ON-ADMISSION PROGNOSTIC BIOMARKERS AND ARTIFICIAL INTELLIGENCE SUPPORTED DECISION-MAKING IN MEDICINE

PhD thesis

Centre for Translational Medicine, Department of Medicine, University of Szeged, Szeged, Hungary

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PUBLICATIONS RELATED TO THE SUBJECT OF THE DISSERTATION

I. **Kiss S**, Gede N, Hegyi P, Németh D, Földi M, Dembrovszky F, Nagy B, Juhász MF, Ocskay K, Zádori N, Molnár Zs, Párniczky A, Hegyi PJ, Szakács Zs, Pár G. Erőss B. Alizadeh H, Early changes in laboratory parameters are predictors of mortality and ICU admission in patients with COVID-19: a systematic review and meta-analysis. Medical Microbiology and Immunology. 2021;210(1):33-47. **(Q2, IF: 4.148)**

II. **Kiss S**, Pintér J, Molontay R, Nagy M, Farkas N, Sipos Z, Fehérvári P, Pecze L, Földi M, Vincze Á, Takács T, Czakó L, Izbéki F, Halász A, Boros E, Hamvas J, Varga M, Mickevicius A, Faluhelyi N, Farkas O, Váncsa Sz, Nagy R, Bunduc S, Hegyi PJ, Márta K, Borka K, Doros A, Hosszúfalusi N, Zubek L, Erőss B, Molnár Zs, Párniczky A, Hegyi P, Szentesi A, Early prediction of acute necrotizing pancreatitis by artificial intelligence: a prospective cohort-analysis of 2387 cases. Sci Rep 12, 7827 (2022). **(D1, IF: 4.996)**

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LIST OF ABBREVIATIONS

AI - artificial intelligence

AEC - absolute eosinophil count

ALC - absolute lymphocyte count

ALP - alkaline phosphatase

ANC - absolute neutrophil count

ANP – acute necrotizing pancreatitis

AP - acute pancreatitis

APGAR - Appearance, Pulse, Grimace, Activity, Respiration

AUC - area under the receiver operator curve

BMI - body mass index

CECT - contrast-enhanced computer tomography

CK - creatine kinase

COVID-19 - coronavirus disease 2019

CRP – C-reactive protein

eGFR - estimated glomerular filtration rate

EPI - exocrine pancreatic insufficiency

GGT - gamma-glutamyl transferase

HbA1c - glycated hemoglobin

ICU - intensive care unit

IL-6 - interleukin-6

LDH - lactate-dehydrogenase

OR - odds ratio

PCT - procalcitonin

QUIPS - Quality In Prognosis Studies

SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2

SHAP - Shapley Additive exPlanations

sHLH - secondary haemophagocytic lymphohistiocytosis

WBC - white blood cells

WMD - weighted mean difference

SUMMARY

The PhD dissertation includes two clinical studies that examine the prognostic significance of specific biomarkers at the time of hospital admission in two common and potentially lethal diseases.

The first study, a meta-analysis, looked at a major scientific and health care issue in recent years, the coronavirus disease 2019 (COVID-19). At the beginning of the pandemic, we sought an extensive analysis to find biomarkers that could help stratify the risk for admission to the intensive care unit (ICU) and mortality. We hypothesized that there is a correlation between early clinical laboratory data and the clinical outcomes of patients with COVID-19. The scientific value of our study was given by the systematization of the exponentially growing amount of data about the incompletely known virus. From our results, it is worth highlighting that our meta-analysis was among the first publications that provided quantitative synthesis on the association between lymphopenia, low CD4+, and CD8+ lymphocyte subsets and worse prognosis in COVID-19.

The second study was about creating and implementing an AI model in a common gastroenterological disease, acute pancreatitis (AP). We aimed to accurately predict pancreatic necrosis at the time of hospital admission and provide a detailed analysis of a large, multi-center cohort study regarding acute necrotizing pancreatitis (ANP). This study is the first to combine prediction of necrosis development and artificial intelligence in AP. The predictive potential of the created model is comparable to the already existing clinical scoring systems and the model is expected to further improve with use. The easy-to-use web application supported by the interpretation of the prediction facilitates early, on-admission prediction of necrosis and allows continuous data maintenance and algorithmic understanding.

1. INTRODUCTION

BIOMARKERS IN MEDICINE

Biomarkers are biological observations that could serve as a surrogate for or predict clinical endpoints or intermediate outcomes that are more challenging to measure[1]. Generally, clinical biomarkers are divided into three main groups: prognostic, predictive, and pharmacodynamic ones[2]. Pharmacodynamic biomarkers deal with drug and target interactions, for instance by standing as a substitute for safety and efficacy endpoints. Predictive and prognostic biomarkers are often used as a synonym; however, while prognostic biomarkers are used to indicate the likely outcome of a disease, predictive biomarkers foretell an anticipated treatment response.

In the past decades, biomarkers received more and more spotlight in science (Figure 1). This is because good biomarkers can have many advantages over the actual endpoints: the possibility of repeated assessment, shorter measurement, and lower price could make them more appealing. Biomarkers can also be outstandingly useful in evaluating long-term outcomes. In a clinical trial that investigates such an endpoint without biomarkers, in order to possess sufficient statistical power to analyze the results, the investigators would require a large population to test and a more extended observation period. Another important aspect of biomarkers is that certain measurements, in a clinical trial or daily clinical practice, could raise an ethical dilemma. For example, when evaluating an acetaminophen overdose, it would be unethical to delay the treatment until the actual proof of the end-organ damage develops; therefore, the plasma concentration of this molecule stands as a replacement and guides clinicians[1,3]. Unfortunately, many promising biomarkers falter at an early stage. If a biomarker is tested on a given population with good results, it does not guarantee the generalizability of the results. Even if they have sufficient predictive potential and the clinical trial ends with a promising area under the receiver operator curve (AUC) value, the clinical usefulness of a biomarker depends not only on this value but also on the shape of the curve itself. It is more probable, that a predictor with almost perfect specificity and sensitivity of around 80% enters clinical practice than a biomarker with both a specificity and a sensitivity of 90%[4]. It is also important to note that biomarkers and the endpoint they predict are often

time-dependent. Due to these limitations, biomarkers are often integrated into clinical scoring systems in order to enhance their supportive potential.

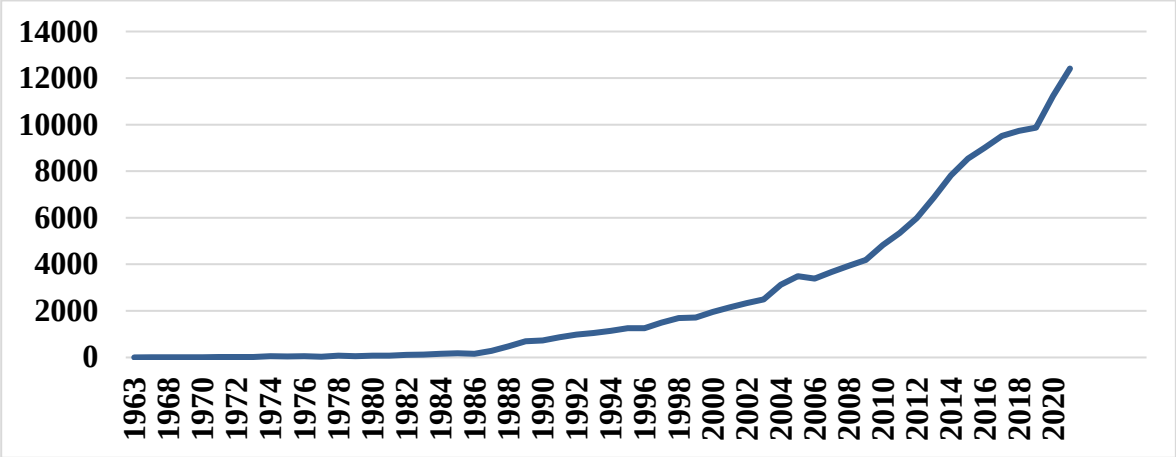

Figure 1: The expanding number of publications on biomarkers identified in MEDLINE database (https://pubmed.ncbi.nlm.nih.gov/, date of access: 2022.04.26.) From inception until 2021. The following search key was used: biomarker OR (surrogate AND (marker OR endpoint)).

CLINICAL SCORING SYSTEMS

Clinical scoring systems are algorithms, which were created to standardize clinical practice, assess clinical risk and prognosis, reduce uncertainty, aid clinical decision-making, prompt missed diagnoses, predict therapeutic response, and improve efficiency[5,6]. As we have seen in the case of biomarkers, we can observe a similar explosive expansion in publications on scoring systems[5].

Naturally, these scores have their own pitfalls. Besides the limitations inherited from the biomarkers integrated into them, clinical scoring systems have their own disadvantages as well. To become successful and enter the clinical practice, they should not be too complicated, and they should possess sufficient sensitivity and specificity. It must be emphasized that these scoring systems are often strongly limited by the conversion of continuous variables to binary ones, which could lower accuracy[7]. Despite the many constraints, we use a lot of efficient clinical scoring systems in our daily practice[8-11], e.g., APGAR (Appearance, Pulse, Grimace, Activity, Respiration) score in pediatrics[12], Wells criteria in calculating the probability of pulmonary embolism[13], or the Glasgow coma scale in emergency medicine and neurology[14].

Furthermore, successful clinical scores are increasingly integrated into clinical trial designs at multiple levels, e.g., assessment for eligibility or comparing patients.

ARTIFICIAL INTELLIGENCE IN MEDICINE

At the dawn of the technical revolution, artificial intelligence (AI) promises to overcome the above-mentioned limitations. AI is a sub-discipline of computer science that refers to the potential of computers to carry out or mimic tasks that are related to intelligent organisms[15]. In the past two decades, there has been meaningful progress in the development of AI[16]. The technological advancement provided the opportunity to make predictive models from extensive data sets and created the possibility of a truly personalized medicine due to AI's ability to handle heterogeneous data sets[15,17]. Since AI has appeared on the scene as a very intriguing modality of data-based decision support, and these models are extensively researched in numerous areas of medicine [18-22].

2. RATIONALE, OBJECTIVES AND HYPOTHESES

We aimed to assess the prognostic role of certain biomarkers in the two clinical trials presented below. The first study looked at a major scientific and health care issue in recent years, the coronavirus disease 2019 (COVID-19). At the beginning of the pandemic, we sought an extensive analysis to find biomarkers that could help stratify the risk for admission to intensive care unit (ICU) and mortality. The second study was about the creation and implementation of an AI model in a common gastroenterological disease, acute pancreatitis (AP). We aimed to accurately predict pancreatic necrosis at the time of hospital admission.

BACKGROUND AND PRIMARY OBJECTIVE OF THE COVID-19 STUDY

COVID-19 is a novel coronavirus infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first detected in Wuhan, China, in December 2019 after a series of pneumonia cases of unknown etiology had emerged[23]. On 11 March 2020, the World Health Organization declared the rapid spread of this virus, a pandemic[24]. Since the initial detection of the virus, more than 510,000,000 cases of COVID-19 have been confirmed worldwide with over 6,200,000 fatal cases[25]. In some patients, symptoms of severe respiratory infection can occur with rapidly developing

acute respiratory distress syndrome and other serious complications, which may be followed eventually by multiple organ failure and death. Despite some knowledge of the clinicopathological features of COVID-19, the correlation between changes in laboratory parameters and the prognosis of patients with COVID-19 is still unclear. However, early studies on COVID-19 cases have shown that increased levels of white blood cells (WBC), decreased numbers of lymphocytes, especially CD8 + cells, increased levels of lactate-dehydrogenase (LDH), creatine kinase (CK), C-reactive protein (CRP), D-dimer, and levels of pro-inflammatory cytokines are associated with more severe inflammation and extensive lung damage with higher rates of admission to intensive care unit (ICU) and mortality[26].

The primary objective of the COVID-19 study was to systematically search in the literature and collect the newly emerged data to synthesize new evidence by meta-analytic calculations. We aimed to explore the significance of changes in the on-admission laboratory parameters. We hypothesized that there is a correlation between early clinical laboratory data and the clinical outcomes of patients with COVID-19.

BACKGROUND AND PRIMARY OBJECTIVE OF THE ACUTE PANCREATITIS STUDY

Acute pancreatitis (AP) affects about 34 per 100,000 people per year, and it is the most frequent gastrointestinal disease requiring acute hospitalization[27,28]. The overall mortality is around 3%[29,30]; however, in about 10–20% of AP cases, acute necrotizing pancreatitis (ANP) develops, thus further increasing the risk of morbidity and mortality[31,32]. The overall mortality of ANP is approximately 15–20%, of which there is a further twofold increase in a third of ANP cases where the necrotic tissue becomes infected[33,34].

Early appraisal of severity and prognosis is crucial in AP, particularly on clinical admission, to identify patients at risk of developing life-threatening complications. In these cases, close monitoring and early intervention may prevent organ dysfunction and a fatal outcome[35,36].

It has long been known that necrosis is a consistent prognostic factor in AP[35]. The diagnosis of this local complication strongly relies on contrast-enhanced computer tomography (CECT) because it has a much higher sensitivity to detect ANP than

ultrasonography[33]. Despite being the gold standard method for diagnosing ANP, CECT has many disadvantages: (1) ANP usually becomes apparent only 72 hours after the onset of symptoms; (2) early and inappropriate CECT may prolong hospitalization; and (3) it is not accessible in every case[37]. There is therefore a need for other methods to supplement ANP assessment.

As the underlying pathophysiology of AP becomes more and more familiar by the accumulation of scientific data, several potential therapeutic targets have been identified[38,39]. Since some of these specific therapies may be available soon, prompt initiation of treatment after early identification of ANP could be even more important.

The primary objective of the second study was to design the first AI model that predicts ANP from on-admission biomarkers and to implement it as an easily accessible online tool. We hypothesized that the combined predictive value of biomarkers measured on hospital admission meets or exceeds those of currently used clinical scoring systems. Furthermore, we assessed all predictors as an individual biomarker. In addition to these, ANP was extensively described in a large, prospective, multicenter cohort study.

3. METHODS

METHODS OF THE COVID-19 STUDY

Study protocol and reporting

This systematic review with meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[40,41]. The review protocol was registered on PROSPERO (CRD42020176836)[42]. As it was stated in the study protocol, due to the rapidly increasing amount of data on the topic of COVID-19, new laboratory parameters not recorded in the protocol were also included in our results (e.g., lymphocyte subpopulations). Furthermore, as a protocol deviation, we should mention the calculation of odds ratios (ORs) based on cut-off values, which served to refine the risk estimates.

Search strategy

The systematic literature search was conducted in MEDLINE (via PubMed), Embase, Cochrane Library (CENTRAL), Scopus, and Web of Science for studies published from 1st January 2020 to 9th April 2020. The following search terms were used: (”covid 19”)

OR ("Wuhan virus") OR (“coronavirus”) OR (“2019 nCoV”) OR ("SARS-cov-2"). There was no restriction on the language of the records.

Selection and eligibility criteria

We selected clinical studies reporting on at least 10 confirmed SARS-CoV-2 infected patients (based on the WHO case definition) and their laboratory findings[43]. Studies were included in the systematic review if data on at least one of the following variables could be extracted: total white blood cell count (WBC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet count, absolute basophil count, absolute eosinophil count (AEC), absolute monocyte count (AMC), C-reactive protein (CRP), hemoglobin, ferritin, lactate dehydrogenase (LDH), creatine kinase (CK), procalcitonin (PCT), fibrinogen, D-dimer, and any interleukins or lymphocyte subsets (CD3+, CD4+, CD8+). The titles, abstracts, and full texts of the studies were screened by four independent review authors in pairs based on predefined criteria. The decision to include a study in the meta-analysis was based upon the assessment of the two review authors and, if necessary, by a third investigator for the resolution of any disagreements. Reference lists in the included studies and reviews on this topic were searched for additional studies. Publications citing the included studies were screened in the Google Scholar academic search engine too. Those studies that had either proven or suspected overlapping populations were included only in the systematic review part of this paper. To clarify these overlaps, we tried to contact the corresponding authors. Studies with more than 10% unclosed cases were excluded.

Data extraction

Four review authors independently extracted data into a standardized data collection form. The following data were extracted from each eligible article: first and second author, publication year, study site, study design, gender, age, and the means, standard deviations, medians, ranges, and interquartile ranges of the laboratory values and specific thresholds with the corresponding intensive care requirement and mortality ratio. Data extraction was validated by a fifth review author. Discrepancies were resolved by a third party.

Statistical analysis

Pooled mean difference (weighted mean difference, WMD) was calculated for continuous outcomes and pooled ORs were calculated for dichotomous outcomes. Random effect model was applied to all the analyses with DerSimonien-Laird estimation[44]. Statistical heterogeneity was analyzed using the I^2 the χ^2 tests to obtain probability values: $p<0.01$ was defined as indicating significant heterogeneity. Where mean with standard deviation was not reported for any of the outcomes, they were estimated from median, interquartiles and range by using the method of Wan[45]. We performed separate analyses for mortality based on the clinical characteristics of the study population: one for all hospitalized COVID-19 patients (the "mixed" population) and the other for only critically ill COVID-19 patients. Small study effect was evaluated by visual assessment of funnel plot asymmetry and by Egger's test where more than ten studies where available. Statistical analyses were performed with Stata 15 SE (Stata Corp). In the case of potentially overlapping study populations, data from the study with higher participant numbers were used for each outcome. ORs were calculated where raw data were available; however, only those meta-analyses were interpreted where at least three non-overlapping studies were available, as required.

Risk of bias assessment

Based on the recommendation of the Cochrane Prognosis Methods Group, the Quality In Prognosis Studies (QUIPS) tool was applied by two independent authors for assessing the risk of bias in the studies included[46]. Any disagreement was resolved based on consensus.

METHODS OF THE ACUTE PANCREATITIS STUDY

Ethical approval and reporting

This cohort study was reported following the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement[47,48]. Ethics approval was obtained from the Hungarian Medical Research Council's Scientific and Research Ethics Committee (22254-1/2012/EKU, 17787-8/2020/EÜIG). Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the Helsinki Declaration.

Data source and eligibility criteria

The analyzed dataset was collected by the Hungarian Pancreatic Study Group between 2012 and 2019. There were 2,461 adult patients enrolled in the patient registry from 30 centers across 13 countries[49]. All patients fulfilled two out of three AP diagnostic criteria based on the revised Atlanta classification[50]. Data were collected by physicians and trained clinical administrators on admission and each day during the whole hospital stay and were stored both on paper and electronically. Relevant clinical data underwent a four-level quality check system before analysis.

In all cases deemed eligible a CECT was performed during hospitalization to assess pancreatic necrosis formation. Exclusion criteria were as follows: (1) no pancreas imaging had been performed; and (2) the mere suspicion of necrosis formation by imaging, which was not confirmed later by CECT.

Eligible participants were divided into two groups: (1) pancreatic necrosis formation was confirmed by a radiologist by CECT during hospitalization; and (2) absence of necrosis development. The dataset was analyzed and compared accordingly.

