enzyme levels including inflammatory markers (CRP and WBC)

Dependent variable: No enzyme elevation (amylase <300, lipase <180), Ref: No

Variable	N	Event N	OR	95% CI	p-value
(Intercept)	3,359	210	0.057	0.020, 0.156	<0.001
Sex	3,359	210			0.607
Female	1,435	65	1	—	
Male	1,924	145	1.09	0.779, 1.54	0.607
Age	3,359	210	0.994	0.984, 1.00	0.214
BMI	3,359	210	1.02	0.994, 1.05	0.136
Diabetes	3,359	210			0.108
No	2,554	136	1	—	
Yes	805	74	1.33	0.939, 1.86	0.104
Chronic pancreatitis	3,359	210			0.004
No	3,006	169	1	—	
Yes	353	41	1.87	1.23, 2.80	0.003
C-reactive protein	3,359	210	1.01	1.01, 1.01	<0.001
White Blood Cell Count	3,359	210	0.953	0.923, 0.983	0.002
Etiology	3,359	210			0.002
Idiopathic	746	56	1	—	
Alcohol-induced	679	51	0.76	0.488, 1.18	0.222
Alcohol-HTG	84	9	0.89	0.365, 1.95	0.784
Biliary	1,463	49	0.457	0.299, 0.695	<0.001
HTG	102	16	0.929	0.445, 1.85	0.84
Other	285	29	1.18	0.714, 1.92	0.504

CRP was included as a continuous variable. WBC was included as a continuous variable. The model otherwise corresponds to the multivariable analysis presented in Table 5 of the main manuscript.

Abbreviations: N: number, Event N: number of patients without diagnostic enzyme elevation, CI: confidence interval, OR: odds ratio, HTG: hypertriglyceridemia

Null deviance = 1,571; Null df = 3,358; Log-likelihood = -687; AIC = 1,399; BIC = 1,479; Deviance = 1,373; Residual df = 3,346; No. Obs. = 3,359

8.2. Study II. – Concomitant virus infection increases mortality and worsens outcome of acute pancreatitis: a systematic review and meta-analysis

8.2.1. Study Search and Selection

Overall, 9,287 records were identified, and after duplicate removal, title, abstract, and full-text selection, 528 studies were included in our review, of which 29 studies with 2,295,172 patients were eligible for meta-analysis (19 investigating concomitant SARS-CoV-2 and 10 reporting concomitant HIV infection). A total of 499 articles with 858 patients were included in the qualitative synthesis. The selection process is detailed in the PRISMA Flowchart (Figure 4)[31].

The basic characteristics of the 29 studies included in the meta-analysis [32-60] are detailed in Table 6[31].

Besides the SARS-CoV-2 and HIV cohort studies, we collected data from 858 cases of AP with concomitant viral infections. The number of articles and patients with different virus infections is presented in Table 7[31].

Among the 858 AP patients with concomitant virus infection, there was a high proportion of missing data. The median age was 39.0 years (Q1:25, Q3:27, N=587). Among the 675 patients where sex was reported, the majority were male (66.2%). The severity of AP is reported in 273 cases (31.8%), of which 92 (33.7%) were severe. Mortality data were available for 781 patients of which 129 (15.0%) died during the AP episode. The basic characteristics of this population are shown in Table 8. Mortality among the reported cases by virus type is presented in Table 9[31].

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

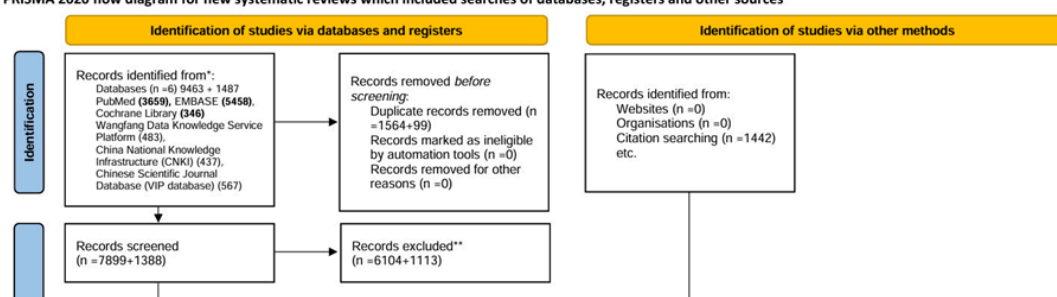


Figure 4. PRISMA 2020 flowchart representing the study selection process [31].

8.2.2. *Basic characteristics of included studies and patients*

A total of 29 cohort studies involving 2,295,172 patients were included in the meta-analysis, comprising populations from multiple countries, including the United States, the United Kingdom, Turkey, and others. Among these, the majority of studies investigated SARS-CoV-2 infection, while a smaller proportion focused on HIV. The sample sizes varied substantially, ranging from small cohorts (n=11) to large national databases exceeding one million patients. The mean age of participants, where reported, ranged from 35.2 to 64.1 years. The investigated outcomes primarily included mortality, severity of AP, and complications. The detailed characteristics of these studies are presented in Table 7.

In addition, 528 articles including 29,990 patients with virus-associated AP were analyzed. SARS-CoV-2 (35.3%) and HIV (63.4%) accounted for the vast majority of infections, while other viral etiologies were rare and mainly reported in case-based studies. The distribution of investigated viruses is summarized in Table 8.

For the qualitative synthesis, 858 patients were included. The median age was 39.0 years (Q1: 25.0; Q3: 57.0), with a predominance of male patients (66.2%). Mortality data were available for 781 patients, among whom 129 (15.0%) died during the AP episode. Severity data were reported in 273 cases, with 33.7% classified as severe AP. However, a substantial proportion of missing data was observed across variables. The baseline characteristics of these cases are shown in Table 9.

Mortality varied by viral etiology, with higher mortality observed in certain infections such as SARS-CoV-2 (17%) and hepatitis viruses, whereas HIV-associated AP showed comparatively lower mortality (9%). Detailed mortality by virus type is presented in Table 10. Overall, these data demonstrate considerable heterogeneity in patient populations, viral etiologies, and reported outcomes.

Table 7: Investigated viruses and the size of the population

Virus	No. of articles	No. of patients	% of all patients
SARS-CoV-2	177	10,576	35.27%
HIV	72	19,025	63.44%
adenovirus	2	5	0.02%
arbovirus	1	4	0.01%
cytomegalovirus	23	26	0.09%
coxsackievirus	8	9	0.03%
dengue virus	9	23	0.08%
EBV	20	20	0.07%
enterovirus	1	1	0.00%
H1N1	4	4	0.01%
hantavirus	21	33	0.11%
HAV	18	29	0.10%
HBV	34	39	0.13%
HCV	37	45	0.15%
hepatitis virus	4	21	0.07%
HEV	21	42	0.14%
HHV-6	1	1	0.00%
HSV	10	10	0.03%
Human T-lymphotropic virus 1	1	1	0.00%
Influenza	2	2	0.01%
Lyssavirus	1	1	0.00%
measles	4	5	0.02%
mumps	10	11	0.04%
Rift Valley fever viruses	1	1	0.00%
rotavirus	3	3	0.01%
VZV	21	24	0.08%
West Nile virus	1	1	0.00%
Multi virus infection	21	28	0.09%
Total Infected	528	29,990	100%
Total Control	29	604,085	100%

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; HIV: human immunodeficiency virus; EBV: Epstein-Barr virus; Influenza A virus subtype H1N1; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus; HHV-6: human herpesvirus 6; HSV: herpes simplex virus; VZV: varicella zoster virus.