ANP was defined as a lack of parenchymal enhancement or findings of peripancreatic necrosis, such as an acute necrotic collection on CECT[51]. Other local (acute peripancreatic fluid collection and pseudocyst) and systemic (new-onset diabetes, heart failure, renal failure, and respiratory failure) complications and disease severity were defined based on the revised Atlanta classification[50]. Data on in-hospital mortality, length of hospital stay, and etiology of AP were also collected.

The assessed predictors of ANP were gender, age, body mass index (BMI), and laboratory parameters measured in the first 24 hours of clinical admission. The following were evaluated: alanine transaminase, albumin, amylase, alkaline phosphatase (ALP), aspartate transaminase, blood urea nitrogen, calcium, C-reactive protein (CRP), creatinine, direct bilirubin, gamma-glutamyl transferase (GGT), glucose, estimated glomerular filtration rate (eGFR), glycated hemoglobin (HbA1c), hematocrit, hemoglobin, lactate dehydrogenase (LDH), lipase, potassium, procalcitonin, red blood cell count, sodium, platelet, total bilirubin, total cholesterol, total protein, total white blood cell count (WBC), and triglyceride.

Predictive modelling

The process of predictive modelling is depicted in Figure 2. Thirty-one variables have been used for modelling. Data quality is provided in the online supplementary material and the appendix of this dissertation[49]. Missing data were handled with a k-nearest-neighbor-based data imputer algorithm (KNNImputer)[52]. The SMOTE algorithm was used to deal with the imbalance in class distribution (number of patients with and without ANP)[53]. Random Forest, Logistic Regression, Catboost, XGBoost, and LightGBM were tested for modelling to identify the best performing machine learning algorithm[54-57]. The catboost, xgboost, lightgbm, and scikit-learn Python packages were applied. The optimal model was chosen based on the receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) value after performing a four-fold cross-validation. The confidence of the best performing model was estimated with a bootstrapping method, namely by re-sampling the training dataset and training a hundred independent copies of the model on these datasets. The confidence of the model prediction was interpreted with the aid of the 10th and the 90th percentiles of the prediction scores.

Shapley Additive exPlanations (SHAP) values were calculated to locally explain the model prediction and to quantify the contribution of each variable provided[58]. Finally, the model was deployed as an online application using the Streamlit Python-based framework.

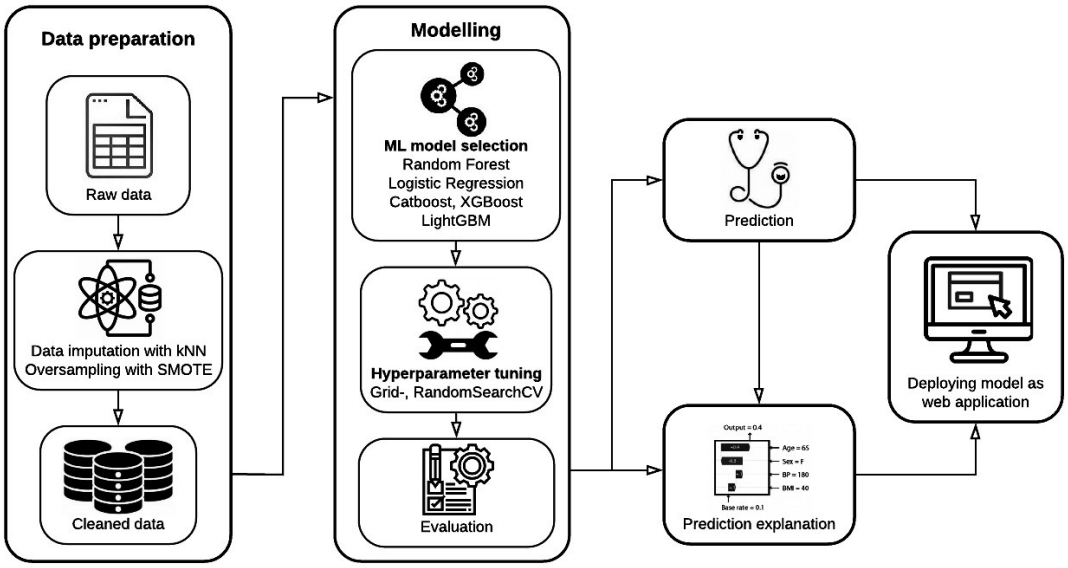

Figure 2. Flowchart representing the process of developing the model

Other statistical analyses

The presence of sampling bias was tested by assessing the representativeness between the cohort analyzed and the whole cohort[49]. The prediction parameters were also compared between patients with and without ANP with the Kolmogorov–Smirnov test and the Chi-squared test. ANP was tested as a risk factor for mortality, severe AP, and local and systemic complications by calculating risk ratios (RR) with the corresponding 95% confidence interval (CI).

4. RESULTS

RESULTS OF THE COVID-19 STUDY

Results of the qualitative and quantitative synthesis are summarized in online supplementary material and the appendix of this dissertation[59].

Systematic search and selection

The results of our search and selection are detailed in the PRISMA-Flowchart shown in Figure 3. Our systematic search yielded 93 eligible studies from 16 countries. We summarize the characteristics of the included studies in the online supplementary material and the appendix of this dissertation[59]. Out of these, fifty-six studies reported on the association of laboratory parameters and mortality[23,60-114]. Of these, forty-eight studies reported on 25,901 patients with all levels of disease severity (the "mixed" population), and eleven other studies discussed critically ill cases with an overall patient number of 2,804. Forty-one studies with 11,935 patients comparing those with and without ICU requirement have also been included in this study[70,77,80,94,115-152]. The incidence of mortality ranged from 6.25% to 61.5% in the mixed population and from 22.35% to 71.19% in the critically ill population. While the prevalence of ICU requirements ranged from 8.76% to 70.59%.

Weighted mean differences

Pooled analyses showed that among all COVID-19 patients mortality was associated with increased baseline WBC (WMD= $2.35x10^9$/L [CI: 1.96, 2.83], $p<0.001$, $I^2=64.5\%$), ANC (WMD= $2.67x10^9$/L [CI: 2.12, 3.21], $p<0.001$, $I^2=71.7\%$), CRP (WMD= 65.65 mg/L [CI: 42.79, 87.50], $p<0.001$, $I^2=99.4\%$), LDH (WMD= 203.79 U/L [CI: 151.86, 255.71], $p<0.001$, $I^2=95.2\%$), PCT (WMD= 0.38 ng/mL [CI: 0.30, 0.47], $p<0.001$,

I^2=91.8%), fibrinogen (WMD= 0.32 g/L [CI: 0.13, 0.50], p=0.001, I^2=52.4%), D-dimer (WMD= 1.31 mg/L [CI: 1.05, 1.57], p<0.001, I^2=84.5%) , ferritin (WMD= 550.20 μg/L [CI: 347.97, 752.43], p<0.001, I^2=15.8%), CK (WMD= 77.59 U/L [CI: 55.31, 99.86], p<0.001, I^2=81.4%) and IL-6 (WMD= 84.26 pg/mL [CI: 49.23, 119.30], p<0.001, I^2=97.5%). In the same population, decreased baseline ALC (WMD= -0.35x10^9/L [CI: -0.43, -0.27] (Figure 4), p<0.001, I^2=94.2%), CD3+ lymphocyte count (WMD= -329.71 cell/μL [CI: -370.82, -288.59], p<0.001, I^2=60.1%), CD4+ lymphocyte count (WMD= -164.24 cell/μL [CI: -190.51, -137.97], p<0.001, I^2=67.0%), CD8+ lymphocyte count (WMD= -115.45 cell/μL [CI: -130.61, -100.30], p<0.001, I^2=55.7%), AEC (WMD= -0.02x10^9/L [CI: -0.03, -0.01], p=0.003, I^2=74.6%), AMC (WMD= -0.05x10^9/L [CI: -0.08, -0.03], p<0.001, I^2=0.0%), and platelet count (WMD= -25.66x10^9/L [CI: -35.56, -15.76], p<0.001, I^2=81.8%) was associated with increased mortality. We have not found significant association between baseline IL-1 and mortality among all COVID-19 patients.

Pooled analyses found that among all critically ill COVID-19 patients, mortality was associated with increased baseline LDH (WMD= 129.34 U/L [CI: 67.73, 190.94], p<0.001, I^2=34.1%), increased CRP (WMD= 45.36 mg/L [CI: 23.50, 87.50], p<0.001, I^2=35.3%), and decreased platelet levels (WMD= -30.19x10^9/L [CI: -44.88, -15.50], p<0.001, I^2=0.0%). We have not identified significant baseline difference between deceased and discharged critically ill patients regarding WBC, ALC, PCT, and D-dimer levels.

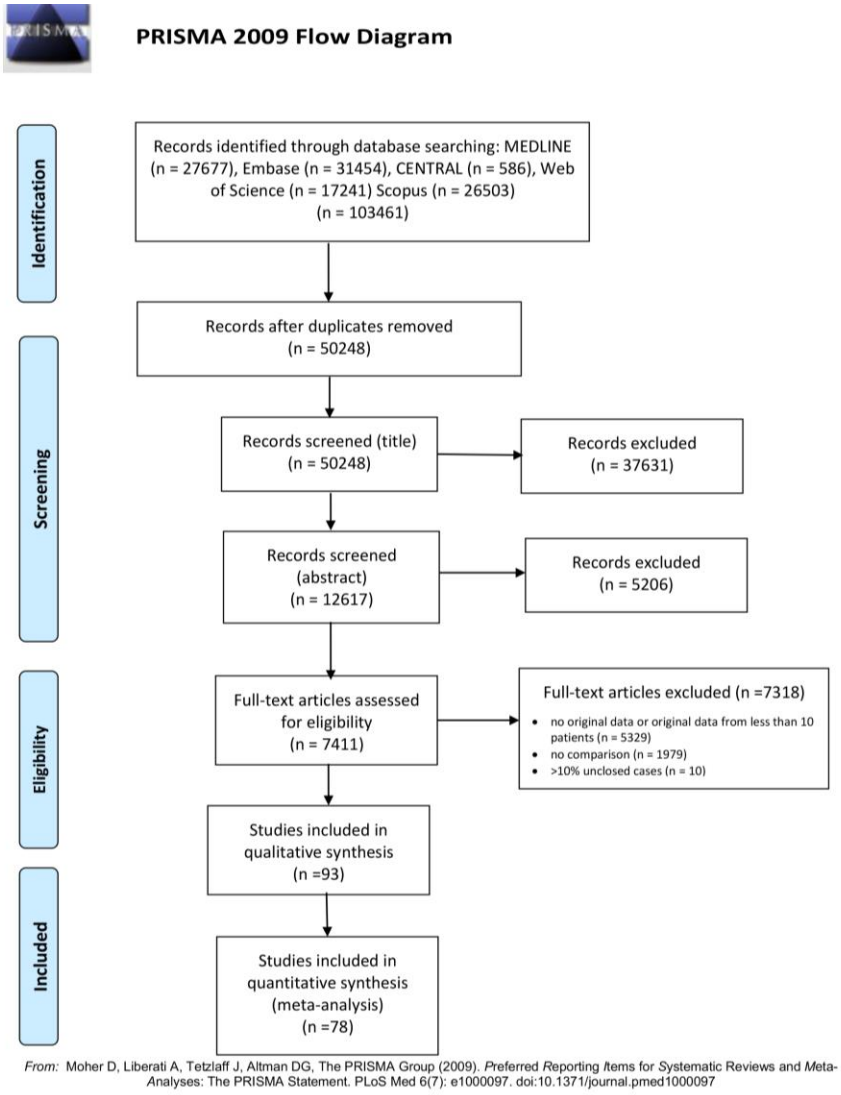

Figure 3: PRISMA Flow Diagram of the COVID-19 study. This diagram details our systematic search and selection process

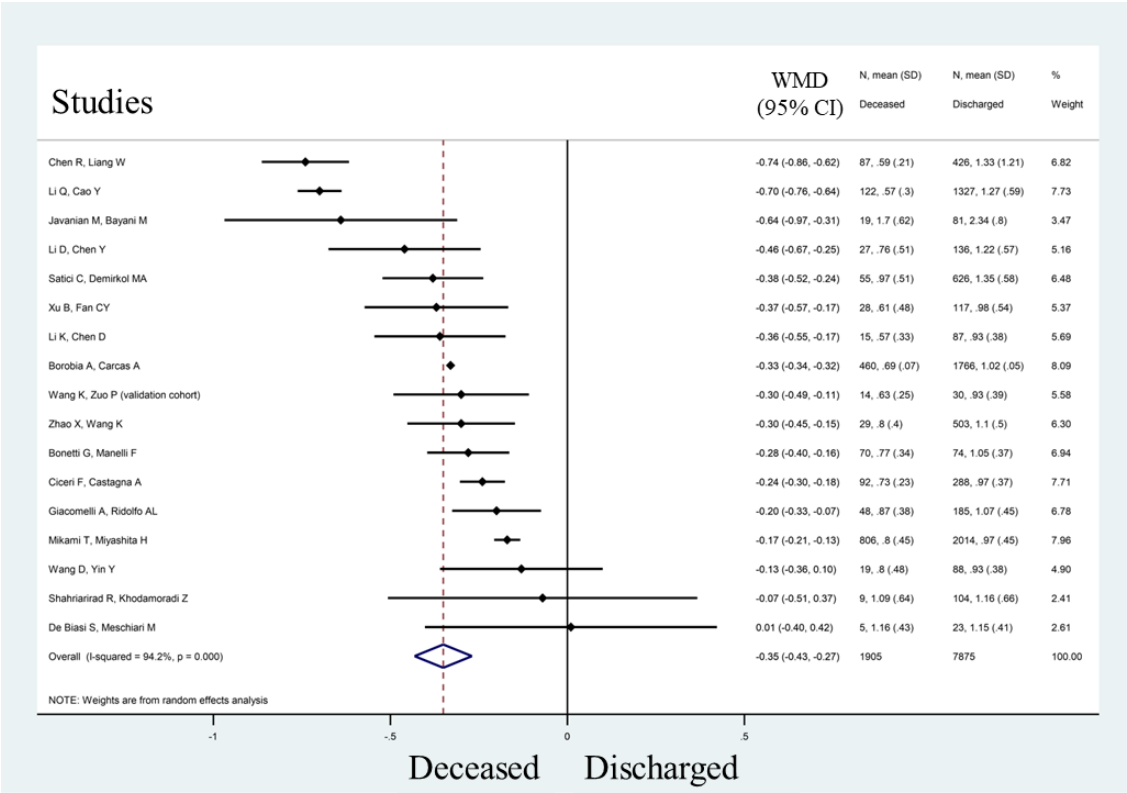

Figure 4: Forest plot representing that decreased baseline absolute lymphocyte count was associated with increased mortality

Pooled analyses revealed that the following baseline laboratory parameters were higher in patients who required intensive care compared to those who did not: WBC (WMD= 1.53x10^9/L [CI: 1.04, 2.02], p<0.001, I^2=68.8%), ANC (WMD= 2.47x10^9/L [CI: 1.71, 3.23], p=0.037, I^2=75.2%), CRP (WMD= 65.65 mg/L [CI: 42.79, 87.50], p<0.001, I^2=99.4%), LDH (WMD= 190.91 U/L [CI: 129.40, 252.42], p<0.001, I^2=90.4%), PCT (WMD= 0.21 ng/mL [CI: 0.05, 0.37], p=0.008, I^2=95.6%), CK (WMD= 54.07 U/L [CI: 28.37, 79.77], p<0.001, I^2=35.2%), fibrinogen (WMD= 1.04 g/L [CI: 0.66, 1.43], p<0.001, I^2=0.0%), D-dimer (WMD= 0.77 mg/L [CI: 0.50, 1.04], p=0.007, I^2=81.1%), ferritin (WMD= 328.28 µg/L [CI: 181.58, 474.99], p<0.001, I^2=15.8%), and IL-6 (WMD= 26.67 pg/mL [CI: 15.98, 37.35], p<0.001, I^2=0.0%). Intensive care requirement was also associated with decreased baseline ALC (WMD= -0.30x10^9/L [CI: -0.37, -0.23], p<0.001, I^2=87.0%), CD3+ lymphocyte count (WMD= -322.56 cell/µL [CI: -589.00, -55.54], p=0.018, I^2=83.5%), CD4+ lymphocyte count (WMD= -142.98 cell/µL [CI: -242.12, -43.85], p=0.005, I^2=82.2%), CD8+ lymphocyte count (WMD= -186.52 cell/µL [CI: -254.84, -118.21], p<0.001, I^2=73.3%), and haemoglobin (WMD= -7.39 g/L

[CI: -11.65, -3.14], p=0.001, I^2=64.1%). No significant association was found between intensive care requirement and baseline AMC, platelet count.

Odds ratios

Among all COVID-19 patients, increased on admission total WBC was found to be a risk factor for mortality (>9.5x10^9/L, OR=3.7 [CI: 1.72, 7.69], p=0.001, I^2=0.0%; >10.0x10^9/L, OR=6.25 [CI: 2.86, 14.29], p<0.001, I^2=85.2%) and intensive care requirement (>9.5x10^9/L, OR=4.52 [CI: 1.95, 10.52], p<0.001, I^2=26.8%; >10.0x10^9/L, OR=2.64 [CI: 1.22, 5.71], p=0.014, I^2=61.3%). These results suggest a stepwise increase in risk for mortality in parallel with the increase of the total WBC threshold. This is depicted on Figure 5. Furthermore, low baseline WBC was associated with decreased mortality (<4.0x10^9/L, OR=0.38 [CI: 0.20, 0.72], p=0.003, I^2=40.6%) and lower risk for intensive care requirement (<3.5x10^9/L, OR=0.42 [CI: 0.18, 0.96], p=0.039, I^2=0.0%).

Low ALC on clinical admission was a risk factor for mortality (<0.8x10^9/L, OR=3.74 [CI: 1.77, 7.92], p=0.001, I^2=65.5%) and intensive care requirement (<1.0x10^9/L, OR=4.54 [CI: 2.58, 7.95], p<0.001, I^2=26.8%; <1.1x10^9/L, OR=2.64 [CI: 1.49, 4.70], p=0.001, I^2=36.4%) among all COVID-19 patients.

Increased baseline ANC was found to be a risk factor for intensive care requirement (>6.3x10^9/L, OR=2.32 [CI: 1.23, 4.37], p=0.009, I^2=0.0%). We could not carry out a meta-analysis for any threshold regarding mortality, however individual studies support its role as a risk factor for mortality[23,85,100].

Assessment of low platelet on admission as a risk factor for mortality provided inconsistent results. Although baseline platelet level under 125x10^9/L was associated with significantly higher risk for mortality among all COVID-19 patients, on admission platelet level below 100x10^9/L and 150x10^9/L did not show significant results. We did not find any threshold that is associated with increased risk for intensive care requirement.

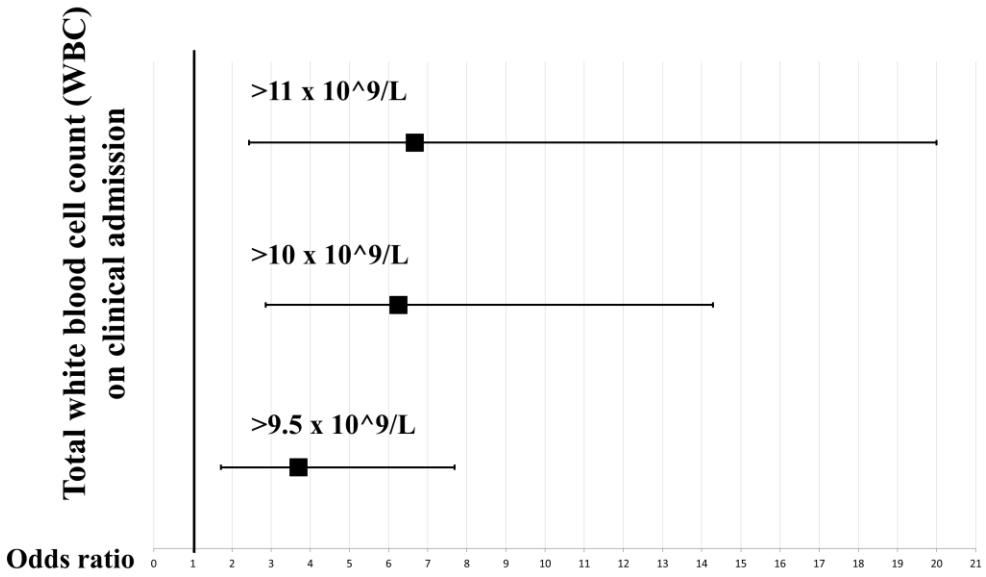

Figure 5: Odds ratios suggest a stepwise increase in risk for mortality parallel with the increase of the total white blood cell threshold

Evaluation of increased CRP showed that baseline level over 10 mg/L and 100 mg/L is associated with increased mortality (OR=4.84 [CI: 1.49, 15.69], p=0.009, I^2=45.8%; OR=2.49 [CI: 1.42, 4.35], p=0.001, I^2=14.7%, respectively); however, the analysis regarding the threshold of 50 mg/L was not significant, which makes these results inconsistent. In case of intensive care requirement, baseline level over 10 mg/L was found to be a risk factor (OR=3.85 [CI: 1.21, 12.22], p=0.022, I^2=55.4%).

On admission LDH over 250 U/L was found to be a risk factor both for mortality (OR=10.88 [CI: 4.48, 26.39], p<0.001, I^2=0.0%) and intensive care requirement (OR=9.44 [CI: 4.412, 24.02], p<0.001, I^2=0.0%).

Baseline procalcitonin level over 0.05 ng/mL was not a risk factor for mortality; however, we found increased risk over the threshold of 0.50 ng/mL (OR=11.97 [CI: 4.75, 30.16], p<0.001, I^2=59.4%). The same thresholds provided non-significant results regarding intensive care requirement.

Increased D-dimer level on admission was found to be a risk factor for mortality (>0.50 mg/L, OR=4.30 [CI: 1.55, 11.98], p=0.005, I^2=83,7; >1.0 mg/L, OR=6.63 [CI: 3.62, 12.14], p<0.001, I^2=45.1%) and intensive care requirement (>0.50 mg/L, OR=3.37 [CI: 1.90, 5.95], p<0.001, I^2=0.0%).

On admission CK level over 185 U/L was associated with increased mortality (OR=3.14 [CI: 1.87, 5.27], p<0.001, I^2=0.0%). We could not carry out a meta-analysis for any threshold regarding intensive care requirement; however individual studies support the role of increased CK as a risk factor[131,137,150].

There was no common threshold for any laboratory parameters with more than three non-overlapping studies; therefore, we were unable to calculate ORs for mortality among critically ill COVID-19 patients. ORs for mortality and intensive care requirements are summarized in the online supplementary material and the appendix of this dissertation[59].

Risk of bias assessment and publication bias

In the case of the overall risk of bias, the evaluation found a low risk of bias for the individual endpoints in approximately 50% of the cases. The risk factors inherent in the studies are primarily borne by the incomplete reporting of the measurements, confounding factors and statistical calculations. Results of risk of bias assessments and evaluation of small-study effect are summarized in online supplementary material and the appendix of this dissertation[59].

RESULTS OF THE ACUTE PANCREATITIS STUDY

Characteristics of the cohort analyzed

2,387 of the 2,461 patients with AP proved to be eligible for the analysis. Characteristics of this population are summarized in Table 1. In 9.76% of the cases, ANP was confirmed. There was a statistically significant difference between patients with and without ANP as regards age, gender, and BMI[49]. A detailed analysis of the results as regards other biomarkers can be found in the online supplementary material and the appendix of this dissertation[49].

ANP was associated with a significantly higher risk for mortality, severe disease course, and all the investigated local and systemic complications (Figure 6). ANP was also associated with longer hospitalization (9.13±6.21 days vs 20.78±19.70 days, p<0.001).

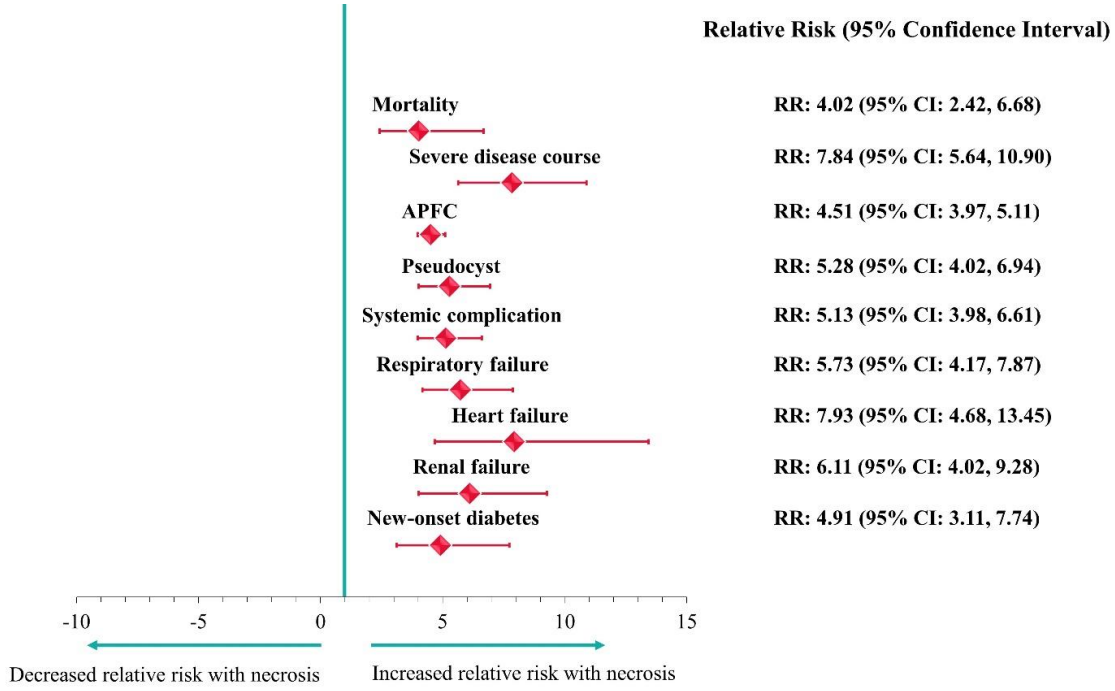

Figure 6. Association between necrosis development and other complications in acute pancreatitis

Model selection and model performance

After an evaluation of the machine learning algorithms, an XGBoost classifier was identified as the best-performing model with an AUC value of 0.757 (standard deviation: 0.012) on cross-validation (Figure 7).

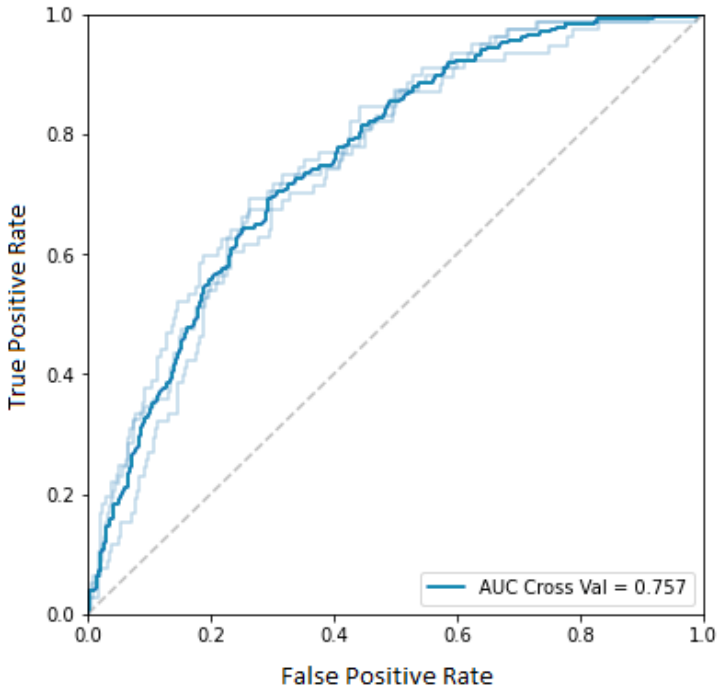

Figure 7. Receiver operating characteristic (ROC) curve for the XGBoost model

The relationship between the size of the data set and the model performance is depicted in Figure 8.

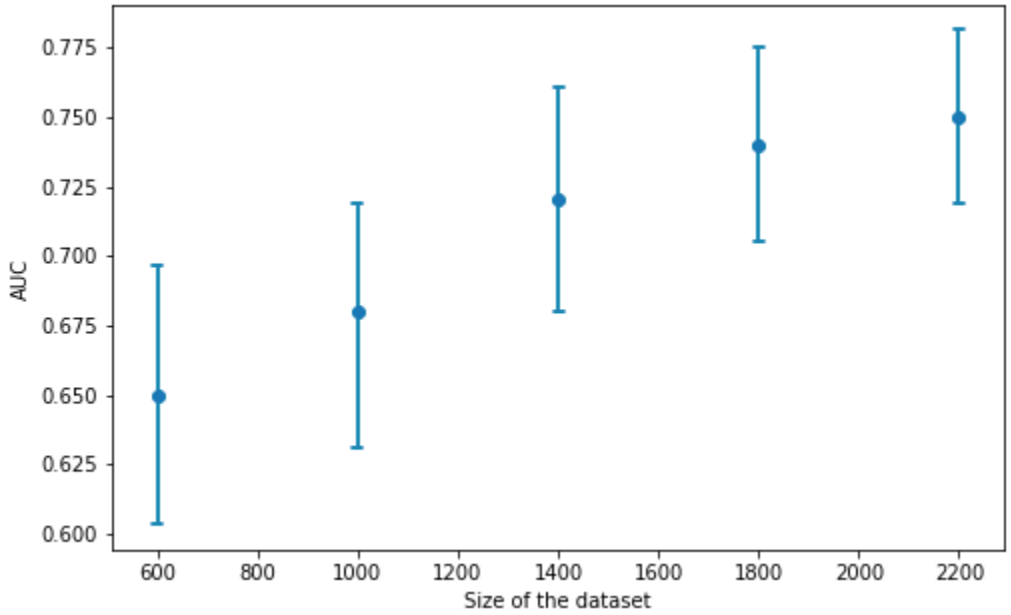

Figure 8. The relationship between the size of the data set and the model performance. The blue dot represents the area under the ROC curve value and the vertical lines show the corresponding confidence intervals.

The steady increase of AUC values implies that our model has not yet reached its maximal prediction performance. Internal validation implies that our model has higher reliability near the endpoints of the prediction spectrum since the confidence intervals are narrower (Figure 9).

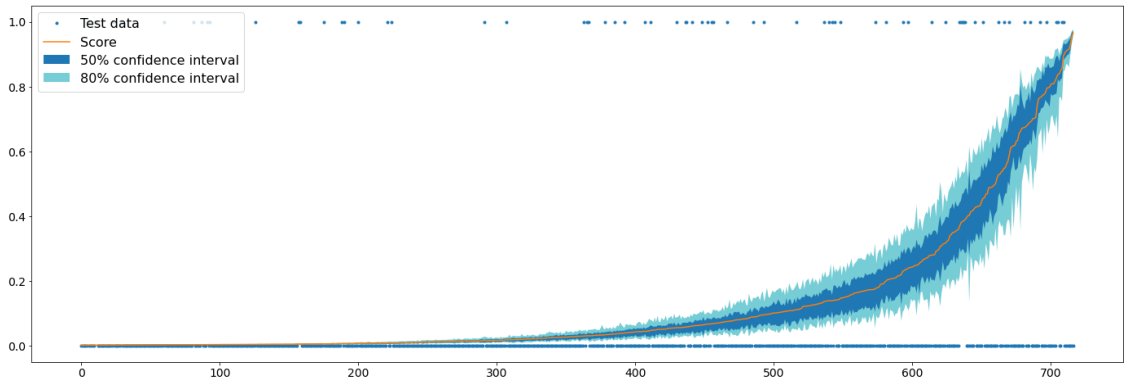

Figure 9. The predicted necrosis probabilities with the corresponding 50% (between the 25th and 50th percentiles) and 80% confidence (between the 10th and 90th percentiles). The assessment of the impact on the model output showed that glucose, CRP, ALP, gender, and WBC have the five highest SHAP values. The most influential predictors are shown in Figure 10 Panel A.

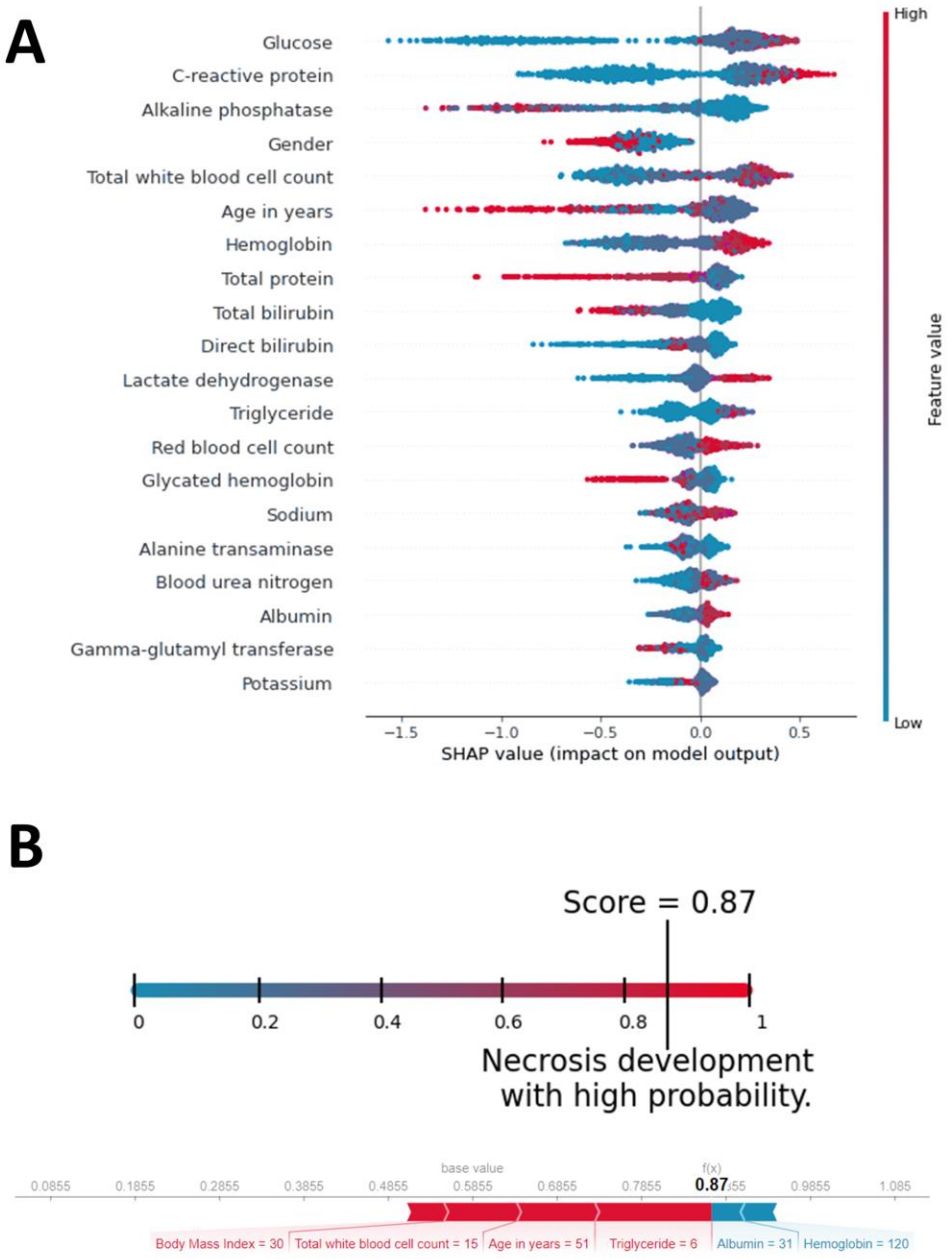

Figure 10. Panel A: the features with the highest impact on model output based on the SHAP values. The higher the predictor is on the list, the bigger the impact on model output. Each patient is represented by a dot. The x-axis represents the extent of the impact on prediction. The color of the dot shows the feature value (e.g., the red color implies higher values). Panel B. An example of prediction and its textual interpretation. The

lower picture highlights the effect of individual predictors and the final necrosis probability provided by the model

Our assessment showed that the predictive potential depends on the number of biomarkers provided. The models built on the top *k* most influential predictors according to their SHAP values show an increasing performance as regards the predictive potential; however, the extent of this improvement decreases with the number of variables provided (Figure 11).

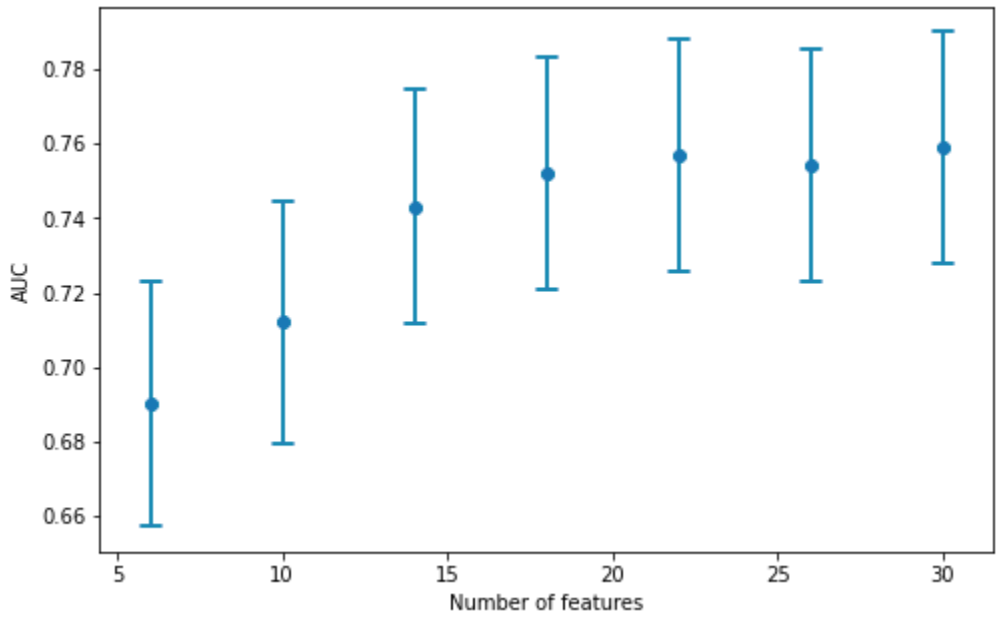

Figure 11. The models build on the *k* predictors with the highest SHAP value.