Table 8. Basic characteristics of cohort studies included in the meta-analysis

Publication data		Demography					Exposure (virus infection)	Assessment outcome
First Author	Year	Country	Population	Age				
				Mean	SD	Range		
S. Pandanaboyana ⁴²	2021	UK	1,777	59.9	17.2	NA	SARS-CoV-2	M, S, C
B. Ebik ¹³	2021	Turkey	322	51.4	12.5	NA	SARS-CoV-2	M, C
M. S. Cappell ³⁰	1995	USA	88	35.2	8.1	4 to 90	HIV	M, C
C. Akarsu ²⁸	2020	Turkey	316	NA	NA	NA	SARS-CoV-2	M
H. V. M. Spiers ⁵⁵	2020	UK	1,628	NA	NA	NA	SARS-CoV-2	M, S
A. Dirweesh ³²	2022	USA	208	57.2	9.7	NA	SARS-CoV-2	M, C
A. Dirweesh ³³	2020	USA	75	49.7	14.8	NA	SARS-CoV-2	M, C
H. Han ³⁴	2019	USA	594,106	52.22	9.79	NA	HIV	M, C
F. G. Haydar ³⁵	2022	Turkey	55	60.3	17.9	NA	SARS-CoV-2	M, S, C
S. Inamdar ³⁶	2020	USA	189	52.36	16.6	NA	SARS-CoV-2	M, C
Y. Jiang ³⁷	2020	USA	28,333	46.5	0.3	18 to 90	HIV	M, C
R. Karaali ³⁹	2021	Turkey	189	57.92	17.99	beyond 18	SARS-CoV-2	M, C
P. T. Kroner ⁴⁶	2023	USA	6,365	48	NA	NA	HIV	M, C
J. Machicado ⁴⁷	2014	USA	72,297	NA	NA	NA	HIV	M
Ò. Miró ⁴⁰	2021	Spain	216	NA	NA	NA	SARS-CoV-2	M, C
J. Omoshoro-Jones ⁴⁸	2011	South Africa	24	NA	NA	26 to 63	HIV	M, S, C
J. Omoshoro-Jones ⁴⁹	2012	South Africa	27	NA	NA	26 to 63	HIV	S
V. S. Parithivel ⁵⁰	1999	USA	54	42	NA	NA	HIV	C
S. K. Patnaik ⁵¹	2021	India	27	NA	NA	NA	SARS-CoV-2	M, S
L. Prodehl ⁵²	2019	South Africa	110	NA	NA	NA	HIV	C
P. M. Radulescu ⁴³	2022	Romania	433	60.76	16.68	NA	SARS-CoV-2	M, C
O. Rotar ⁵³	2021	Ukraine	11	NA	NA	NA	SARS-CoV-2	M, S, C
J. Samanta ⁴⁴	2022	India	315	40.35	13	NA	SARS-CoV-2	M, S, C
H. Vatansev ⁴⁵	2021	Turkey	29	64.07	3.23	NA	SARS-CoV-2	M, S, C
F. Anderson ²⁹	2017	South Africa	627	NA	NA	12 to 89	HIV	M, C
D. Kang ³⁸	2023	Korea	4,133	NA	NA	beyond 18	SARS-CoV-2	M
H. Chaudhry ³¹	2023	USA	1,581,585	NA	NA	NA	SARS-CoV-2	M, C
C. Varghese ⁵⁶	2022	UK	1,476	NA	NA	NA	SARS-CoV-2	M, C
O. Sierra ⁵⁴	2021	Spain	157	NA	NA	NA	SARS-CoV-2	M, S, C

UK: United Kingdom; USA: United States of America; HIV: human immunodeficiency virus; M: mortality; S: severity of acute pancreatitis; C: complication of acute

pancreatitis; NA: not applicable; SD: standard deviation; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 9. Basic characteristics of cases included in the qualitative analysis

Age (years)	N=587
Mean (SD)	40.1 (20.9)
Median (Q1, Q3)	39.0 (25.0,57.0)
Min, Max	1.42, 94.0
Missing	271 (31.6%)
Sex	N=675
Female	228 (26.6%)
Male	447 (52.1%)
Missing	183 (21.3%)
Mortality	N=781
Alive	652 (76.0%)
Dead	129 (15.0%)
Missing	77 (9.0%)
Severity of AP	N=273
Mild	62 (22.7%)
Moderate	12(4.3%)
Severe	92(33.7%)
Mild or moderate	107(39.2%)
Missing	585(68.2%)

Table 10: Mortality of cases by virus type

Type of Virus Infection	Alive (N=652)(% within the virus population)	Died (N=129)(% within the virus population)	Overall (N=781)
Adenovirus	3 (60%)	2 (40%)	5 (0.6%)
Arbovirus (Yellow Fever)	0 (0%)	4 (100%)	4 (0.5%)
Cytomegalovirus	19 (73%)	7 (27%)	26 (3.3%)
Coxsackievirus	7 (87.5%)	1 (12.5%)	8 (1.0%)
Dengue Virus	6 (60%)	4 (40%)	10 (1.3%)
Hepatitis virus E	15 (75%)	5 (25%)	20 (2.6%)
Enterovirus	1 (100%)	0 (0%)	1 (0.1%)
Influenza A virus subtype H1N1	4 (100%)	0 (0%)	4 (0.5%)
Hantavirus	31 (94%)	2 (6%)	33 (4.2%)
Hepatitis virus A	26 (90%)	3 (10%)	29 (3.7%)
Hepatitis virus B	26 (67%)	13 (33%)	39 (5.0%)
Hepatitis virus C	44 (98%)	1 (2%)	45 (5.8%)
Hepatitis Virus	2 (25%)	6 (75%)	8 (1.0%)
Hepatitis virus E	38 (90%)	4 (10%)	42 (5.4%)
Human herpesvirus 6	0 (0%)	1 (100%)	1 (0.1%)
Human Immunodeficiency Virus	168 (91%)	16 (9%)	184 (23.6%)
Herpes simplex virus	9 (90%)	1 (10%)	10 (1.3%)
Human T-Lymphotropic Virus 1	1 (100%)	0 (0%)	1 (0.1%)
Influenza	2 (100%)	0 (0%)	2 (0.3%)
Lyssavirus	1 (100%)	0 (0%)	1 (0.1%)
Measles	3 (60%)	2 (40%)	5 (0.6%)
Multi Virus Infection	18 (64%)	10 (36%)	28 (3.6%)
Mumps	11 (100%)	0 (0%)	11 (1.4%)
Rift Valley Fever Viruses	1 (100%)	0 (0%)	1 (0.1%)
Rotavirus	3 (100%)	0 (0%)	3 (0.4%)
Severe acute respiratory syndrome coronavirus 2	194 (83%)	41 (17%)	235 (29.9%)
Varicella-zoster virus	19 (79%)	5 (21%)	24 (3.1%)
West Nile Virus	0 (0%)	1 (100%)	1 (0.1%)

8.2.3. SARS-CoV-2 infection worsens acute pancreatitis prognosis

8.2.3.1. Mortality of acute pancreatitis

We detected an 18% (CI: 0.12-0.27, $I^2=89\%$) prevalence of in-hospital mortality among the SARS-CoV-2-infected population of 10,053 patients, notably higher than the 6% (CI: 0.04-0.10, $I^2=89\%$) in the control group of 1,572 patients. Further details are presented in Table 11[31].