Application

The current version of the model can be accessed at http://necro-app.org/. At least five of the available predictors must be provided to use the application. This limit was applied based on the relation between the size of the dataset and the desired accuracy[153]. The application is aided by a built-in BMI calculator and validations to filter out invalid values. The model offers a numerical probability value between 0 and 1. The higher the number, the higher the risk for ANP becomes. These numerical values are also supplied with a textual interpretation. For educational purposes, the effect of the biomarkers on prediction is also indicated (Figure 10 Panel B). By checking an extra field, the application assigns a confidence interval in addition to the numerical value. This adds

further clarification to the predicted necrosis probability; however, it takes some extra time.

5. DISCUSSION

SUMMARY OF FINDINGS

In the COVID-19 meta-analysis, we have assessed the correlations between changes in laboratory parameters and the outcomes of patients with SARS-CoV-2 infection. In doing so, we have identified many laboratory parameters that could be crucial for the timely identification of patients at higher risk of adverse outcomes.

The acute pancreatitis study describes the first AI model designed to predict ANP. In addition to creating this model, we also implemented it as an easily accessible online tool. Furthermore, ANP was extensively described in a large, prospective, multicenter cohort study.

ELABORATION AND EXPLANATION

COVID-19 study

In the early stages of the pandemic, healthcare workers and scientists had a hard time systematizing the accumulating evidence. One estimate suggests that more than 200,000 COVID-19-related articles, including preprints, had been published by early December of 2020[154]. Along with several other meta-analyses, our study sought to systematize this vast amount of data focusing on on-admission biomarkers.

Our study provided further evidence for a remarkable early prognostic value of ALC in COVID-19 since we found that low absolute lymphocyte count on admission presents a significant risk for critical illness and mortality, but probably with different thresholds. In addition to these early changes, it has been reported that absolute lymphocyte counts remained low for additional few days in survivors and improved later, while in non-survivors, lymphopenia did not improve and in the majority of cases this further progressed[84,113]. Lymphocyte depletion might be explained by direct viral damage or by the imbalance of inflammatory mediators[155].

We also found that CD3 +, CD4 + and CD8 + cells were greatly decreased in non-survivors[26,137]. Importantly, these lymphocyte subsets play a role in viral clearance, reducing overreaction of the immune system, and developing long-term immunity, including that achieved after vaccination[155-157].

We have noted that patients with a higher total WBC on admission had a poorer prognosis, while low total WBC levels were found to be a protective factor. Higher total WBC values are probably due mainly to increased levels of neutrophils[158]. In support of this idea, higher neutrophil counts also "predisposed" patients to unfavorable disease outcomes[159]. In light of our current knowledge, this might not be surprising since neutrophils are responsible for the production of pro-inflammatory mediators. Overproduction of these mediators, the so-called cytokine storm, has been suggested as a major cause of critical illness and mortality in COVID-19[160].

It is important to note that increased levels of proinflammatory mediators such as CRP, fibrinogen and IL-6 were associated with worse outcomes. In agreement with previous studies, we found higher ferritin levels in non-survivors and critically ill patients. The laboratory profile in COVID-19 indicates hyperinflammation and may resemble secondary hemophagocytic lymphohistiocytosis (sHLH). However, other diagnostic criteria of sHLH have been rarely observed in COVID-19[161-163]. This knowledge may help to identify therapeutic targets to minimize the cytokine storm. In addition, identifying those at higher risk of a cytokine storm is essential for treating them appropriately in advance[164].

Procalcitonin is not typically increased in viral infections; thus, its elevated level at admission may not seem to be a significant finding in patients with COVID-19. Interestingly, according to our results, increased PCT levels have a predictive value for mortality, but not for intensive care requirement. An increase in its level might be associated with worse prognosis, possibly because of a bacterial superinfection, which could contribute to a rapid deterioration in the clinical course of disease towards multi-organ failure and death[165].

Compared to SARS-CoV, low platelet levels in COVID-19 are less common findings on admission[166]. Although we found lower platelet levels in deceased patients compared to discharged ones, our pooled analyses did not indicate a clear prognostic role for platelet counts. However, studies found decreasing levels of platelet in patients are associated with adverse outcomes during the hospital stay[125,167]. Thus, continuous monitoring of platelet counts may be required, even if its level initially gives no cause for concern.

Elevated D-dimer level is a typical sign of coagulation abnormalities in COVID-19[168]. In our meta-analysis, increased D-dimer level was associated with worse prognosis in every comparison, except for the mean baseline D-dimer level between deceased and discharged critically ill patients ($p = 0.149$). However, the interpretation of these findings is uncertain since D-dimer levels can depend on several factors, including the presence of comorbidities or inflammatory processes[168].

The general indicators of tissue damage, elevated LDH and CK, were also associated with unfavorable outcomes in our meta-analysis, but none of these two laboratory parameters is specific for a special condition.

The underlying causes of the laboratory abnormalities are not entirely understood. Thus, further studies, including animal experiments, histological and pathological examinations, and clinical trials might give insight and identify potential therapeutic targets. More studies are required to further specify the thresholds applicable in clinical practice and resolve the contradiction in the role of certain biomarkers. Besides static values, the dynamics of laboratory parameters would be worth further studying.

Acute pancreatitis study

The global incidence of pancreatic diseases, including AP, is increasing over time. Therefore, supporting clinical decision-making and developing and improving evidence-based guidelines are extremely important. The Hungarian Pancreatic Study Group aims to contribute to this process by formulating evidence-based guidelines for pancreatic diseases[169-174] and conducting multicenter international cohort studies[30,175-188], among them the cohort study presented in this dissertation, focusing on ANP. With the occurrence of ANP in around one-tenth of patients, our results are comparable with previously reported data[189,190]. The importance of ANP in determining the disease course and outcome is well-known[191,192]. Schepers et al. found that 38% of the patients with ANP developed respiratory, cardiovascular or renal system failure[193]. In our cohort, necrosis was also associated with a four to eight-fold increased risk of local and systematic complications, severe disease course, and mortality. We also confirmed their observation regarding prolonged hospitalization indicating the impact of ANP on short-term (i.e., in-hospital) outcomes. However, the importance of pancreatic necrosis development also lies in the long-term complications.

Recent studies investigated this topic and shed light on long-term outcomes. A meta-analysis of long-term follow-up studies found that the pooled prevalence of exocrine pancreatic insufficiency (EPI) after ANP is between 41 and 58% depending on the extent of necrosis[194]. In a cohort study by Maatman et al., this ratio was only 19%[51]. The discrepancy in the frequency can be attributed to that. While the meta-analysis accounted for EPI during both the hospital stay and follow-up, the cohort assessed EPI after the resolution of AP. Furthermore, the retrospective nature of data has an inherent limitation, which can also explain this difference. In addition to the increased frequency of EPI, they found endocrine insufficiency in 35% of the patients with a median follow-up of 46 months. Despite the fact that our study covered the time of hospitalization, our results imply that necrosis formation increases the risk of new-onset diabetes.

Since ANP is a potent prognostic factor for the short-term severity of AP and could forecast long-term consequences, it would be ideal for identifying these patients as soon as possible. The prediction of ANP was attempted by numerous scoring systems and biomarkers; however, each of them has its own limitations[195]. The Balthazar Computer Tomography Severity Index (CTSI) possesses a higher positive predictive value for necrosis than most commonly used prediction methods, e.g. the Ranson score and the APACHE II score, but it is limited by the availability of CECT[196]. It must be noted that ANP usually becomes apparent after two to three days after disease onset, and that prevents on-admission prediction in certain cases. The application of other scoring systems without mandatory CECT is restricted by their complexity. The Ranson score has eleven factors, which have to be assessed on admission and after 48 hours[197]. The APACHE II score is superior to the scores noted above in terms of flexibility and speed; however, its sensitivity and specificity are far lower[198]. Two prospective studies compared CTSI, Ranson score, and APACHE II score in predicting necrosis development[7,199]. Despite limitation in terms of patient number and the slightly different AUC values for necrosis, they concluded that the positive predictive value decreases in the following order: CTSI, Ranson score, and APACHE II. It must be emphasized that these scoring systems are strongly limited by the conversion of continuous variables to binary ones and this topic should be investigated by more mathematical models with better accuracy[7].

Artificial intelligence has appeared on the scene as a very intriguing modality of data-based decision support, and these models are extensively researched in numerous areas of medicine, including pancreatobiliary diseases[18]. In the last decade, multiple AI algorithms have been developed in AP[200]. Most of these models were designed to predict the occurrence of a specific complication or disease severity. The most commonly used score in critical care is the APACHE II score; however, three AP severity AI models have been reported to outperform this score[201-203]. The AI model developed by Keogan et al. was compared to the CTSI and Ranson scores, both of which were found inferior in terms of predicting the severity of AP[204]. It should be noted that this study assessed the disease severity with LOH and not with the revised Atlanta classification. Despite the positive results, these prediction systems, except for the artificial neural network by Mofidi et al.[203], are limited by the overlap between the data used for model training and the validation. Furthermore, these models need another step after validation. Despite the tremendous efforts and scientific results, much of this knowledge has not been applied in everyday clinical practice[205]. In order to bring these complex models to the bedside, they need to be implemented as easy-to-use and broadly accessible tools[206].

Our study was not designed to predict severity but to assess the probability of necrosis formation on clinical admission. Although we had a different outcome, we aimed to overcome the limitations of most previous models and find a way to use our AI model. As suggested by Shung et al., AI-assisted tools have to overcome many challenges[206]. First of all, we must have high-quality data. This issue was addressed in our study with a four-level data quality check system. The second main challenge is ongoing data maintenance. Our model was constructed such that the new data could be incorporated after validation. Since the predictive potential of the model shows an increasing trend, this could contribute to better accuracy. Algorithmic understanding is also a key factor. The help of physicians, who will eventually use the AI model, is crucial to confirm the performance of such a tool. Furthermore, practitioners could help in differentiating between valid predictions with actual signals and distorted predictions masked by confounding variables[206]. Our web-based application shows the weighted impact of the individual biomarkers in each decision. This tool thus meets these expectations. Consequently, the next step will be screening for these confounding factors while

continuously incorporating new data and monitoring the feasibility of the bedside application of this model.

STRENGTHS AND LIMITATIONS OF THE RESULTS

COVID-19 study

Up to our knowledge, at the time of the systematic search, our study was the most comprehensive meta-analysis that assesses associations between on-admission laboratory parameters and mortality, as well as intensive care requirement. Compared to meta-analyses prior to our study[207-235], our work contained the widest coverage of laboratory parameters in this topic with the largest sample size, from 16 different countries. We also analyzed the role of early laboratory parameters in an important subgroup: in patients who were critically ill on admission and had consequently higher mortality. We strictly evaluated all studies to avoid pooling studies with potentially overlapping populations and unclosed cases.

This meta-analysis has some limitations. Because of the nature of the studies included, selection bias can occur, particularly in the case of parameters that are not routinely measured[113]. There was considerable heterogeneity in some analyses. Additionally, because of some studies with a high risk of bias, our results need to be interpreted cautiously. High risk of bias among studies mainly resulted from the significant differences in baseline characteristics of patients. Patients with advanced age and comorbidities are at higher risk both for more severe COVID-19 and for laboratory abnormalities. Conversion of medians to means could also distort our results. The visual assessment of funnel plots and Egger's tests detected small-study effects in most of the analyses concerning WMD analyses.

Acute pancreatitis study

Our study has multiple strengths and some limitations. Although the predictive potential of this model is similar to that of currently available predictive scoring systems, it has multiple advantages over them. It provides risk assessment with any five of the predictors in our study, which are commonly assessed in daily practice. Therefore, this better reflects everyday clinical practice. To the best of our knowledge, this is the first AI model to strive to predict the development of ANP on clinical admission. We designed our model on a much larger population, as compared to the already existing prognostic AI

models in AP, and there was no overlap between the original and validation population. Furthermore, we placed great emphasis on the interpretation of the model for physicians and its implementation by creating an online application. Nevertheless, in addition to predictive model development, ANP was extensively analyzed.

In addition to these strengths, the present study has some limitations. Firstly, as we move further from the endpoint of the prediction spectrum, the confidence of the model becomes wider, and prediction becomes less reliable. Secondly, the cross-validated AUC value of our XGBoost model is currently in the fair range[236]. Thirdly, data imputation can also introduce bias. Most of these limitations can be overcome. Based on our analyses, we could reach better predictive potential by increasing the training sample size and more data could provide a more accurate imputation as well. Therefore, by using the application, making further predictions with more data, the model itself could improve.

It should be highlighted that AI models should not be considered as a substitute for human intelligence[200]. These tools, including our model, were designed to facilitate physicians' decision-making and every prediction should be interpreted in accordance with the clinical picture.

CONCLUSION AND IMPLICATIONS OF THE FINDINGS

COVID-19 study

We have shown that laboratory parameters on admission serve as important and early prognostic factors in COVID-19. These early findings could help to allocate resources and serve as a basis for future studies by narrowing down from a number of frequently measured biomarkers to those that have presumably higher prognostic significance.

Acute pancreatitis study

Development of ANP is associated with several short- and long-term complications, e.g., endocrine insufficiency, but CECT is not performed solely and exclusively to confirm necrosis in AP. Therefore, by knowing the high risk for necrosis development, we can identify a group of patients who need closer follow-up. Nevertheless, our model can aid physicians when CECT is either contraindicated or not available. Also, as soon as new therapies emerge, early identification of ANP will become even more important. Further research is needed on other potential predictive factors, which could be incorporated into the current model to further improve predictions.

6. SUMMARY OF NOVEL FINDINGS AND FUTURE PERSPECTIVES

Our COVID-19 study evaluated the available scientific evidence in the first wave of the pandemic, when the original virus strain from Wuhan was spreading. The scientific value of our study was given by the systematization of the exponentially growing amount of data about the incompletely known virus. As a result, it was included as a source in many future publications. From our results, it is worth highlighting that our meta-analysis was among the first publications that provided quantitative synthesis on the association between lymphopenia, low CD4+, and CD8+ lymphocyte subsets and worse prognosis in COVID-19. Naturally, with the appearance of new strains, these results had to be reevaluated; however, these associations can also be observed with the new variants[237-240]. Due to the amount of available data and the much more detailed knowledge related to SARS-CoV-2, future plans include a more detailed examination of certain specific biomarkers and the reevaluation of the associations in the case of newly emerging strains. The first AI algorithm estimating ANP risk was designed in our study. The predictive potential of this model is comparable to the already existing clinical scoring systems and the model is expected to further improve with use. The easy-to-use web application supported by the interpretation of the prediction facilitates early, on-admission prediction of necrosis and allows continuous data maintenance and algorithmic understanding. As a next step, we would like to test and evaluate our application in other AP populations. Further research is also planned to assess and incorporate other biomarkers in order to improve the predictive potential.

Nevertheless, we plan to continue our research on prognostic biomarkers and AI algorithms in pediatric population at Heim Pál National Pediatric Institute, which is one of the Translational Medicine Centers in Hungary.

7. THESIS ACKNOWLEDGEMENT

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8. SCIENTOMETRICS

The metrics and the publications rely on the MTMT2 system (https://m2.mtmt.hu/, Accessed: 2022.08.31.), the Scimago Journal Ranking (https://www.scimagojr.com/, Accessed: 2022.08.31.), and the Clarivate Journal Citation Reports (https://jcr.clarivate.com/jcr/home, Accessed: 2022.08.31.).

SUMMARY

Sum of scientific papers: 52 (D1:17, Q1:28, Q2:7, Q3:0, Q4:0)[40,48,241-290]

Cumulative impact factor based on Clarivate Journal Citation Reports: 252.571

First and last author impact factor based on Clarivate Journal Citation Reports: 20.765

Cumulative citations based on MTMT2 system: 421 (independent: 402)

Hirsch index based on MTMT2 system: 8

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10. APPENDIX

I.

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ORIGINAL INVESTIGATION

Early changes in laboratory parameters are predictors of mortality and ICU admission in patients with COVID-19: a systematic review and meta-analysis

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Abstract

Despite the growing knowledge of the clinicopathological features of COVID-19, the correlation between early changes in the laboratory parameters and the clinical outcomes of patients is not entirely understood. In this study, we aimed to assess the prognostic value of early laboratory parameters in COVID-19. We conducted a systematic review and meta-analysis based on the available literature in five databases. The last search was on July 26, 2020, with key terms related to COVID-19. Eligible studies contained original data of at least ten infected patients and reported on baseline laboratory parameters of patients. We calculated weighted mean differences (WMDs) for continuous outcomes and odds ratios (ORs) with 95% confidence intervals. 93 and 78 studies were included in quantitative and qualitative syntheses, respectively. Higher baseline total white blood cell count (WBC), C-reactive protein (CRP), lactate-dehydrogenase (LDH), creatine kinase (CK), D-dimer and lower absolute lymphocyte count (ALC) ($WMD_{ALC} = -0.35 \times 10^9$/L [CI −0.43, −0.27], $p < 0.001$, $I^2 = 94.2\%$; $< 0.8 \times 10^9$/L, $OR_{ALC} = 3.74$ [CI 1.77, 7.92], $p = 0.001$, $I^2 = 65.5\%$) were all associated with higher mortality rate. On admission WBC, ALC, D-dimer, CRP, LDH, and CK changes could serve as alarming prognostic factors. The correct interpretation of laboratory abnormalities can guide therapeutic decisions, especially in early identification of potentially critical cases. This meta-analysis should help to allocate resources and save lives by enabling timely intervention.

Keywords Covid-19 · Laboratory · Prognosis · Survival · Mortality · Meta-analysis

Introduction

Coronavirus disease-19 (COVID-19) is a novel coronavirus infection caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which was first detected in Wuhan, China, in December 2019 after a series of pneumonia cases of unknown aetiology had emerged [1]. On 11 March 2020, WHO declared the rapid spread of this virus a pandemic [2]. Since the initial detection of the virus, more than 25,000,000 cases of COVID-19 have been confirmed worldwide with over 850,000 fatal cases [3].

In some patients, symptoms of severe respiratory infection can occur with rapidly developing acute respiratory distress syndrome and other serious complications, which may be followed eventually by multiple organ failure and death. Therefore, early diagnosis and timely treatment of critical cases are crucial.

Despite some knowledge of the clinicopathological features of COVID-19, the correlation of changes in laboratory parameters and the prognosis of patients with COVID-19 is still unclear. However, studies on COVID-19 cases have shown that increased levels of white blood cells (WBC), decreased numbers of lymphocytes, especially CD8 + cells, increased levels of lactate-dehydrogenase (LDH), creatine kinase (CK), C-reactive protein (CRP), D-dimer, and levels of pro-inflammatory cytokines are associated with more

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severe inflammation and extensive lung damage with higher rates of admission to intensive care unit (ICU) and mortality [4]. A better understanding of early prognostic clinical laboratory parameters could save many lives by enabling timely intervention and better resource allocation since ICU capacity is limited in most countries. In this meta-analysis, we aimed to explore the significance of changes in the laboratory parameters and assessed the correlation between clinical laboratory data and the clinical outcomes of patients with COVID-19.