Ten articles [36; 37; 39; 40; 42-45; 47; 48], which were eligible for the two-arm study-based (2-level) meta-analysis, reported 79 deaths in 378 AP patients (20.9%) with concomitant SARS-CoV-2 infection versus 132 deaths in 1,572 AP patients (8.4%) without infection in hospital. Our analysis showed that patients with concurrent SARS-CoV-2 infection and AP exhibited heightened odds of in-hospital mortality compared to the control group (OR: 3.15, CI: 2.08-4.76, $I^2=1\%$, Figure 5). Three articles [46; 55; 59] reported on 30-day mortality (OR: 4.68, CI: 0.52-41.75, $I^2=23\%$, Figure 6) and showed a similar but not statistically significant result[31].

Table 11: Prevalence of different outcomes from 3-level meta-analysis model in infected and control populations

Virus	Outcome	Proportion Infected	CI 95%	No. of studies	No. of patients	Proportion Control	CI 95%	No. of studies	No. of patients
SARS-CoV-2	In-hospital mortality	0.18	0.12-0.27	14	10,053	0.06	0.04-0.10	10	1,572
SARS-CoV-2	Mild acute pancreatitis	0.46	0.18-0.77	5	294	0.69	0.36-0.90	4	2,008
SARS-CoV-2	Moderate acute pancreatitis	0.29	0.16-0.48	5	294	0.22	0.11-0.37	4	2,008
SARS-CoV-2	Severe acute pancreatitis	0.28	0.10-0.59	5	294	0.10	0.03-0.32	4	2,008
SARS-CoV-2	Necrosis	0.12	0.05-0.27	6	9,775	0.08	0.03-0.18	5	773
SARS-CoV-2	Respiratory organ failure	0.33	0.01-0.97	4	75	0.37	0.01-0.98	2	95
SARS-CoV-2	Acute kidney injury	0.28	0.17-0.42	6	9,775	0.20	0.11-0.34	3	325
HIV	In-hospital mortality	0.04	0.01-0.18	5	21,101	0.04	0.01-0.16	4	602,077
HIV	Sepsis	0.04	0.01-0.21	3	21,033	0.04	0.01-0.19	3	602,033

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HIV: Human Immunodeficiency Virus

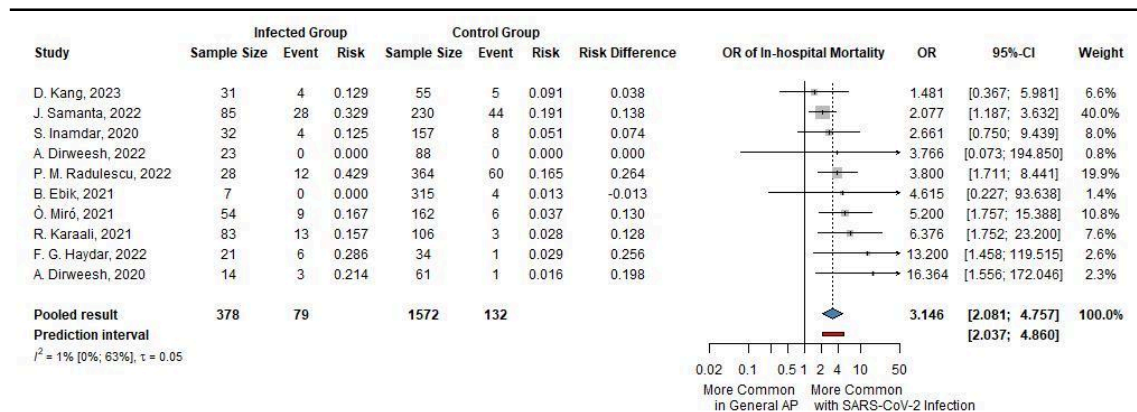


Figure 5. In-hospital mortality in acute pancreatitis patients with vs. without severe acute respiratory syndrome coronavirus 2 infection [31]

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AP: acute pancreatitis;
OR: odds ratio; CI: confidence interval

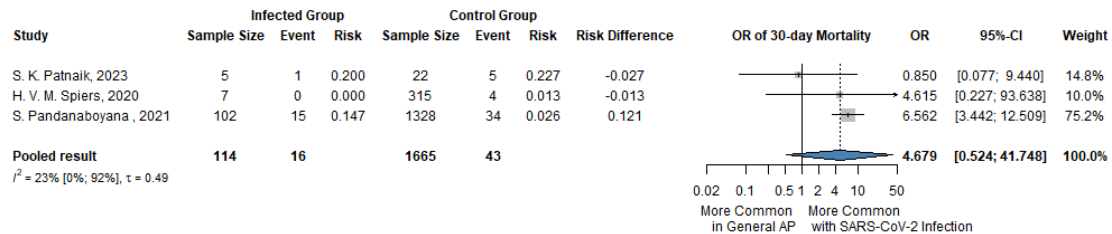


Figure 6. Forest plot of 30-day mortality in Coronavirus disease 2019 subgroup [31]

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AP: acute pancreatitis;
OR: odds ratio; CI: confidence interval

8.2.3.2. Severity of acute pancreatitis

The prevalence of severe AP in the infected group was 28% (CI: 0.10-0.59, $I^2=96\%$) vs. the 10% in the control group (CI: 0.03-0.32, $I^2=96\%$), whereas the prevalence for mild AP was 46% and 69%, respectively (Table 11). Patients with SARS-CoV-2 infection had higher odds for moderate or severe AP (OR: 2.72, CI: 1.03-7.15, $I^2=66\%$), as shown in Figure 7. Severe AP tended to be more common in the exposure group (OR: 4.91, CI: 0.44-54.66, $I^2=91\%$, Figure 8). However, the difference was not significant. Mild AP was less prevalent in patients with SARS-CoV-2 infection, as indicated by an OR of 0.37 (CI: 0.14-0.97, $I^2=66\%$, Figure 9). Overall, more severe AP are observed in SARS-CoV-2 infected population[31].

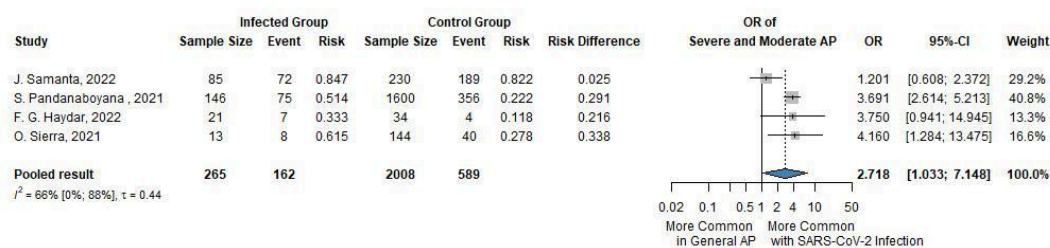


Figure 7 Moderate or severe acute pancreatitis in patients with severe acute respiratory syndrome coronavirus 2 infection vs. without infection [31]

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AP: acute pancreatitis; OR: odds ratio; CI: confidence interval

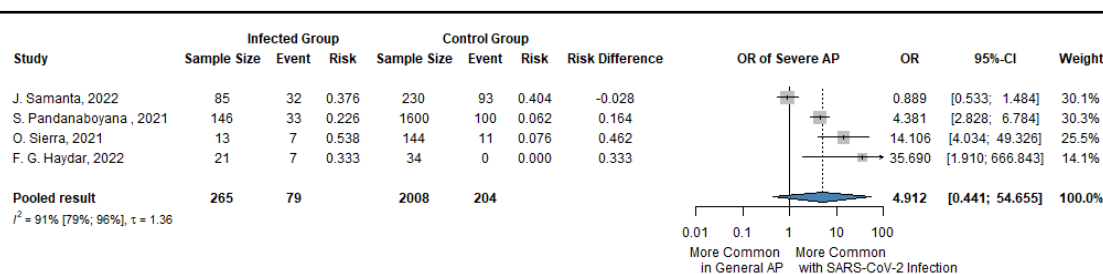


Figure 8. Forest plot of risk of severe acute pancreatitis in Coronavirus disease 2019 subgroup [31]

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AP: acute pancreatitis; OR: odds ratio; CI: confidence interval

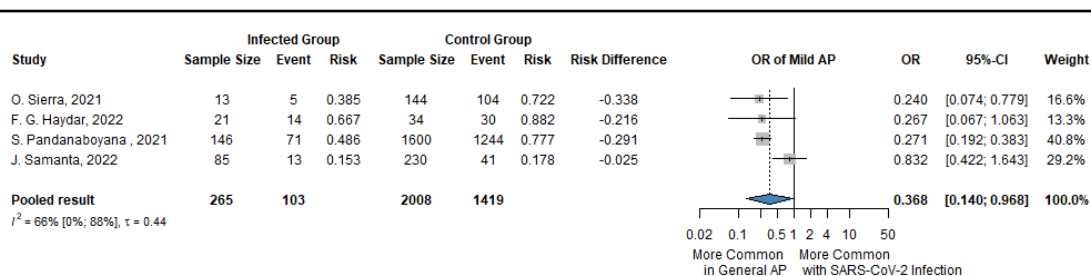


Figure 9. Forest plot of risk of mild acute pancreatitis in Coronavirus disease 2019 subgroup [31]

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AP: acute pancreatitis; OR: odds ratio; CI: confidence interval

8.2.3.3. Complications of acute pancreatitis

The risk of necrosis was notably increased in individuals with concurrent SARS-CoV-2 infection and AP, with an OR of 1.84 (CI: 1.13-2.98, $I^2=0\%$, Figure 10). Acute kidney injury as another complication had an OR of 1.44 (CI: 0.54-3.84, $I^2=0\%$, Figure 11)[31]. Prevalences of different complications in the infected and control groups are shown in Table 12[31].

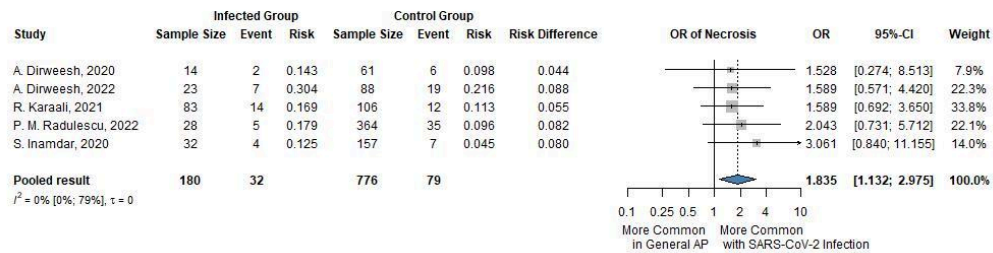


Figure 10. Necrosis in acute pancreatitis patients with severe acute respiratory syndrome coronavirus 2 infection vs. without infection [31]

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AP: acute pancreatitis; OR: odds ratio; CI: confidence interval

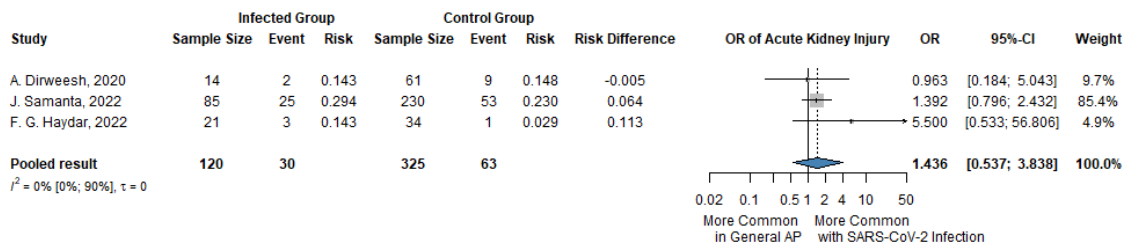


Figure 11. Forest plot of risk of acute kidney injury in Coronavirus disease 2019 subgroup [31]

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AP: acute pancreatitis; OR: odds ratio; CI: confidence interval

8.2.4. HIV infection had no impact on investigated acute pancreatitis outcomes

8.2.4.1. In-hospital mortality

The lack of a significant increase in in-hospital mortality in AP patients with HIV co-infection, as indicated by an OR of 1.12 (CI: 0.92-1.37, $I^2=0\%$, Figure 12A), shows that mortality is not significantly different between the infected and control groups[31].