Methods

This systematic review with meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [5]. The review protocol was registered on PROSPERO (CRD42020176836).

Search strategy

The systematic literature search was conducted in MEDLINE (via PubMed), Embase, Cochrane Library (CENTRAL), Scopus, and Web of Science for studies published from 1st January 2020 to 9th April 2020. The following search terms were used: (”covid 19”) OR (“Wuhan virus”) OR (“coronavirus”) OR (“2019 nCoV”) OR (“SARS-cov-2”). There was no restriction on the language of the records.

Selection and eligibility criteria

We selected clinical studies reporting on at least ten confirmed SARS-CoV-2 infected patients (based on the WHO case definition) and their laboratory findings. Studies were included in the systematic review of data on at least one of the following variables could be extracted: total white blood cell count (WBC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet count, absolute basophil count, absolute eosinophil count (AEC), absolute monocyte count (AMC), C-reactive protein (CRP), haemoglobin, ferritin, lactate dehydrogenase (LDH), creatine kinase (CK), procalcitonin (PCT), fibrinogen, D-dimer, and any interleukins or lymphocyte subsets (CD3 + , CD4 + , CD8 +). The titles, abstracts, and full texts of the studies were screened by four independent review authors in pairs based on predefined criteria. The decision to include a study in the meta-analysis was based upon the assessment of the two reviewers and, if necessary, by a third reviewer for the resolution of any disagreements. Reference lists in the included studies and reviews on this topic were searched for additional studies. Publications citing the included studies were screened in the Google Scholar academic search engine too. Those studies that had either proven or suspected overlapping populations were included only in the systematic review part of this paper. To clarify these overlaps, we tried to contact the corresponding authors. Studies with more than 10% unclosed cases were excluded.

Data extraction

Four review authors independently extracted data into a standardized data collection form. The following data were extracted from each eligible article: first and second author, publication year, study site, study design, gender, age, and the means, standard deviations, medians, ranges, and interquartile ranges (IQR) of the laboratory values and specific thresholds with the corresponding intensive care requirement and mortality ratio. Data extraction was validated by a fifth review author. Discrepancies were resolved by a third party.

Risk of bias assessment

Based on the recommendation of the Cochrane Prognosis Methods Group, the QUIPS tool was applied by two independent authors for assessing the risk of bias in the studies included. Any disagreement was resolved based on consensus [6].

Statistical analysis

Pooled mean difference (weighted mean difference, WMD) was calculated for continuous outcomes and pooled odds ratios (ORs) were calculated for dichotomous outcomes. Random effect model was applied to all of the analyses with DerSimonien-Laird estimation. Statistical heterogeneity was analysed using the I^2 the χ^2 tests to obtain probability values: $p < 0.01$ was defined as indicating significant heterogeneity. Where mean with standard deviation was not reported for any of the outcomes, they were estimated from median, interquartiles and range using the method of Wan (2014) [7]. We performed separate analyses for mortality based on the clinical characteristics of the study population: one for all hospitalized COVID-19 patients (the “mixed” population) and the other for only critically ill COVID-19 patients. Small study effect was evaluated by visual assessment of funnel plot asymmetry and by Egger’s test were more than ten studies where available. Statistical analyses were performed with Stata 15 SE (Stata Corp). In the case of potentially overlapping study populations, data from the study with higher participant numbers were used for each outcome. ORs were calculated where raw data were available, however, only

those meta-analyses were interpreted where at least three non-overlapping studies were available, as required.

Results

The results of our search and selection are detailed in the PRISMA-Flowchart shown in Fig. 1. Our systematic search yielded 93 eligible studies from 16 countries. We summarize the characteristics of the included studies in Supplementary Table 1. Out of these, fifty-six studies reported on the association of laboratory parameters and mortality. [8–63]. Of these, forty-eight studies reported on 25,901 patients with all levels of disease severity (the "mixed" population), and eleven other studies discussed critically ill cases with an overall patient number of 2804. Forty-one studies with 11,935 patients comparing those with and without ICU requirement have also been included in this review [8, 19, 26, 29, 43, 64–100].

The incidence of mortality ranged from 6.25 to 61.5% in the mixed population and from 22.35 to 71.19% in the critically ill population. While the prevalence of ICU requirements ranged from 8.76 to 70.59%.

Results of the qualitative and quantitative synthesis are summarized in Supplementary Tables 2, 3, 4.

Weighted mean differences

Pooled analyses showed that among all COVID-19 patients mortality was associated with increased baseline WBC (WMD = 2.35×10^9/L [CI 1.96, 2.83], $p < 0.001$, $I^2 = 64.5\%$), ANC (WMD = 2.67×10^9/L [CI 2.12, 3.21], $p < 0.001$, $I^2 = 71.7\%$), CRP (WMD = 65.65 mg/L [CI 42.79, 87.50], $p < 0.001$, $I^2 = 99.4\%$), LDH (WMD = 203.79 U/L [CI 151.86, 255.71], $p < 0.001$, $I^2 = 95.2\%$), PCT (WMD = 0.38 ng/mL [CI 0.30, 0.47], $p < 0.001$, $I^2 = 91.8\%$), fibrinogen (WMD = 0.32 g/L [CI 0.13, 0.50], $p = 0.001$, $I^2 = 52.4\%$), D-dimer (WMD = 1.31 mg/L [CI 1.05, 1.57], $p < 0.001$, $I^2 = 84.5\%$), ferritin (WMD = 550.20 µg/L [CI 347.97, 752.43], $p < 0.001$, $I^2 = 15.8\%$), CK (WMD = 77.59 U/L [CI 55.31, 99.86], $p < 0.001$, $I^2 = 81.4\%$) and IL-6 (WMD = 84.26 pg/mL [CI 49.23, 119.30], $p < 0.001$, $I^2 = 97.5\%$). In the same population, decreased baseline ALC (WMD = -0.35x10^9/L [CI −0.43, −0.27], $p < 0.001$, $I^2 = 94.2\%$), CD3 + lymphocyte count (WMD = − 329.71 cell/µL [CI − 370.82, − 288.59], $p < 0.001$, $I^2 = 60.1\%$), CD4 + lymphocyte count (WMD = − 164.24 cell/µL [CI − 190.51, − 137.97], $p < 0.001$, $I^2 = 67.0\%$), CD8 + lymphocyte count (WMD = − 115.45 cell/µL [CI − 130.61, − 100.30], $p < 0.001$, $I^2 = 55.7\%$), AEC (WMD = -0.02×10^9/L [CI −0.03, −0.01], $p = 0.003$, $I^2 = 74.6\%$), AMC (WMD = -0.05×10^9/L [CI −0.08, −0.03], $p < 0.001$, $I^2 = 0.0\%$), and platelet count (WMD = -25.66×10^9/L [CI −35.56, −15.76], $p < 0.001$, $I^2 = 81.8\%$) was associated with increased mortality. (Fig. 2) We have not found significant association between baseline IL-1 and mortality among all COVID-19 patient.

Pooled analyses found that among all critically ill COVID-19 patients, mortality was associated with increased baseline LDH (WMD = 129.34 U/L [CI 67.73, 190.94], $p < 0.001$, $I^2 = 34.1\%$), increased CRP (WMD = 45.36 mg/L [CI 23.50, 87.50], $p < 0.001$, $I^2 = 35.3\%$), and decreased platelet levels (WMD = -30.19×10^9/L [CI −44.88, −15.50], $p < 0.001$, $I^2 = 0.0\%$). We have not identified significant baseline difference between deceased and discharged critically ill patients regarding WBC, ALC, PCT, and D-dimer levels.

Pooled analyses revealed that the following baseline laboratory parameters were higher in patients who required intensive care compared those did not: WBC (WMD = 1.53×10^9/L [CI 1.04, 2.02], $p < 0.001$, $I^2 = 68.8\%$), ANC (WMD = 2.47×10^9/L [CI 1.71, 3.23], $p = 0.037$, $I^2 = 75.2\%$), CRP (WMD = 65.65 mg/L [CI 42.79, 87.50], $p < 0.001$, $I^2 = 99.4\%$), LDH (WMD = 190.91 U/L [CI 129.40, 252.42], $p < 0.001$, $I^2 = 90.4\%$), PCT (WMD = 0.21 ng/mL [CI 0.05, 0.37], $p = 0.008$, $I^2 = 95.6\%$), CK (WMD = 54.07 U/L [CI 28.37, 79.77], $p < 0.001$, $I^2 = 35.2\%$), fibrinogen (WMD = 1.04 g/L [CI 0.66, 1.43], $p < 0.001$, $I^2 = 0.0\%$), D-dimer (WMD = 0.77 mg/L [CI 0.50, 1.04], $p = 0.007$, $I^2 = 81.1\%$), ferritin (WMD = 328.28 µg/L [CI 181.58, 474.99], $p < 0.001$, $I^2 = 15.8\%$), and IL-6 (WMD = 26.67 pg/mL [CI 15.98, 37.35], $p < 0.001$, $I^2 = 0.0\%$). Intensive care requirement was also associated with decreased baseline ALC (WMD = -0.30×10^9/L [CI −0.37, −0.23], $p < 0.001$, $I^2 = 87.0\%$), CD3 + lymphocyte count (WMD = − 322.56 cell/µL [CI − 589.00, − 55.54], $p = 0.018$, $I^2 = 83.5\%$), CD4 + lymphocyte count (WMD = − 142.98 cell/µL [CI − 242.12, − 43.85], $p = 0.005$, $I^2 = 82.2\%$), CD8 + lymphocyte count (WMD = − 186.52 cell/µL [CI − 254.84, − 118.21], $p < 0.001$, $I^2 = 73.3\%$), and haemoglobin (WMD = − 7.39 g/L [CI − 11.65, − 3.14], $p = 0.001$, $I^2 = 64.1\%$). No significant association was found between intensive care requirement and baseline AMC, platelet count.

Odds ratios

Among all COVID-19 patients, increased on admission total WBC was found to be a risk factor for mortality (> 9.5×10^9/L, OR = 3.7 [CI 1.72, 7.69], $p = 0.001$, $I^2 = 0.0\%$; > 10.0×10^9/L, OR = 6.25 [CI 2.86, 14.29], $p < 0.001$, $I^2 = 85.2\%$) and intensive care requirement (> 9.5×10^9/L, OR = 4.52 [CI 1.95, 10.52], $p < 0.001$, $I^2 = 26.8\%$; > 10.0×10^9/L, OR = 2.64 [CI 1.22, 5.71],

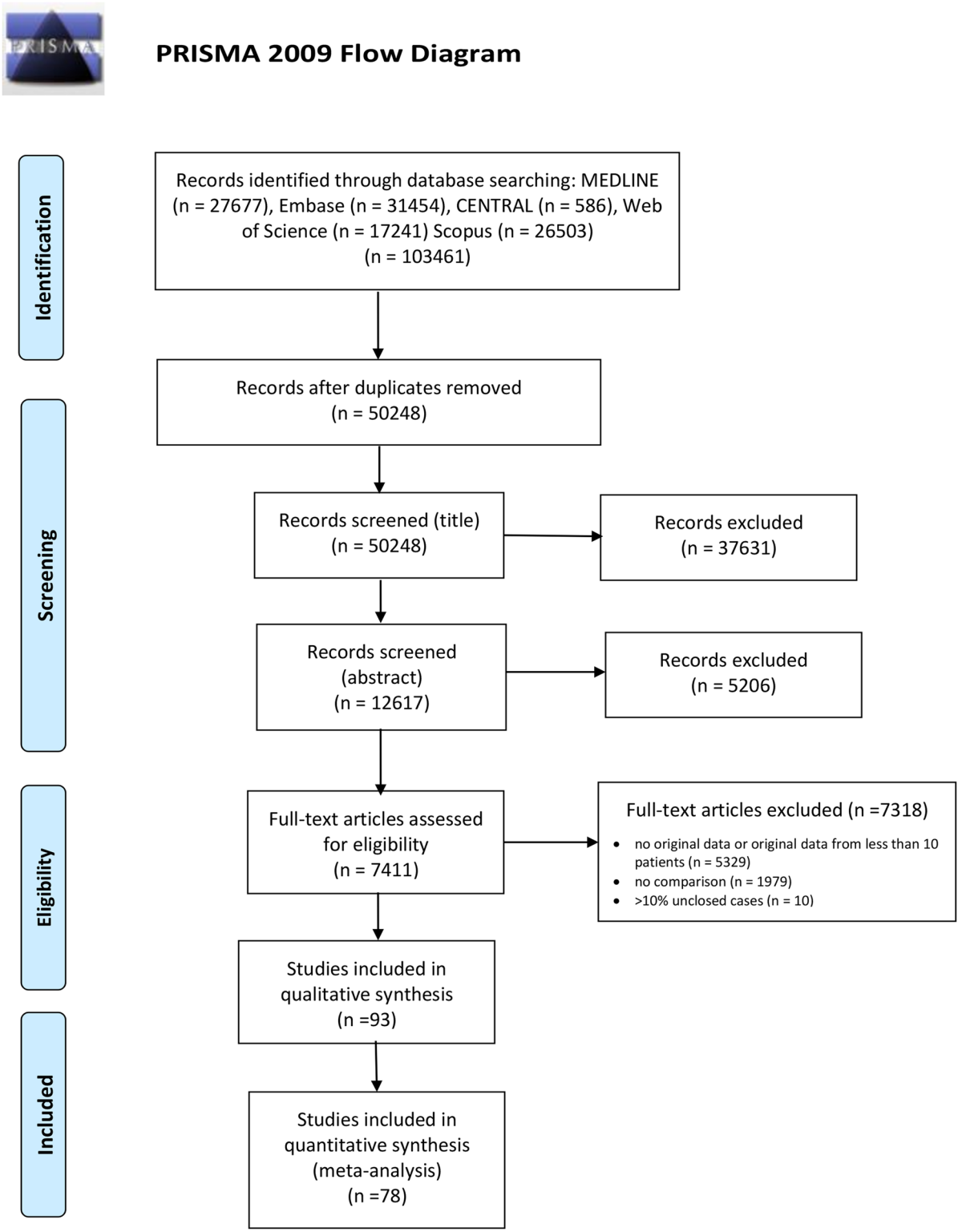

Fig. 1 PRISMA Flow Diagram showing the systematic search and selection process

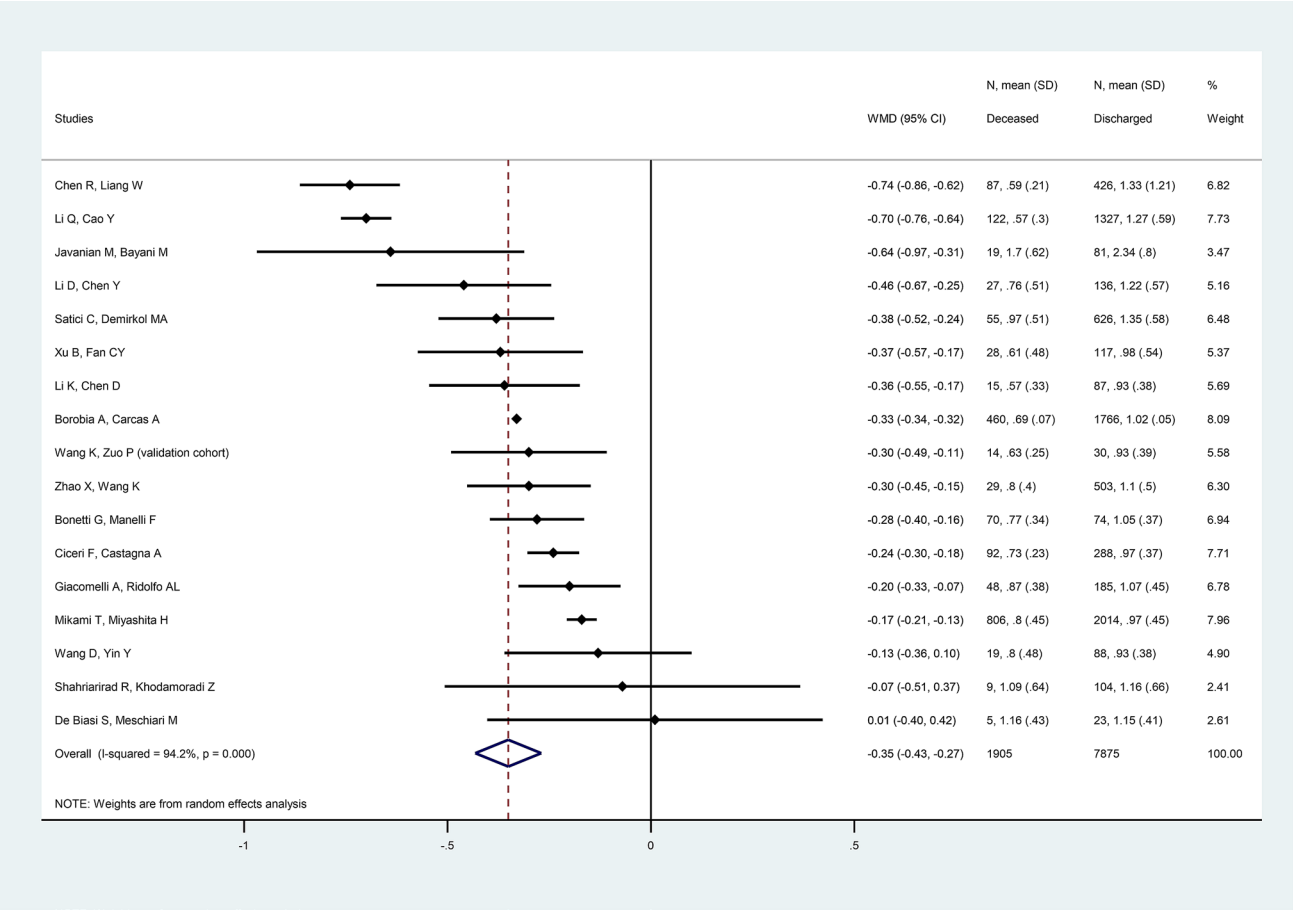

Fig. 2 Forest plot representing that decreased baseline absolute lymphocyte count was associated with increased mortality

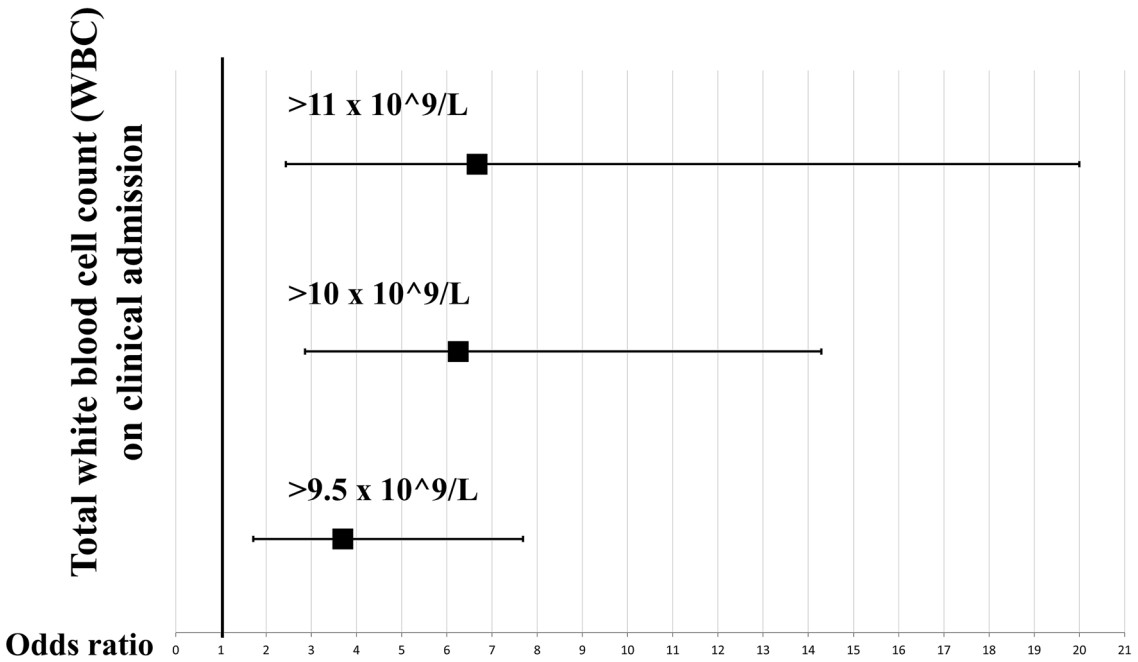

Fig. 3 Odds ratios suggest a stepwise increase in risk for mortality parallel with the increase of the total white blood cell threshold

$p = 0.014$, $I^2 = 61.3\%$). These results suggest a stepwise increase in risk for mortality in parallel with the increase of the total WBC threshold. This is depicted on Fig. 3. Furthermore, low baseline WBC was associated with decreased mortality ($< 4.0 \times 10^9$/L, OR = 0.38 [CI 0.20, 0.72], $p = 0.003$, $I^2 = 40.6\%$) and lower risk for intensive care requirement ($< 3.5 \times 10^9$/L, OR = 0.42 [CI 0.18, 0.96], $p = 0.039$, $I^2 = 0.0\%$).