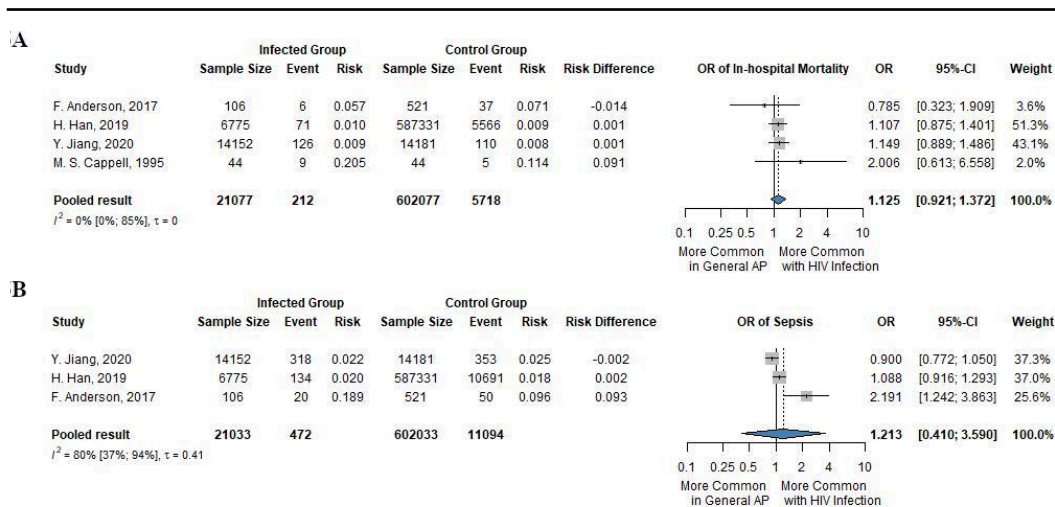


Figure 12. Acute pancreatitis outcomes in patients with concomitant human immunodeficiency virus infection. A. In-hospital mortality. B. Sepsis. [31]

HIV: human immunodeficiency virus; AP: acute pancreatitis; OR: odds ratio; CI: confidence interval

8.2.4.2. Sepsis

The odds of sepsis in individuals with both HIV infection and AP, with an OR of 1.21 (CI: 0.41-3.59, $I^2=80\%$, Figure 12B), show that the risk of sepsis has no significant difference between the infected and control groups[31].

8.2.5. Survival of acute pancreatitis patients with SARS-CoV-2 and hepatitis B virus (HBV) infection

Out of the 321 cases, we had follow-up time data, and data for time to death were available for 129 cases. The estimated survival probability was 55% (HBV) and about 53% (SARS-CoV-2) for patients presented at 90 days. Survival curves for patients infected with SARS-CoV-2 and HBV are shown in Table 12 and Figure 13. The curve reflected the similar trend for survival probability in both subgroups[31].

Table 12: 90-day survival probability for HBV and SARS-CoV-2 infected acute pancreatitis patients

	90 days survival probability	95% CI	number of patients	number of deaths	number of censored
HBV	0.55	0.36 - 0.85	21	8	5
SARS-CoV-2	0.53	0.4 - 0.69	108	32	63

CI: confidence interval; HBV: hepatitis virus B; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

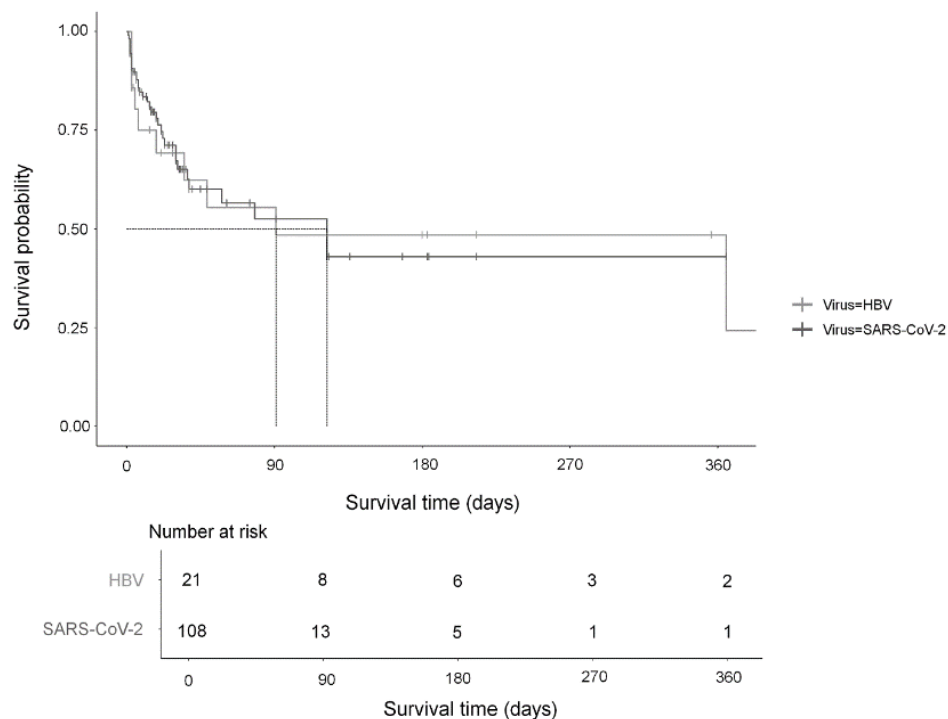


Figure 13. Kaplan-Meier Curve for AP patients with SARS-CoV-2 and HBV infection [31]

HBV: Hepatitis virus B; SARS-CoV-2: Severe acute respiratory syndrome coronavirus
2

8.2.6. Risk of Bias Assessment

The risk of bias assessments for cohort studies was presented in Table 13. Based on the QUIPS tool, 10 articles had a low risk of bias, 17 had a high and 2 had a moderate risk. In the COVID subgroup, the funnel plot for in-hospital mortality based on visual inspection showed a low risk for potential publication bias (Figure 14). The number of studies in the other analyses was highly limited. Therefore, the assessment of heterogeneity, publication bias, and influence of individual studies is limited or not reasonable. Among the cases included in the systematic review, the high proportion of severe AP and mortality may also be due to publication bias[31].

Table 13: Tabular display of risk of bias assessment for cohort studies with Quality in Prognostic Studies (QUIPS) tool

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting	Overall risk of bias
S. Pandanaboyana, 2021	"+"	"+"	?	"+"	"+"	"+"	"+"
B. Ebik, 2021	"+"	"+"	"_"	?	?	?	"_"
M S Cappell, 1995	?	?	?	"+"	?	"+"	"_"
C. Akarsu, 2020	?	"+"	"+"	"+"	?	"+"	?
H. V. M. Spiers, 2020	?	?	?	"+"	"+"	?	"_"
A. Dirweesh, 2022	?	?	"+"	"+"	?	"+"	"_"
A. Dirweesh, 2020	?	?	"+"	"+"	?	?	"_"
H. Han, 2019	"+"	"+"	"+"	"+"	"+"	"+"	"+"

F. G. Haydar, 2022	"+"	"+"	"+"	"+"	?	"+"	"+"
S. Inamdar, 2020	"+"	"+"	"+"	"+"	"+"	"+"	"+"
Y. Jiang, 2020	?	?	?	"+"	"+"	?	"_"
R. Karaali, 2021	"+"	"+"	"+"	"+"	?	"+"	"+"
P. T. Kroner, 2023	"_"	?	?	"+"	"+"	?	"_"
J. Machicado, 2014	"_"	?	?	"+"	?	"_"	"_"
Ò. Miró, 2021	"+"	"+"	?	"+"	"+"	"+"	"+"
J. Omoshoro-Jo nes, 2011	?	?	?	"+"	?	"_"	"_"
J. Omoshoro-Jo nes, 2012	?	?	?	"+"	?	"+"	"_"
V. S. Parithivel, 1999	?	?	?	"+"	?	"+"	"_"
S. K. Patnaik, 2021	?	?	"_"	?	?	"_"	"_"
L. Prodehl, 2019	"+"	?	"+"	"+"	?	"+"	?
P. M. Radulescu, 2022	"+"	"+"	"+"	"+"	"?"	"+"	"+"
O. Rotar, 2021	"_"	"?"	"?"	"?"	"_"	"_"	"_"
J. Samanta, 2022	"+"	"+"	"+"	"+"	"+"	"+"	"+"
H. Vatansev, 2021	"+"	"+"	"+"	"?"	"?"	"_"	"_"
F Anderson, 2017	"?"	"+"	"+"	"?"	"?"	"+"	"_"
D. Kang, 2023	?	?	"+"	"+"	?	"+"	"_"
H. Chaudhry, 2023	?	?	"+"	"+"	?	?	"_"
C. Varghese, 2022	"+"	"+"	"+"	"+"	"+"	"+"	"+"

O. Sierra, 2021	"+"	"+"	"+"	"+"	"?"	"+"	"+"
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Green: low risk of bias; yellow: moderate risk of bias; red: high risk of bias

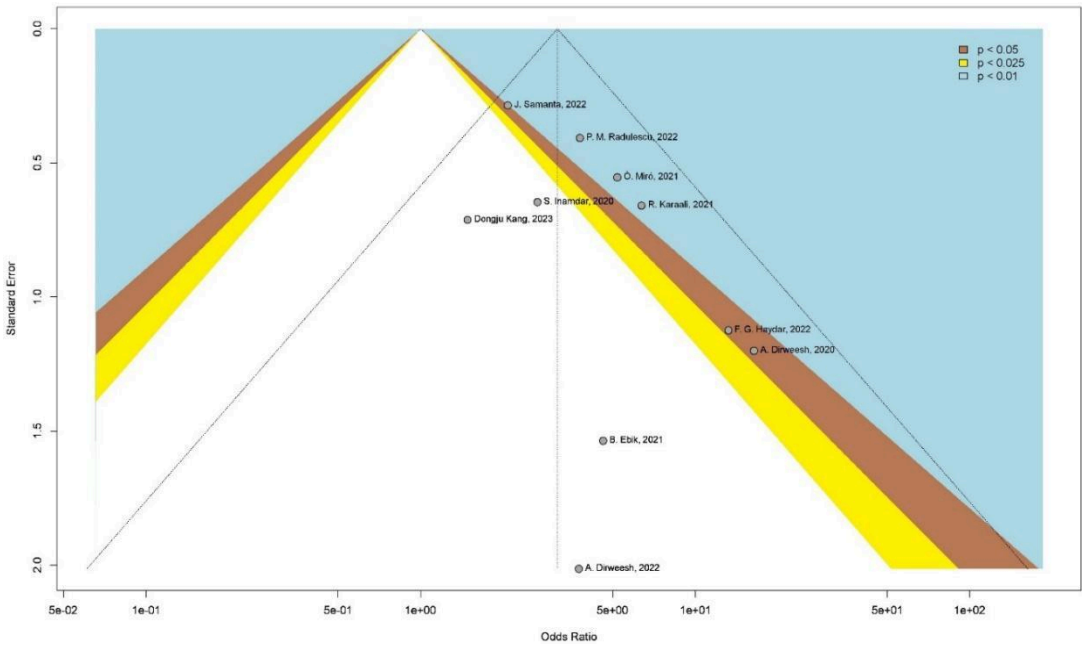


Figure 14: Publication bias assessment using funnel plot for in-hospital mortality in COVID subgroup [31]

9. DISCUSSION

9.1. Diagnostic Limitations and Host-Related Modifiers

This thesis first addresses an important yet underrecognized aspect of AP: the limitations of current diagnostic criteria in the presence of host-related factors.

Our findings demonstrate that several patient-related characteristics, including DM, CP, smoking, and alcohol-related etiology, are associated with lower pancreatic enzyme levels at presentation. Diabetes mellitus showed an independent association with non-diagnostic enzyme levels in the primary multivariable analysis; however, this association was attenuated and no longer statistically significant after additional adjustment for inflammatory markers. Importantly, we identified that a clinically relevant proportion of patients (6.7%) present without diagnostic enzyme elevation, despite fulfilling other diagnostic criteria for AP.

These findings are consistent with previous smaller-scale cohort studies and experimental data suggesting that pancreatic enzyme release may be attenuated in specific clinical contexts. Prior studies have reported reduced amylase and lipase levels in patients with chronic pancreatic damage, particularly in the setting of fibrosis and reduced acinar cell mass. Similarly, metabolic conditions such as DM have been associated with altered exocrine pancreatic function and impaired enzyme secretion.

However, the existing literature has largely been limited by small sample sizes, single-center designs, or specific subpopulations. In contrast, the present study extends these observations at an international, multicenter level, providing more robust and generalizable evidence that “enzyme-negative” AP is not a rare or incidental phenomenon but represents a distinct and clinically meaningful subgroup. Importantly, these findings suggest that AP should not be viewed as a biochemically uniform disease, as the detectability of pancreatic injury appears to be strongly influenced by the host-related biological context.

Several pathophysiological mechanisms may explain these findings. Chronic pancreatic injury, as seen in CP or long-standing alcohol use[61], leads to progressive fibrosis and loss of acinar cells, thereby reducing the capacity for enzyme production and release [62; 63]. In addition, recurrent episodes of AP may further diminish exocrine reserve [64]. In metabolic conditions such as diabetes, altered insulin signaling and

microvascular changes may impair pancreatic function [65-67]. Smoking has also been implicated in pancreatic fibrosis and vascular dysfunction, which may further contribute to reduced enzyme output [68]. Importantly, reduced enzyme elevation should not be interpreted as evidence of milder disease, particularly in patients with chronic pancreatic injury or metabolic comorbidities, where substantial pancreatic inflammation may occur despite limited biochemical response[18; 69; 70].

The attenuation of the association between diabetes mellitus and non-diagnostic enzyme levels after adjustment for CRP and WBC also warrants cautious interpretation. Inflammatory markers may act as potential confounders if differences in inflammatory burden are associated with both diabetes and pancreatic enzyme levels. Alternatively, inflammatory responses may lie on the causal pathway between diabetes-related biological alterations and pancreatic injury, in which case adjustment for CRP and WBC could represent partial adjustment for a mediator. Conversely, because CRP and WBC are also consequences of the acute inflammatory process of AP, their relationship with diabetes and pancreatic enzyme levels may reflect the clinical stage or severity of the acute disease rather than a simple causal pathway. Given the observational and post hoc nature of the analysis, the present data cannot definitively distinguish between these possibilities. Therefore, diabetes should be considered an important associated host factor, but its role as an independent determinant of non-diagnostic enzyme levels should not be interpreted as definitively established.