Low ALC on clinical admission was a risk factor for mortality ($< 0.8 \times 10^9$/L, OR = 3.74 [CI 1.77, 7.92], $p = 0.001$, $I^2 = 65.5\%$) and intensive care requirement ($< 1.0 \times 10^9$/L, OR = 4.54 [CI 2.58, 7.95], $p < 0.001$, $I^2 = 26.8\%$; $< 1.1 \times 10^9$/L, OR = 2.64 [CI 1.49, 4.70], $p = 0.001$, $I^2 = 36.4\%$) among all COVID-19 patients. (Fig. 4).

Increased baseline ANC was found to be a risk factor for intensive care requirement ($> 6.3 \times 10^9$/L, OR = 2.32 [CI 1.23, 4.37], $p = 0.009$, $I^2 = 0.0\%$). We could not carry out a meta-analysis for any threshold regarding mortality, however individual studies support its role as a risk factor for mortality [23, 34, 49].

Assessment of low platelet on admission as a risk factor for mortality provided inconsistent results. Although baseline platelet level under 125×10^9/L was associated with a significantly higher risk for mortality among all COVID-19 patients, on admission platelet level below 100×10^9/L and 150×10^9/L did not show significant results. We did not find any threshold that is associated with increased risk for intensive care requirement.

Evaluation of increased CRP showed that baseline level over 10 mg/L and 100 mg/L is associated with increased mortality (OR = 4.84 [CI 1.49, 15.69], $p = 0.009$, $I^2 = 45.8\%$; OR = 2.49 [CI 1.42, 4.35], $p = 0.001$, $I^2 = 14.7\%$, respectively), however, the analysis regarding the threshold of 50 mg/L was not significant, which makes these results inconsistent. In case of intensive care

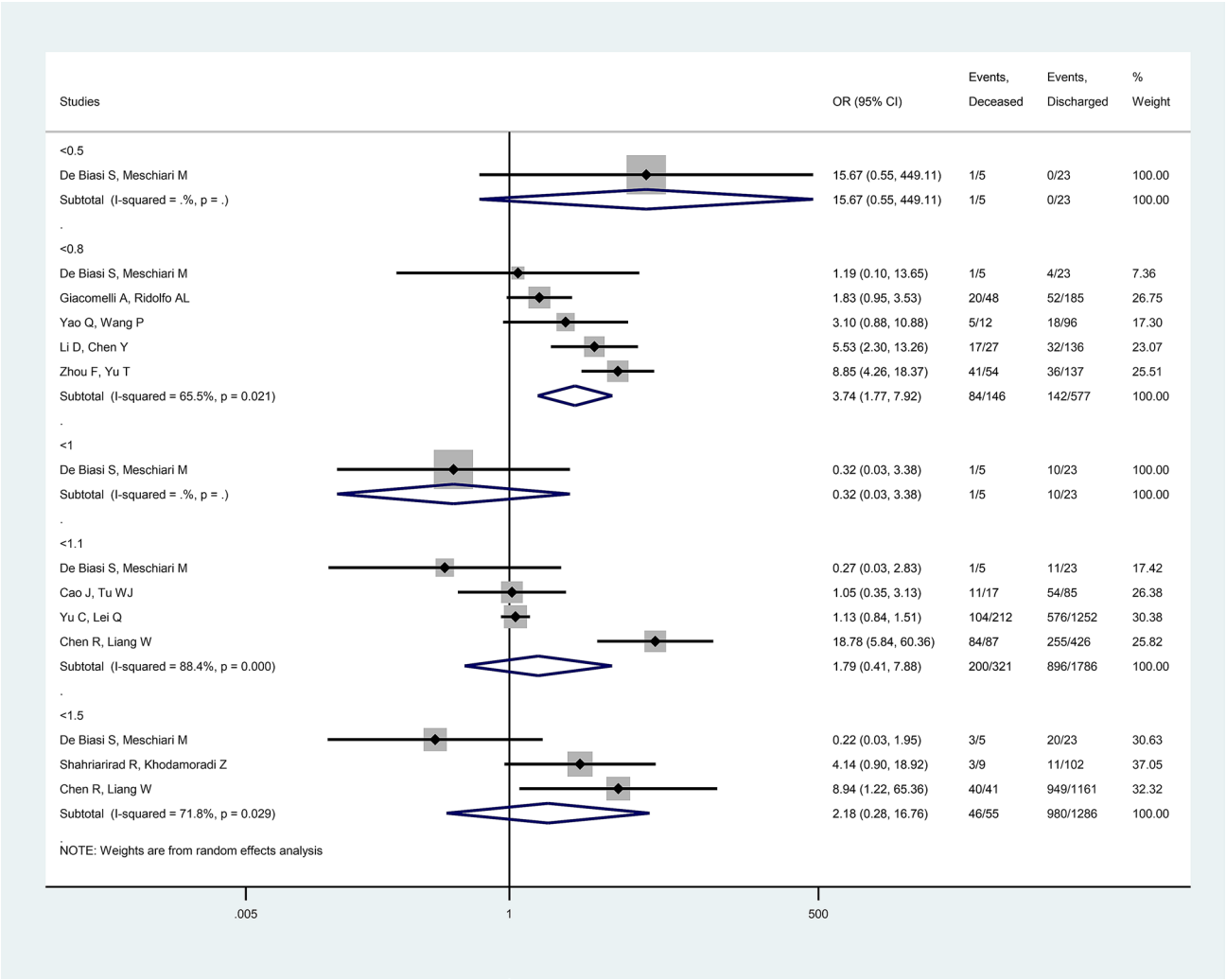

Fig. 4 Forest plot representing that low absolute lymphocyte count carries and increased risk for mortality

requirement, baseline level over 10 mg/L was found to be a risk factor (OR = 3.85 [CI 1.21, 12.22], $p = 0.022$, $I^2 = 55.4\%$).

On admission LDH over 250 U/L was found to be a risk factor both mortality (OR = 10.88 [CI 4.48, 26.39], $p < 0.001$, $I^2 = 0.0\%$) and intensive care requirement (OR = 9.44 [CI 4.412, 24.02], $p < 0.001$, $I^2 = 0.0\%$).

Baseline procalcitonin level over 0.05 ng/mL was not a risk factor for mortality, however, we found increased risk over the threshold of 0.50 ng/mL (OR = 11.97 [CI 4.75, 30.16], $p < 0.001$, $I^2 = 59.4\%$). The same thresholds provided non-significant results regarding intensive care requirement.

Increased D-dimer level on admission was found to be a risk factor for mortality (> 0.50 mg/L, OR = 4.30 [CI 1.55, 11.98], $p = 0.005$, $I^2 = 83,7$; > 1.0 mg/L, OR = 6.63 [CI 3.62, 12.14], $p < 0.001$, $I^2 = 45.1\%$) and intensive care requirement (> 0.50 mg/L, OR = 3.37 [CI 1.90, 5.95], $p < 0.001$, $I^2 = 0.0\%$).

On admission CK level over 185 U/L was associated with increased mortality (OR = 3.14 [CI 1.87, 5.27], $p < 0.001$, $I^2 = 0.0\%$). We could not carry out a meta-analysis for any threshold regarding intensive care requirement, however, individual studies support the role of increased CK as a risk factor [79, 85, 98].

There was no common threshold for any laboratory parameters with more than three non-overlapping studies, therefore, we were unable to calculate ORs for mortality among critically ill COVID-19 patients. ORs for mortality and intensive care requirements are summarized in Supplementary Table 3.

Risk of bias assessment and publication bias

Results of risk of bias assessments and evaluation of small-study effect are summarized in Supplementary Figures and among limitations of this study.

Discussion

In this meta-analysis, we have assessed the correlations between changes in laboratory parameters and the outcomes of patients with COVID-19. In doing so, we have identified many laboratory parameters that could be crucial for the timely identification of patients at higher risk of adverse outcomes.

This is the most comprehensive meta-analysis that assesses associations between on-admission laboratory parameters and mortality, as well as intensive care requirement. Compared with previous meta-analyses, [101–129]. our work contains the widest coverage of laboratory parameters in this topic with the largest sample size, from 16 different countries. To the best of our knowledge, this study is the only meta-analysis which assessed all potential thresholds for the investigated parameters regarding mortality and intensive care requirement. We also analysed the role of early laboratory parameters in an important subgroup: in patients who were critically ill on admission and had consequently higher mortality. We strictly evaluated all studies to avoid pooling studies with potentially overlapping population and unclosed cases.

Our study provides further evidence for a remarkable early prognostic value of ALC in COVID-19 since we found that low absolute lymphocyte levels on admission present a significant risk for critical illness and mortality, but probably with different thresholds. In addition to these early changes, it has been reported that absolute lymphocyte counts remained low for an additional few days in survivors and improved later, while in non-survivors, lymphopenia did not improve and in the majority of cases this further progressed [33, 62]. Lymphocyte depletion might be explained by direct viral damage or by the imbalance of inflammatory mediators [130].

We also found that CD3 +, CD4 + and CD8 + cells were greatly decreased in non-survivors [4, 85]. Importantly, these lymphocyte subsets play a role in viral clearance, reducing overreaction of the immune system [131],. and developing long-term immunity including that achieved after vaccination [130, 132].

We have noted that patients with a higher total WBC on admission had a poorer prognosis, while low total WBC levels were found to be a protective factor. Higher total WBC values are probably due mainly to increased levels of neutrophils [133]. In support of this idea, higher neutrophil counts also "predisposed" patients to unfavourable disease outcomes [134]. In light of our current knowledge, this might not be surprising since neutrophils are responsible for the production of pro-inflammatory mediators. Overproduction of these mediators, the so-called cytokine storm, has been suggested as a major cause of critical illness and mortality in COVID-19 [135].

It is important to note that increased levels of proinflammatory mediators such as CRP, fibrinogen and IL-6 were associated with worse outcomes. In agreement with previous studies, we found higher ferritin levels in non-survivors and critically ill patients. The laboratory profile in COVID-19 indicates hyperinflammation and may resemble secondary haemophagocytic lymphohistiocytosis (sHLH). However, other diagnostic criteria of sHLH have been rarely observed in COVID-19 [136–138].

This knowledge may help to identify therapeutic targets to minimize the cytokine storm. In addition, identifying those at higher risk of a cytokine storm is essential for treating them appropriately in advance [139].

Procalcitonin is not typically increased in viral infections; thus its elevated level at admission may not seem to

be a significant finding in patients with COVID-19. Interestingly, according to our results, increased PCT levels have a predictive value for mortality, but not for intensive care requirement. An increase in its level might be associated with worse prognosis, possibly because of a bacterial superinfection, which could contribute to a rapid deterioration in the clinical course of disease towards multiorgan failure and death [140].

Compared to SARS-CoV, low platelet levels in COVID-19 are less common findings on admission. [141]. Although we found lower platelet levels in deceased patients compared to discharged ones, our pooled analyses did not indicate a clear prognostic role for platelet counts. However, studies found decreasing levels of platelet in patients are associated with adverse outcomes during the hospital stay [142, 143]. Thus, continuous monitoring of platelet counts may be required, even if its level initially gives no cause for concern.

Elevated D-dimer level is a typical sign of coagulation abnormalities in COVID-19 [144]. In our meta-analysis, increased D-dimer level was associated with worse prognosis in every comparison, except for the mean baseline D-dimer level between deceased and discharged critically ill patients ($p = 0.149$). However, the interpretation of these finding is uncertain since D-dimer levels can depend on several factors, including the presence of comorbidities or inflammatory processes [145].

The general indicators of tissue damage, elevated LDH and CK, were also associated with unfavourable outcomes in our meta-analysis, but none of these two laboratory parameters are specific for a special condition.

The underlying causes of the laboratory abnormalities are not entirely understood. Thus, further studies, including animal experiments, histological and pathological examinations, and clinical trials might give insight and identify potential therapeutic targets. More studies are required to further specify the thresholds applicable in clinical practice and resolve the contradiction in the role of certain biomarkers. Besides static values, the dynamics of laboratory parameters would worth further studying.

This meta-analysis has some limitations. Because of the nature of studies included, selection bias can occur, particularly in the case of parameters that are not routinely measured [62]. There was considerable heterogeneity in some analyses. Additionally, because of some studies with a high risk of bias, our results need to be interpreted cautiously. High risk of bias among studies mainly resulted from the significant differences in baseline characteristics of patients. Patients with advanced age and comorbidities are at higher risk both for more severe COVID-19 and for laboratory abnormalities. Conversion of medians to means could also distort our results. The visual assessment of funnel plots and Egger's tests detected small-study effects in most of the analyses concerning WMD analyses.

In conclusion, we have shown that laboratory parameters on admission serve as important and early prognostic factors. These findings should help to allocate resources and potentially to save lives by enabling timely intervention.

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Author contributions SK: preparation of the draft of the manuscript, selection of studies, data extraction, risk of bias assessment; GN: statistical analysis, preparation of the standardized data collection sheet; PH: substantial contribution in study design; DN: statistical analysis; MF: selection of studies, data extraction; FD: selection of studies, data extraction; BN: data extraction, risk of bias assessment; MFJ: selection of studies, preparation of the standardized data collection sheet, stylistic and grammatical revision of the manuscript; KO: risk of bias assessment, stylistic and grammatical revision of the manuscript; ZM: expert in the field of anaesthesiology and intensive therapy, substantial contribution in study design and interpretation of data, preparation of the manuscript; NZ: substantial contribution in study design, validation of the data extraction; AP: preparation of the study protocol; PJH: preparation of the standardized data collection sheet, stylistic and grammatical revision of the manuscript; ZS: participation in the design of the study and its coordination; PG: provided revisions to the scientific content of the manuscript; BE: provided revisions to the scientific content of the manuscript; AH: expert in the field of haematology, substantial contribution in study design and interpretation of data, preparation of study protocol and the first draft of the manuscript.

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Availability of data and material (data transparency) The data that support the findings of this study are available from the corresponding author, [A.H.], upon reasonable request.

Compliance with ethical standards

Conflict of interest Authors do not have any conflicts of interest to declare.

Ethical approval This study was prepared in accordance with the Committee on Publication Ethics (COPE) guidelines to respect third parties rights such as copyright and/or moral rights. Ethical approval was not required to conduct this project as data is not individualized and primary data was not collected. Not required as data is not individualized and primary data was not collected.

Consent to participate Not required as data is not individualized and primary data was not collected.

Consent to publish The corresponding author accepts responsibility for releasing this material on behalf of any and all co-authors.

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Study name	Study design	Study site	Period of enrolment	Sample size	Characteristics of participants	Prevalence of mortality/ICU admission (%)
Studies assessing the risk for mortality in all COVID-19 patients						
Al-Samkari H, Leaf RK	retrospective cohort	5 hospitals in Boston, Massachusetts, USA	1 March-5 April, 2020	252	n.r.	11.51
Asghar MS, Kazmi, SJH	retrospective cohort	Karachi, Pakistan	March-April, 2020	100	mean age: 52.58±15.68, 31% female	22.00
Barman HA, Atici A	retrospective cohort	3 hospitals in Istanbul, Turkey	20 March - 20 April, 2020	607	age n.r., 45% female	16.97
Bhargava A, Fukushima EA	retrospective observational study	St John Hospital, Detroit, Michigan, USA	8 March-8 April, 2020	197	mean age: 60.6±16.2, 47.7% female	n.r.
Bazzan M, Montaruli B	n.r.	Turin, Italy	n.r.	88	age n.r., 31.8% female	10.23
Bonetti G, Manelli F	retrospective cohort	Emergency Department of the Valcamonica Hospital, Esine, Brescia, Lombardy, Italy	1 March-30 March, 2020	144	age n.r., 33.3% female	48.61
Borobia A, Carcas A	retrospective cohort	La Paz University Hospital, Madrid, Spain	25 February-19 April, 2020	2226	median age 61 (IQR 46-78), 51.8% female	20.66
Cao J, Tu WJ	retrospective cohort	Zhongnan Hospital, Wuhan, China	3 January - 1 February, 2020	102	median age 54 (IQR 37-67), 48% female	16·7
Chen L, Yu J	retrospective cohort	5 hospitals in China	20 January- 4 April, 2020	1859	median age 59 (IQR 45-68), 49,76 % female	11.12
Chen R, Liang W	retrospective cohort	575 hospitals in China	until 31 January, 2020	1590	n.r.	3.14
Chen R, Sang L	retrospective cohort	Wuhan, China	until 22 March, 2020	548	mean age 56±14.5, 42.9% female	18.79
Chen X, Zhao B	retrospective cohort	General Hospital of Central Theater Command, PLA, China	1 February-19 February, 2020	48	mean age 64.6±18.1, 22.9% female	6.25
Ciceri F, Castagna A	retrospective cohort	San Raffaele Hospital, Milan, Italy	25 February- 24 March, 2020	410	median age 76 (IQR 67-82) 27.1 % female	24.61
De Biasi S, Meschiari M	case-control	Infectious Diseases Clinics of the University Hospital in Modena, Italy	12 March-30 March, 2020	29	mean age 61.89±14, 17.24% female	17.24
Fan JL, Wang H	retrospective cohort	Zhongnan Hospital of Wuhan University in Wuhan, China	18 January-8February, 2020	21	mean age 62.5±12.6, 47.7 % female	19.05
Galloway JB, Norton S	observational cohort	King's College Hospital and Princess Royal University Hospital, London, UK	1 March- 17 April, 2020	1157	median age: 71 (IQR 57,82), 42.4% female	21.10
Gan J, Li J	retrospective case-control	Tongji Hospital, Wuhan, China	6 February - 8 March, 2020	95	median age 65 (IQR 56-76), 39% female	41.05
Giacomelli A, Ridolfo AL	prospective cohort	Luigi Sacco Hospital in Milan, Italy	21 February-19 March, 2020	233	median age 61 (IQR 50-72), 30.9% female	20.60
Javanian M, Bayani M	retrospective cohort	Ayatollah Rohani, Shahid Beheshti and Yahyanejad hospitals, Babol, Iran	25 February- 12 March, 2020	100	mean age 60.12±13.87, 49% female	19.00
Li D, Chen Y	retrospective cohort	West China Hospital, Sichuan University, Chengdu, China	31 January-18 February, 2020	163	n.r.	16.56
Li K, Chen D	retrospective cohort	Tongji Hospital, Wuhan, China	31 January- 25 March, 2020	102	median age 57 (IQR 45-70), 42% female	14.71
Li L, Yang L	retrospective cohort	Wuhan Union Hospital, Wuhan, China	1 January- 22 February, 2020	93	mean age 51±17.5, 44% female	26.88
Li Q, Cao Y	retrospective cohort	7 centers of 5 hospitals in China	20 January- 4 April, 2020	1449	median age 57 (IQR 42-66), 49% female	8.42
Li Y, Peng S	retrospective cohort	Thoracic Surgery Department, Tongji	1 January - 20 February, 2020	25	infected health car staff with a median	20.00

		Hospital, Wuhan, China			age of 32 (22-51) and infected hospitalized patients with a median age of 61 (range 51-69); 65% female	
Liu Y, Sun W	retrospective cohort	the Central Hospital of Wuhan, China	2 January- 1 March, 2020	383	median age: 46 (IQR (34–61), 57.7% female	12.8
Long H, Nie L	retrospective cohort	Tianyou Hospital affiliated to the Wuhan University of Science and Technology, Wuhan, China	18 January- 5 March, 2020	75	age n.r., 46.7 % female	30,67
Luo M, Liu J	retrospective cohort	Wuhan Pulmonary Hospital and Tongji Hospital, Huazhong University of Science and Technology, China	9 January- 31 March, 2020	1018	median age 61 (IQR 49-69), 48.8 % female	19.74
Mikami T, Miyashita H	retrospective cohort	8 hospitals in New York, USA	13 March - 17 April, 2020	2820	age n.r., 42.9% female	28.58
Omrani-Nava V, Maleki I	case controll	Mazandaran University of Medical Sciences, Iran	February-March, 2020	93	mean age: 56.3±15.2, 45.2% female	n.r.
Price-Haywood EG, Burton J	retrospective cohort	Ochsner Health, New Orleans, Louisiana, USA	1 March-11 April, 2020	3481	age n.r., 60% female	n.r.
Rivera-Izquierdo M, Valero-Ubierna MDC	retrospective case-series	Hospital Universitario, Clínico San Cecilio, Granada, Spain	16 March-10 April, 2020	238	mean age: 64.7±15.4, 45% female	25.6
Ruan Q, Yang K	retrospective cohort	Jinyintan and Tongji Hospital, Wuhan, China	n.r.	150	age n.r., 32% female	45.3
Salacup G, Bryan K	retrospective cohort	Philadelphia, USA	1 March- 24 April, 2020	244	median age 66 (IQR 58-76), 49% female	21.31
Satici C, Demirkol MA	retrospective cohort	Gaziosmanpasa Research and Training Hospital, University of Health Sciences, Istanbul, Turkey	2 April- 1 May, 2020	681	mean age 56.9±15.7, 49% female	8.08
Shahriarirad R, Khodamoradi Z	retrospective cohort	university affiliated hospitals in Shiraz, Iran	20 February-20 March, 2020	113	mean age 53.7±16.58, 37.2% female	7.96
Violi F, Cangemi R	retrospective cohort	5 COVID-19 dedicated centers in Italy	March-April, 2020	319	age n.r., 39.5% female	20.06
Wang D, Yin Y	retrospective cohort	Zhongnan Hospital of WuhanUniversity and Xishui People's Hospital, Wuhan, China	until 10 February, 2020	107	median age 51 (IQR 36-65), 46.7% female	17.76
Wang K, Zuo P TRAINING COHORT	prospective cohort	First People's Hospital of Jiangxia District in Wuhan, China	7 January-11 February, 2020	296	mean age 47.32 ±14.95, 52.7% female	6.42
Wang K, Zuo P VALIDATION COHORT	retrospective cohort	Infection department of Union Hospital in Wuhan, China	1 January-20 February, 2020	44	mean age 55.2±16.8, 45.5% female	31.82
Xu B, Fan CY	retrospective cohort	Hubei Provincial Hospital of traditional Chinese and Western medicine, Wuhan, China	26 December, 2019-1 March, 2020	145	age n.r., 47.6% female	19.31
Yang H, Yang LC	retrospective cohort	Tonji Hospital, Wuhan, China	29 January.20 March, 2020	94	age n.r., 52% female	13.83
Yao Q, Wang P	retrospective cohort	Dabieshan Medical Center, Huanggang city, Hubei Province, China	30 January- 11 February, 2020	108	median age 52 (IQR 37-58), 50.4% female	11.11
Ye W, Chen G	retrospective cohort	Wuhan Pulmonary Hospital, Hubei Province, China	1 January - 16 March, 2020	349	median age 62 (IQR 21-69), 48% female	14.90
Yu C, Lei Q	retrospective cohort	Tongji Hospital, Wuhan, China	14 January- 28 February, 2020	1464	median age 64 (IQR 51-71) 49.7 % female	61.50

Zhang L, Yan X	retrospective cohort	Wuhan Asia General Hospital, Wuhan, China	14 January-28 February, 2020	1464	median age: 64 (IQR 51-71), 49.7% female	14.48
Zhao L, Zhang YP	retrospective cohort	Tongji Hospital, Wuhan, China	9 February-16 February, 2020	51	n.r.	11.74
Zhao X, Wang K	prospective cohort	First People's Hospital of Jiangxia District, Wuhan, China	7 January-28 February, 2020	532	age n.r., 53.8 % female	54.51
Zhou F, Yu T	retrospective cohort	Jinyintan Hospital and Wuhan Pulmonary Hospital, Wuhan, China	29 December, 2019-31 January, 2020	191	mean age 56 (IQR 46-67), 38% female	28.27
Studies assessing the risk for intensive care requirement in all COVID-19 cases						
Aggarwal S, Garcia-Telles N	retrospective cohort	Des Moines, Iowa, USA	1 March- 4 April, 2020	16	mean age 67 (IQR: 38-95), 25% female	50.00
Al-Samkari H, Leaf RK	retrospective cohort	5 hospitals in Boston, Massachusetts, USA	1 March-5 April, 2020	400	age n.r., 43% female	36.00
Asghar MS, Kazmi, SJH	retrospective cohort	Karachi, Pakistan	March-April, 2020	100	mean age: 52.58±15.68, 31% female	33.00
Bhargava A, Fukushima EA	retrospective observational study	St John Hospital, Detroit, Michigan, USA	8 March-8 April, 2020	197	mean age: 60.6±16.2, 47.7% female	38.07
Burian E, Jungman F	retrospective cohort	Munich, Germany	March-April, 2020	65	mean age: 61.5±17, 35.4% female	43.08
Cai SH, Liao W	retrospective cohort	Dongguan People's Hospital, Nanfang hospital and the First Affiliated Hospital of Xiamen University, China	23 January-14 February, 2020	96	age n.r., 43.75% female	n.r.
Cecconi M, Piovani D	retrospective cohort	Humanitas Research Hospital, Rozzano, Italy	22 February- 22 March, 2020	239	mean age: 63.9 ± 14.0, 29.3% female	17.15
Chan SSW, Dheepa C	retrospective cohort	Tan Tock Seng Hospital, Singapore	24 February-28 March, 2020	75	median age 50 (IQR: 30-62), 33.3% female	26.67
Chen J, Tangkai Q	retrospective cohort	Shanghai Public Health Clinical Center, Shanghai, China	20 January-6 February, 2020	249	median age:51 (IQR 36–64), 49.4% female	8.84
Chen R, Sang L	retrospective cohort	Wuhan, China	until 22 March, 2020	548	mean age: 56±14.5, 42.9% female	8.76
Cugno M, Meroni PL	prospective ohort	Milan, Italy	n.r.	31	median age: 59 (range 31-85), 32.3% female	45.16
D'Alessandro M, Cameli P	prospective cohort	Siena University Hospital, Italy	n.r.	22	median age: 63 (IQR: 59-68), 27.3% female	54.55
Du RH, Liu LM	retrospective observational study	Wuhan Pulmonary Hospital, Tianyou Hospital and Central Hospital of Wuhan, China	25 December, 2019-15 February, 2020	109	mean age: 70.7±10.9, 32.1% female	46.79
Fan BE, Chong VCL	retrospective cohort	National Centre for Infectious Diseases, Singapore	23 January - 28 February, 2020	67	median age: 42 (IQR: 35-54), 44,8% female	13.43
Feng Y, Ling Y	retrospective cohort	Jinyintan Hospital in Wuhan, Shanghai Public Health Clinical Center in Shanghai, and Tongling People's Hospital in Anhui, China	1 January. 15 February, 2020	476	n.r.	14.71
Galloway JB, Norton S	observational cohort	King's College Hospital and Princess Royal University Hospital, London, UK	1 March- 17 April, 2020	1157	median age: 71 (IQR 57,82), 42.4% female	13.57
Goshua G, Pine AB	cross-sectional study	Yale New Haven Hospital, Connecticut, USA	13 April-24 April, 2020	68	mean age: 62±16, 40% female	70.59
Hong KS, Lee KH	retrospective cohort	Yeungnam University Medical Center in Daegu, South Korea	in December, 2019	98	mean age: 55.4±17.1, 61.2% female	13.27

Huang C, Wang Y	prospective cohort	Jinyintan Hospital, Wuhan, China	16 December, 2019-2 January 2020	41	median age: 49 (IQR: 41-58), 27·0% female	31.71
Ihle-Hansen H, Berge T	n.r.	University of Oslo, Norway	3 March-31 March, 2020	42	median age: 72.5 (range 30-95), 33.3% female	21.23
Israelsen SB, Kristiansen KT	retrospective case-series	Hvidovre Hospital, Copenhagen, Denmark	10 March-23 April, 2020	175	median age:71 (IQR 55-81), 51.4%	15.43
Khamis F, Al-Zakwani I	retrospective case-series	Royal Hospital and Al Nahdha Hospital, Oman	24 February-24 April, 2020	63	mean age: 48±16, 15% female	38.10
Lagi F, Piccica M	retrospective cohort	Infectious and Tropical Disease Unit of the University Hospital, Florence,Tuscany, Italy	5 February-26 March, 2020	84	median age: 62 (IQR 51-72), 34.5% female	19.05
Li H, Xiang X	retrospective cohort	Tianyou Hospital of Wuhan University of Science and Technology, China	18 January-26 February, 2020	132	mean age: 62.05±12.68, 43.2% female	12.12
Liu R, Wang Y	retrospective cohort	Renmin Hospital of Wuhan University, China	22 January-25 February, 2020	154	mean age: 64±14, 45.5% female	28.57
Liu Y, Yang Y	retrospective case-series	Shenzhen Third People's Hospital, China	10 January-20 January, 2020	12	age n.r., 25% female	50.00
McElvaney OJ, McEvoy NL	n.r.	Royal College of Surgeons in Ireland, Dublin, Ireland	n.r.	40	mean age: 55.5±17.7, 37.5% female	50.00
Murk J, Biggelar R	retrospective cohort	Elisabeth-Tweesteden Hospital, the Netherlands	26 February-20 March, 2020	100	age n.r., 33% female	19.00
Omrani-Nava V, Maleki I	case controll	Mazandaran University of Medical Sciences, Iran	February-March, 2020	93	mean age: 56.3±15.2, 45.2% female	n.r.
Ortiz-Bizuela E, Villanueva-Reza M	prospective cohort	211-bed referral hospital for adults, Mexico City, Mexico	26 February-23 March, 2020	140	median age: 49 (IQR 39-61.25), 39.3% female	20.71
Petrilli CM, Jones SA	prospective cohort	NYU Langone Health, New York, USA	1 March-8April, 2020	2729	median age: 63 (IQR 51.74), 38.7% female	36.28
Romana PF, Fabio DZ	retrospective cohort	Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, Italy	6 March- 16 April, 2020	515	median age: 65 (IQR 53-77), 37.3% female	14.95
Suleyman G, Fadel RA	retrospective case-series	Henry Ford Health System in metropolitan Detroit, Michigan, USA	9 March-17 March, 2020	335	mean age: 61.4±15.4, 53.5% female	42.90
Sun DQ, Wang TY	retrospective cohort	The First Affiliated Hospital of Wenzhou Medical University, China	February, 2020	32	median age: 61 (IQR 54-73),37.5% female	28.13
Urra JM, Cabrera CM	retrospective case-control study	University Hospital of Ciudad Real, Spain	1 March-15 April, 2020	172	age n.r., 28.3% female	15.70
Wang DW, Hu B	retrospective case-series	Zhongnan Hospital, Wuhan, China	1 January- 28 January	138	median age 56 (IQR: 42-68) 45·7 % female	26.09
Wang F, Hou H	retrospective cohort	Tongji Hospital, Wuhan, China	January, 2020	65	mean age: 57.11±13.03, 43% female	23.08
Wang R, Pan M	retrospective cohort	No.2 People's Hospital of Fuyang City, China	20 January-9 February, 2020	125	mean age: 41.46±15.09, 43.2% female	20.00
Wu J, Huang J	retrospective cohort	Wuhan Hankou Hospital and No. 6 Hospital of Wuhan, China	26 December, 2019- 15 March, 2020	2041	age NA, 58.2% female	34.15
Yang L, Liu J	retrospective case-series	Yichang Central People's Hospital, a designated hospital in Yichang, Hubei Province, China	30 January-8 February, 2020	200	mean age: 55±17.1, 51% female	14.50

Zeng Z, Ma YAC	retrospective cohort	5 hospitals in China	22 January-14 March, 2020	461	median age: 45 (IQR 34.5-57), 51.48 % female	11.93
Zhou Y, Fu B	n.r.	The First Affiliated Hospital of University of Science and Technology, Hefei, Anhui, China	n.r.	33	age n.r., 33.3% female	36.36
Studies assessing the risk for mortality in critically ill COVID-19 patients						
Auld S, Caridi-Scheible M	retrospective cohort	6 COVID-19 designated ICU in 3 hospitals in Atlanta, Georgia, USA	6 March-17 April, 2020	217	median age: 64 (IQR: 54-73), 45.2% female	29.66
Bhatraju KP, Ghassemieh BJ	retrospective case-series	9 hospitals in the USA	24 February-March 9, 2020	28	mean age: 64±18, 37% female	42.86
Borobia A, Carcas A	retrospective cohort	La Paz University Hospital, Madrid, Spain	25 February-19 April, 2020	75	median age 64 (IQR 54-71), 24% female	73.33
Cen Y, Chen X	retrospective cohort	Huoshenshan Hospital, General Hospital of the Central Theatre Command of the PLA, and mobile cabin hospitals in Wuhan, China	from 10 January, 2020	65	age n.r., 50.8% female	66.15
Cummings MJ, Darryl Abrams	prospective observational cohort	two NewYork-Presbyterian hospitals affiliated with Columbia University Irving Medical Center in northern Manhattan, USA	2 March-April 1, 2020	1150	median age: 62 (IQR 51–72), 33% female	22.35
Fan H, Zhang L	retrospective cohort	Jinyintan Hospital, Wuhan, China	30 December, 2019-16 Fenruary, 2020	73	mean age: 58.36±14.31, 32.9% female	64.38
He XW, Lai JS	retrospective cohort	Tongji Medical College, Huazhong University of Science and Technology, China	3 February. 24 February, 2020	54	median age: 68 (IQR 59.8-74.39, 37% female	48.15
Huang W, Li C	retrospective cohort	Tongji Hospital, Wuhan, China	29 January-6 March, 2020	615	age n.r., 38.2% female	37.72
Li J, Li M	retrospective cohort	the Central Hospital of Wuhan, China	1 January- 20 February, 2020	134	median age: 67 (IQR 56-75), 38.98 % female	71.19
Xu J, Yang X	retrospective cohort	Wuhan Union Hospital, Jinyintan Hospital, and Wuhan Third Hospital, China	12 January-3 February, 2020	239	mean age: 62.5±13.3, 40.2% female	61.51
Zou X, Li S	retrospective cohort	Tongji Hospital, Wuhan, China	10 January-10 February, 2020	154	mean age: 60.68±13, 56.5% female	33.77

Supplementary Table 1: Characteristics of included studies
In-hospital mortality: all patients were either dead or discharged· and no unclosed cases were included·
ICU=intensive care unit, SD=standard deviation, IQR=interquartile range, n.r.= not reported