The clinical implications of these findings are substantial. Current diagnostic criteria for AP incorporate three complementary components: characteristic abdominal pain, elevated pancreatic enzymes, and characteristic imaging findings, with the diagnosis generally established when two of these three criteria are fulfilled. Therefore, the present findings do not indicate a failure of the complete diagnostic criteria. Rather, they highlight the limitations of relying on pancreatic enzyme elevation alone, particularly in patients with host-related factors associated with lower enzyme levels. In enzyme-negative presentations, greater attention to the clinical presentation and appropriate imaging may therefore help avoid delayed recognition of AP and inappropriate exclusion of the diagnosis. More fundamentally, these findings raise the question of whether pancreatic enzyme interpretation should account for relevant host-related modifiers rather than being applied uniformly across all patient populations.

An additional methodological consideration is the use of fixed absolute thresholds for pancreatic enzyme elevation in the present analysis. Although these thresholds were predefined for the registry analysis, clinical diagnostic practice generally interprets pancreatic enzyme elevation in relation to the laboratory-specific upper limit of normal. Differences in assay methods, analytical platforms, and reference ranges across participating centers may therefore have influenced the classification of patients as having or not having diagnostic enzyme elevation. In addition, potential center effects cannot be completely excluded, particularly given the uneven distribution of patients across participating centers. Consequently, the observed associations should be interpreted with consideration of possible inter-center and laboratory-related variability. Future multicenter studies using laboratory-specific reference ranges and center-adjusted analyses could help determine whether these findings remain consistent across different diagnostic settings.

In addition, pancreatic enzyme concentrations are highly time-dependent, and delayed presentation after symptom onset may further contribute to falsely low enzyme levels in certain patients. This temporal variability further complicates the interpretation of pancreatic enzyme measurements in routine clinical practice.

Notably, the integration of traditional statistical methods and machine learning approaches in this study provides complementary evidence supporting these observations. While multivariable regression identified independent associations, machine learning models revealed complex, non-linear interactions between host factors, supporting the robustness of the findings. Together, these results highlight the need for a more nuanced, patient-centered approach to AP diagnosis, potentially incorporating risk-adjusted thresholds or greater emphasis on imaging and clinical presentation. Future diagnostic frameworks may benefit from integrating host-related modifiers into risk-adjusted diagnostic algorithms rather than relying solely on fixed biochemical cutoffs.

9.2. Prognostic Impact of Viral Infections on Acute Pancreatitis

The second major focus of this thesis is the impact of systemic viral infections on the prognosis of AP, with particular emphasis on SARS-CoV-2 and HIV. Beyond these two major viral entities, the available literature also implicates several other viruses,

including hepatitis viruses, cytomegalovirus, and Old World hantaviruses, although evidence for these pathogens is largely limited to case reports and small case series. Collectively, these findings suggest that viral-associated AP represents a clinically heterogeneous and likely underrecognized subgroup of AP.

Our meta-analysis found that SARS-CoV-2 infection was associated with worse outcomes in patients with AP, including higher mortality, greater disease severity, and a higher risk of complications. These findings are in line with multiple large international cohort studies conducted during the COVID-19 pandemic, which consistently reported excess mortality and more severe systemic inflammation in patients with concomitant infection [71; 72].

The mechanisms underlying this association are likely multifactorial. SARS-CoV-2 infection is characterized by a dysregulated immune response, including hyperinflammation and cytokine release, which may exacerbate pancreatic injury. Endothelial dysfunction and microvascular impairment, both hallmarks of COVID-19, may further compromise pancreatic perfusion [73]. In addition, organ cross-talk between the lungs, pancreas, and other systems may amplify systemic disease severity, contributing to worse clinical outcomes [74].

Importantly, severe COVID-19 and severe AP appear to share several overlapping inflammatory and metabolic pathways. Previous studies have demonstrated similarities in inflammatory mediator profiles between severe COVID-19 and severe AP, distinguishing both conditions from their milder forms. In both diseases, lipotoxicity[75] and excessive release of unsaturated fatty acids may contribute to mitochondrial dysfunction, cytokine storm, and ultimately multi-organ failure. These shared mechanisms may partly explain the observed association between concomitant SARS-CoV-2 infection and more severe clinical outcomes in AP. [76; 77].

Emerging evidence also suggests that SARS-CoV-2 may potentially contribute to pancreatic injury through mechanisms involving pancreatic cell infection, endothelial injury, locoregional thrombosis, and microvascular dysfunction [78]. These mechanisms provide biological plausibility for a potential contribution of SARS-CoV-2 to pancreatic injury. However, given the predominantly observational nature of the available clinical evidence, the present meta-analysis cannot establish whether SARS-CoV-2 directly causes pancreatic injury or whether the observed association reflects shared systemic

mechanisms and disease severity. In contrast, our analysis did not identify a statistically significant association between HIV infection and AP-related mortality or complications. This finding may initially appear counterintuitive, given the known immunological alterations associated with HIV. However, it is consistent with more recent evidence suggesting that, in the era of effective antiretroviral therapy, HIV infection behaves as a chronic, controlled condition rather than an acute systemic stressor [79].

Earlier studies that reported worse outcomes in HIV-infected patients were often conducted in settings with limited access to antiretroviral therapy or involved patients with advanced immunosuppression. In such contexts, opportunistic infections, malnutrition, and uncontrolled viral replication likely contributed to poorer outcomes. In contrast, contemporary cohorts predominantly include patients receiving effective therapy, with improved immune function and reduced systemic vulnerability [80]. Nevertheless, disparities in healthcare access and delayed treatment initiation may still influence AP outcomes in low-resource settings.

The relationship between HIV and AP also remains biologically complex. In addition to the effects of immunosuppression itself, several antiretroviral agents have been associated with pancreatic toxicity [81], while opportunistic infections such as cytomegalovirus may directly involve the pancreas [82]. Furthermore, co-infections with hepatitis B or C virus may further modify the clinical course of AP in HIV-positive patients [83]. These findings suggest that the prognostic impact of HIV may depend not only on the infection itself but also on treatment status, immune function, coexisting infections, and healthcare context.

Interestingly, patients with virus-associated AP described in the literature tend to be younger and more frequently male compared with general AP populations. In addition, these patients often demonstrate higher rates of severe disease and mortality [84]. Although this observation may partly reflect publication bias toward more severe cases, it may reflect a distinct clinical phenotype or differences in case ascertainment and reporting.

These findings underscore the importance of considering the evolving clinical context when interpreting the impact of comorbid conditions. While acute systemic insults such as SARS-CoV-2 infection may amplify disease severity, chronic infections under

effective treatment may have a substantially attenuated impact on AP outcomes. At the same time, certain viruses may function not only as prognostic modifiers but also as direct etiological contributors to pancreatic injury. Together, these observations highlight the need for increased clinical vigilance and a broader etiological perspective when evaluating patients with AP in the setting of systemic viral infection.

9.3. Integrated Interpretation

When integrating the findings of both studies, a consistent pattern emerges: host-related factors play a critical role in shaping both the manifestation and the detectability of AP. Acute systemic conditions, such as SARS-CoV-2 infection, may be associated with greater disease severity through mechanisms including systemic inflammation and organ cross-talk. In contrast, chronic conditions such as DM or CP may attenuate biochemical responses, thereby masking the disease and limiting the sensitivity of standard diagnostic criteria.

This dual effect highlights a fundamental limitation in current approaches to AP diagnosis and risk stratification. Together, these findings support a more individualized framework that accounts for both acute systemic insults and chronic host-related modifiers in the assessment and management of AP.

9.4. Strengths and Limitations

This thesis has several key strengths. First, it combines two complementary methodological approaches, including a prospective multicenter registry, and a large international meta-analysis thereby enabling both population-level inference and detailed patient-level analysis. Second, the inclusion of internationally diverse cohorts enhances the generalizability of the findings across different healthcare systems. Third, the use of both traditional statistical modelling and machine learning approaches strengthens the robustness and interpretability of the results, with consistent findings across methodologies. Finally, the integration of diagnostic and prognostic perspectives provides a comprehensive framework for understanding host-related modifiers in AP.

Several limitations should also be acknowledged. The registry-based analysis, although based on prospectively collected data, was conducted as a post hoc investigation, which limits causal inference. Missing data led to the exclusion of a subset of patients and may have introduced selection bias. In addition, enzyme measurements were primarily

assessed at admission, limiting evaluation of temporal dynamics. The use of fixed enzyme thresholds may also have introduced misclassification because laboratory-specific reference ranges and assay methods may differ across participating centers. Although machine learning analyses provide insight into variable importance, they remain exploratory and should be interpreted alongside conventional statistical results.

The meta-analysis has several additional limitations. First, the included studies were predominantly observational, which limits causal inference and leaves the possibility of residual confounding. Second, substantial heterogeneity in study populations, definitions of viral infection, clinical settings, and outcome assessment may affect the consistency and generalizability of the pooled estimates. Importantly, the risk-of-bias assessment identified a substantial proportion of cohort studies with a high risk of bias. Therefore, the observed associations, particularly those concerning mortality and severe complications, should be interpreted as associations rather than definitive causal effects. Residual confounding may arise from differences in age, comorbidities, disease severity, healthcare access, treatment strategies, or other factors associated with both viral infection and AP outcomes.

These limitations reduce the certainty with which the findings can be translated into causal clinical recommendations. The results support increased clinical awareness and closer assessment of patients with concomitant viral infection, particularly SARS-CoV-2, but they should not be interpreted as establishing that viral infection itself directly causes adverse AP outcomes. Similarly, the absence of a statistically significant association for HIV should not be interpreted as evidence that HIV has no effect on AP prognosis. Further well-designed prospective studies with standardized definitions, comprehensive adjustment for potential confounders, and more consistent outcome assessment are needed to clarify the independent prognostic contribution of specific viral infections.

10. CONCLUSIONS

Taken together, the findings of this thesis reveal a dual impact of host-related factors in AP: they not only influence the reliability and interpretability of diagnostic markers but also modify disease severity and prognosis. As a result, host-related variability may introduce important challenges in both clinical decision-making and the epidemiological assessment of AP.

In conclusion, this thesis emphasizes that AP should not be considered a biologically uniform disease entity. Instead, its detectability, clinical presentation, and progression are strongly shaped by host characteristics, which should therefore be integrated into future diagnostic frameworks, risk stratification models, and individualized management strategies to improve patient outcomes.

11. IMPLICATIONS FOR PRACTICE

The present findings underscore the necessity for refined clinical management of AP. SARS-CoV-2 co-infection markedly exacerbates disease severity, complications, and mortality, whereas HIV co-infection exerts a negligible impact. Risk stratification should incorporate viral status to guide monitoring and intervention intensity. Moreover, diabetes, CP, smoking, and alcohol-related etiologies are associated with reduced serum amylase and lipase, increasing the likelihood of underdiagnosis. A comprehensive diagnostic approach, integrating imaging, clinical assessment, and enzyme evaluation, is therefore warranted. Leveraging predictive models can further inform individualized management, enhancing diagnostic accuracy and optimizing patient outcomes in AP.

12. IMPLICATIONS FOR RESEARCH

12.1. Methodology and Study Design

This thesis demonstrates the value of combining systematic review, meta-analysis, and large-scale prospective registry data to investigate AP outcomes. Future research should continue to integrate multi-center, high-quality datasets and apply advanced statistical approaches, including multi-level modelling and machine learning, to capture complex interactions between host factors, comorbidities, and external stressors. Prospective studies with standardized reporting of pancreatic enzyme levels, viral infections, and clinical outcomes are warranted to reduce heterogeneity and enhance reproducibility. In addition, careful consideration of missing data, bias assessment, and robust validation strategies remains essential for improving study reliability.

12.2. New Areas

Emerging evidence from this work highlights several novel research directions. First, the mechanisms underlying reduced pancreatic enzyme expression in diabetes, CP, and lifestyle-related exposures require further investigation. Second, the impact of additional viral infections beyond SARS-CoV-2 and HIV on AP prognosis warrants exploration. Third, integrating patient-specific factors, comorbidities, and viral exposures into mechanistic or translational studies could elucidate pathophysiological pathways that influence enzyme expression and AP severity, providing a basis for targeted interventions. Finally, research evaluating guideline adaptation and diagnostic thresholds in populations with altered enzyme responses could optimize early recognition and management of AP.

13. IMPLICATIONS FOR POLICY MAKERS

SARS-CoV-2 significantly worsens AP outcomes, highlighting the need for integrated infectious disease surveillance and timely access to diagnostics and intensive care for high-risk populations. Comorbidities such as diabetes, CP, and lifestyle factors reduce pancreatic enzyme levels, potentially leading to underdiagnosis; policies should support guideline adaptation to account for these modifiers. Training healthcare providers on atypical AP presentations and prioritizing resource allocation for vulnerable groups are essential. Furthermore, standardized multicenter registries and real-world data integration can inform evidence-based policies, improve diagnostic accuracy, and optimize clinical management.

14. FUTURE PERSPECTIVES

Future research should focus on advancing a more individualized approach to AP, integrating viral status, comorbidities, and biochemical variability into clinical decision-making frameworks. Improved understanding of the mechanisms underlying reduced pancreatic enzyme levels may refine diagnostic thresholds and reduce misclassification. The incorporation of large-scale, harmonized international datasets and real-world evidence will be essential to validate findings across diverse populations. In addition, adapting clinical guidelines to reflect atypical presentations and external stressors, such as viral infections, may enhance early diagnosis, risk stratification, and ultimately improve patient outcomes.

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16. BIBLIOGRAPHY

16.1. Publications Related to the Thesis

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