Study name	N^0 of patients in the analysis (N^0 of studies)	Weighted Mean Difference with worse prognosis (95% Confidence Interval)	p-value	I-squared test (p-value)
Mortality in "mixed" population (deceased vs discharged)				
White blood cell × 10^9/L	7743 (20)	**2.35 (1.96, 2.83)**	**p<0.001**	64.5% (p<0.001)
Lymphocyte × 10^9/L	9780 (17)	**-0.35 (-0.43, -0.27)**	**p<0.001**	94.2% (p<0.001)
CD3+ lymphocyte cell/µL	2775 (4)	**-329.71 (-370.82, -288.59)**	**p<0.001**	60.1% (p=0.057)
CD4+ lymphocyte cell/µL	2775 (4)	**-164.24 (-190.51, -137.97)**	**p<0.001**	67.0% (p=0.028)
CD8+ lymphocyte cell/µL	2775 (4)	**-115.45 (-130.61, -100.30)**	**p<0.001**	55.7% (p=0.080)
Neutrophil granulocyte × 10^9/L	7210 (12)	**2.67 (2.12, 3.21)**	**p<0.001**	71.7% (p<0.001)
Eosinophil granulocyte × 10^9/L	762 (3)	**-0.02 (-0.03, -0.01)**	**p=0.003**	74.6% (p=0.019)
Monocyte × 10^9/L	2670 (7)	**-0.05 (-0.08, -0.03)**	**p<0.001**	0.0% (p=0.583)
Platelet × 10^9/L	9570 (20)	**-25.66 (–35.56, -15.76)**	**p<0.001**	81.8% (p<0.001)
Haemoglobin g/L	5522 (14)	**-3.69 (-6.51, -0.87)**	**p=0.010**	71.9% (p<0.001
C-reactive protein mg/L	9093 (21)	**65.65 (43.79, 87.50)**	**p<0.001**	99.4% (p<0.001)
Lactate dehydrogenase (U/L)	8314 (16)	**203.79 (151.86, 255.71)**	**p<0.001**	95.2% (p<0.001)
Procalcitonin ng/mL	9900 (12)	**0.38 (0.30, 0.47)**	**p<0.001**	91.8% (p<0.001)
Fibrinogen g/L	6476 (7)	**0.32 (0.13, 0.50)**	**p=0.001**	52.1% (p=0.051)
D-dimer mg/L	12540 (22)	**1.31 (1.05, 1.57)**	**p<0.001**	84.5% (p<0.001)
Ferritin µg/L	8274 (11)	**550.20 (347.97, 752.43)**	**p<0.001**	15.8% (p=0.305)
Creatine kinase (U/L)	5047 (9)	**77.59 (55.31, 99.86)**	**p<0.001**	81.4% (p<0.001)
Interleukin-1 pg/mL	1116 (3)	0.27 (-0.14, 0.67)	p=0.197	95.1% (p<0.001)
Interleukin-6 pg/mL	7023 (8)	**84.26 (49.23, 119.30)**	**p<0.001**	97.5% (p<0.001)
Mortality among critically ill patients (deceased vs discharged)				
White blood cell × 10^9/L	326 (3)	-0.27 (-1.64, 1.10)	p=0.697	19.9% (p=0.287)
Lymphocyte × 10^9/L	403 (4)	-0.12 (-0.28, 0.03)	p=0.119	75.5% (p=0.007)
Platelet × 10^9/L	401 (4)	**-30.19 (-44.88, -15.50)**	**p<0.001**	0.0% (p=0.896)
C-reactive protein mg/L	423 (4)	**45.36 (23.50, 67.21)**	**p<0.001**	35.3% (p=0.200)
Lactate dehydrogenase (U/L)	189 (3)	**129.34 (67.73, 190.94)**	**p<0.001**	34.1% (p=0.219)
Procalcitonin ng/mL	124 (3)	0.13 (-0.23, 0.48)	p=0.479	88.9% (p<0.001)
D-dimer mg/L	411 (4)	1.69 (-0.61, 3.99)	p=0.149	85.5% (p<0.001)
Intensive care requirement (ICU vs non-ICU)				
White blood cell × 10^9/L	5130 (22)	**1.53 (1.04, 2.02)**	**p<0.001**	68.8% (p<0.001)
Lymphocyte × 10^9/L	8063 (23)	**-0.30 (-0.37, -0.23)**	**p<0.001**	87.0% (p<0.001)
CD3+ lymphocyte cell/µL	269 (3)	**-322.56 (-589, -55.54)**	**p=0.018**	83.5% (p=0.002)
CD4+ lymphocyte cell/µL	302 (4)	**-142.98 (-242.12, -43.85)**	**p=0.005**	82.2% (p=0.001)
CD8+ lymphocyte cell/µL	302 (4)	**-186.52 (-254.84, -118.21)**	**p<0.001**	74.3% (p=0.009)
Neutrophil × 10^9/L	2357 (18)	**2.47 (1.71, 3.23)**	**p=0.037**	75.2% (p<0.001)
Monocyte × 10^9/L	510 (6)	-0.06 (-0.14, 0.02)	p=0.146	58.7% (p=0.033)
Platelet × 10^9/L	2606 (21)	-4.26 (–18.44, 8.87)	p=0.492	66.4% (p<0.001)
Haemoglobin g/L	1647 (14)	**-7.39 (-11.65, -3.14)**	**p=0.001**	64.1% (p=0.001)
C-reactive protein mg/L	4402 (17)	**68.51 (53.19, 83.83)**	**p<0.001**	79.8% (p<0.001)
Lactate dehydrogenase (U/L)	2425 (16)	**190.91 (129.40, 252.42)**	**p<0.001**	90.4% (p<0.001)
Procalcitonin ng/mL	3763 (8)	**0.21 (0.05, 0.37)**	**p=0.008**	95.6% (p<0.001)
Fibrinogen g/L	695 (3)	**1.04 (0.66,1.43)**	**p<0.001**	0.0% (p=0.900)
D-dimer mg/L	3417 (15)	**0.77 (0.50, 1.04)**	**p=0.007**	81.1% (p<0.001)
Ferritin µg/L	2168 (3)	**328.28 (181.58, 474.99)**	**p<0.001**	15.8% (p=0.305)
Creatine kinase (U/L)	1586 (8)	**54.07 (28.37, 79.77)**	**p<0.001**	35.2% (p=0.148)
Interleukin-6 pg/mL	258 (4)	**26.67 (15.98, 37.35)**	**p<0.001**	0.0% (p=0.592)

Supplementary Table 2: Summary for the results of the quantitative synthesis for continuous outcomes.

Laboratory parameter	Threshold	N⁰ of patients in the analysis (N⁰ of studies)	Odds ratio with worse prognosis (95% Confidence Interval)	p-value	I-squared test (p-value)
Mortality in "mixed" population (deceased vs discharged)					
White blood cell × 10^9/L	<3.5	191 (2)	0.98 (0.24, 4.04)	p=0.976	0.0% (p=0.829)
	<4.0	4609 (7)	**0.38 (0.20, 0.72)**	**p=0.003**	40.6% (p=0.120)
	>9.5	302 (3)	**3.70 (1.72, 7.69)**	**p=0.001**	0.0% (p=0.523)
	>10.0	4747 (7)	**6.25 (2.86, 14.29)**	**p<0.001**	85.2 (p<0.001)
	>11.0	96 (1)	**6.67 (2.44, 20.0)**	**p<0.001**	-
Lymphocyte × 10^9/L	<0.5	28 (1)	14.67 (0.55, 449.11)	p=0.108	-
	<0.8	723 (5)	**3.74 (1.77, 7.92)**	**p=0.001**	65.5% (p=0.021)
	<1.0	28 (1)	0.32 (0.03, 3.38)	p=0.347	-
	<1.1	2107 (4)	1.79 (0.41, 7.88)	p=0.442	88.4% (p<0.001)
	<1.5	1341 (3)	2.18 (0.28, 16.76)	p=0.456	71.8% (p=0.029)
Platelet × 10^9/L	<100	328 (3)	3.42 (0.40, 29.38)	p=0.262	63.7% (p=0.064)
	<125	630 (3)	**8.10 (3.54, 18.54)**	**p<0.001**	32.7% (p=0.227)
	<150	1644 (5)	1.07 (0.66, 1.74)	p=0.770	0.0% (p=0.680)
	>400	204 (2)	3.37 (0.12, 91.10)	p=0.471	70.5% (p=0.066)
	>450	113 (1)	1.06 (0.12, 9.26)	p=0.960	-
C-reactive protein mg/L	>3.0	102 (1)	7.15 (0.41, 125.74)	p=0.179	-
	>5.0	528 (2)	6.25 (0.07, 592.58)	p=0.430	77.2 (p=0.036)
	>8.0	146 (2)	0.41 (0.11, 1.58)	p=0.195	0.0% (p=0.452)
	>10.0	1823 (4)	**4.84 (1.49, 15.67)**	**p=0.009**	45.8% (p=0.137)
	>50.0	375 (3)	1.34 (0.36, 5.02)	p=0.667	48.3% (p=0.145)
	>100	514 (3)	**2.49 (1.42, 4.35)**	**p=0.001**	14.7% (p=0.310)
	>150	1001 (2)	**2.92 (2.22, 3.84)**	**p<0.001**	0.0% (p=0.826)
Lactate dehydrogenase (U/L)	>214	3014 (2)	2.74 (0.14, 53.68)	p=0.506	77.1% (p=0.036)
	>245	141 (1)	**22.59 (2.96, 172.16)**	**p=0.003**	-
	>250	763 (3)	**10.88 (4.48, 26.39)**	**p<0.001**	0.0% (p=0.705)
	>350	27 (1)	0.07 (0.001, 1.91)	p=0.114	-
	>440	1492 (2)	1.56 (0.48, 5.13)	p=0.460	32.1% (p=0.225)
	>445	561 (2)	2.59 (0.12, 57.11)	p=0.548	81.7% (p=0.019)
Procalcitonin ng/mL	>0.05	4167 (3)	10.38 (0.26, 411.70)	p=0.213	96.0% (p<0.001)
	>0.10	164 (1)	**9.09 (4.17, 20.00)**	**p<0.001**	-
	>0.25	164 (1)	**12.50 (3.85, 33.33)**	**p<0.001**	-
	>0.50	1392 (4)	**11.97 (4.75, 30.16)**	**p<0.001**	59.4% (p=0.061)
D-dimer mg/L	>0.50	2920 (8)	**4.30 (1.55, 11.98)**	**p=0.005**	83.7% (p<0.001)
	>0.55	77 (1)	**9.77 (3.05, 31.33)**	**p<0.001**	-
	>1.0	895 (6)	**6.63 (3.62, 12.14)**	**p<0.001**	45.1% (p=0.105)
	>1.11	85 (1)	**4.07 (142, 11.67)**	**p=0.009**	-
	>2.0	1983 (2)	6.82 (0.77, 60.36)	p=0.084	66.1% (p=0.086)
	>2.5	280 (2)	8.77 (0.28, 270.16)	p=0.214	78.8% (p=0.030)
	>3.0	116 (2)	**18.09 (4.63, 70.69)**	**p<0.001**	0.0% (p=0.330)
Creatine kinase (U/L)	>185	428 (3)	**3.14 (1.87, 5.27)**	**p<0.001**	0.0% (p=0.458)
	>190	135 (2)	1.48 (0.47, 4.68)	p=0.506	0.0% (p=0.774)
Intensive care requirement (ICU vs non-ICU)					
White blood cell × 10^9/L	<3.5	460 (4)	**0.42 (0.18, 0.96)**	**p=0.039**	0.0% (p=0.501)
	<4.0	963 (7)	0.71 (0.37, 1.39)	p=0.323	32.9% (p=0.177)
	>9.5	482 (5)	**4.53 (1.95, 10.52)**	**p<0.001**	26.8% (p=0.243)

	>10.0	725 (4)	**2.64 (1.22, 5.71)**	**p=0.014**	61.3% (p=0.051)
	>11.0	96 (1)	**5.67 (2.21, 14.59)**	**p<0.001**	-
Lymphocyte × 10^9/L	<0.4	100 (1)	0.59 (0.07, 5.08)	p=0.629	-
	<0.6	100 (1)	1.08 (0.32, 3.95)	p=0.899	-
	<0.8	100 (1)	1.39 (0.49, 3.95)	p=0.542	-
	<1.0	831 (5)	**4.54 (2.58, 7.95)**	**p<0.001**	22.3% (p=0.273)
	<1.1	1267 (8)	**2.64 (1.49, 4.70)**	**p=0.001**	36.4% (p=0.138)
	<1.5	100 (1)	1.30 (0.47, 3.66)	p=0.613	-
	>3.2	315 (4)	1.38 (0.29, 6.67)	p=0.689	0.0% (p=0.687)
Neutrophil granulocyte × 10^9/L	>6.3	186 (3)	**2.32 (1.23, 4.37)**	**p=0.009**	0.0% (p=0.416)
	<1.8	109 (1)	0.12 (0.01, 2.24)	p=0.154	-
	<1.0	67 (1)	**439.40 (19.09, 9658.21)**	**p<0.001**	-
Platelet × 10^9/L	<100	331 (5)	1.60 (0.61, 4.19)	p=0.335	28.3% (p=0.233)
	<125	926 (5)	1.39 (0.80, 2.42)	p=0.243	0.0% (p=0.755)
	<150	479 (3)	1.05 (0.67, 1.65)	p=0.840	0.0% (0.641)
	>350	132 (1)	0.34 (0.02, 6.17)	p=0.468	-
	>400	158 (2)	**3.63 (1.13, 11.68)**	**p=0.031**	0.0% (p=0.347)
C-reactive protein mg/L	>5.0	499 (1)	16.00 (0.97, 263.34)	p=0.052	-
	>6.0	71 (1)	0.40 (0.12, 1.36)	p=0.143	-
	>10.0	948 (6)	**3.85 (1.21, 12.22)**	**p=0.022**	55.4% (p=0.047)
	>50.0	108 (2)	**5.53 (1.45, 21.15)**	**p=0.012**	0.0% (p=0.625)
	>100	730 (2)	**6.25 (4.23, 9.23)**	**p<0.001**	0.0% (p=0.850)
Lactate dehydrogenase (U/L)	>240	12 (1)	0.28 (0.01, 8.42)	p=0.465	-
	>245	40 (1)	7.06 (0.79, 62.72)	p=0.080	-
	>248	52 (1)	6.60 (0.77, 56.37)	p=0.085	-
	>250	301 (3)	**9.44 (4.12, 24.02)**	**p<0.001**	0.0% (p=0.953)
	>550	67 (1)	**8.48 (1.71, 42.13)**	**p=0.009**	-
Procalcitonin ng/mL	>0.05	517 (4)	14.78 (6.06, 36.03)	p<0.001	48.8% (p=0.118)
	>0.10	39 (1)	3.50 (0.82, 14.93)	p=0.090	-
	>0.12	132 (1)	3.12 (0.73, 13.23)	p=0.124	-
	>0.25	40 (1)	4.33 (0.62, 30.25)	p=0.139	-
	>0.50	1389 (7)	1.92 (0.92, 4.00)	p=0.081	57.6% (0.92, 4.00)
D-dimer mg/L	>0.50	837 (5)	**3.37 (1.90, 5.95)**	**p<0.001**	0.0% (p=0.780)
	>0.55	54 (1)	**6.58 (1.81, 23.96)**	**p=0.004**	-
	>1.00	400 (1)	**2.70 (1.75, 4.17)**	**p<0.001**	-
	>2.50	400 (1)	1.26 (0.69, 2.32)	p=0.454	-

Supplementary Table 3: Summary for the results of the quantitative synthesis for on admission laboratory thresholds

Study authors and year of publication	Results of the study regarding the association between baseline laboratory parameter and mortality/intensive care requirement
Studies assessing the risk for mortality in all COVID-19 patients	
Chen X, Zhao B 2020	Interleukin-6 <100 pg/mL vs ≥100 pg/mL (0/42 vs 3/3 death, respectively; p=0.001) *(Comment from review authors: This study was excluded from the quantitative synthesis because of the possibility of overlapping with other studies with higher patient number. See "Methods" section of the manuscript.)*
Galloway JB, Norton S 2020	Absolute lymphocyte count $x10^9$/L HR=0.46 (95% CI: 0.26, 0.84), p=0.010 Absolute neutrophil count $x10^9$/L HR=1.06 (95% CI: 1.02, 1.09), p<0.001 C-reactive protein mg/L HR= 1.06 (95% CI: 1.02, 1.09), p<0.001 *(Comment from review authors: HRs were adjusted for age and sex.)*
Li L, Yang L 2020	Total white blood cell count (p=0.201) (survivor: $4.6x10^9$/L (3.8–5.8); non-survivor $5.2x10^9$/L (3.9–5.9)) Absolute lymphocyte count (p=0.001) (survivor: $1.2x10^9$/L (0.9–1.6); non-survivor $0.8x10^9$/L (0.6–1.2)) Absolute neutrophil count (p=0.045) (survivor: $2.8x10^9$/L (2.2–3.6); non-survivor $3.8x10^9$/L (2.7–5.2)) Platelet count (p=0.002) (survivor: $181x10^9$/L (147–224); non-survivor $136x10^9$/L (112–173)) Haemoglobin (p=0.717) (survivor: 131 g/L (120–146); non-survivor 133 g/L (16.8)) Lactate dehydrogenase (p<0.001) (survivor: 204 U/L (173–248); non-survivor 373 U/L (151)) Creatine kinase (survivor: 59.5 U/L (40.8–116); non-survivor 186 U/L (124–300)) C-reactive protein (p<0.001) (survivor: 7.7 mg/L (3.9–15.7); non-survivor 77 mg/L (44)) D-dimer (p=0.064) (survivor: 0.3 mg/L (0.2–0.5); non-survivor 0.6 mg/L (0.3–2.1)) Ferritin (p=0.094) (survivor: 489 µg/L (381); non-survivor 810 µg/L (409)) *(Comment from review authors: Values are given in mean (SD) or median (IQR). Haemoglobin, lactate dehydrogenase, and C-reactive protein levels were reported in different measures (median and mean) in the two group. This study was excluded from the quantitative synthesis because of the possibility of overlapping with other studies with higher patient number. See "Methods" section of the manuscript.)*
Li Y, Peng S 2020	Absolute lymphocyte count <$1.1x10^9$/L (among survivors 18/20 vs among non-survivors 4/5; p=0.504) Total white blood cell count <$4x10^9$/L (among survivors 11/20 vs among non-survivors 1/5; p=1.000) Total white blood cell count <$9.5x10^9$/L (among survivors 9/20 vs among non-survivors 4/5; p=0.322) Increase of LDH (among survivors 11/20 vs among non-survivors 3/5; p=1.000) Increase of C-reactive protein (among survivors 13/20 vs among non-survivors 3/5; p=1.000) Increase of ferritin (among survivors 7/20 vs among non-survivors 2/5; p=1.000) Increase of D-dimer (among survivors 9/20 vs among non-survivors 2/5; p=1.000) *(Comment from review authors: Thresholds were not specified for lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer.)*
Liu Y, Sun W 2020	Platelet count <138 $x10^9$/L HR=5.42 (95% CI: 1.89, 15.60) → first quartile Platelet count 138–174 $x10^9$/L HR=2.20 (95% CI: 0.69, 7.02) → second quartile

	Platelet count 174–213 x10^9/L HR=2.29 (95% CI: 0.72, 7.31) → third quartile Platelet count >213x10^9/L HR=0.46 (95% CI: 0.26, 0.84) → fourth quartile P value trend: <0.001 (estimated using median value of each quartile) *(Comment from review authors: only the first threshold provided significant results.)*
Omrani-Nava V, Maleki I 2020	Lymphopenia OR=7.86 (95% CI: 0.43, 142.74), p=0.163 Thrombocytopenia OR=0.53 (95% CI: 0.04, 6.67), p=0.624 CRP (positive) OR=0.56 (95% CI 0.08, 3.75), p=0.553 *(Comment from review authors: data from 93 confirmed COVID-19 patients and 186 healthy controls Normal values reported: absolute lymphocyte count: 1,000-4,000 per mm^3; platelet: 150,000-450,000 per mm^3)*
Price-Haywood EG, Burton J 2020	Absolute lymphocyte count <1000/µL HR=1.33 (95% CI: 1.01, 1.74) Platelet count <150,000/µL HR=1.26 (95% CI: 1.00, 1.60) Procalcitonin >0.25 ng/mL HR=1.40 (95% CI: 1.06, 1.84) C-reactive protein >8.2 ng/mL HR=1.01 (95% CI: 0.49, 2.08) *(Comment from review authors: HRs were adjusted for race, age, sex, Charlson Comorbidity Index score, indicators for baseline vital signs and laboratory measures above or below predefined clinical thresholds (respiratory rate; levels of aspartate aminotransferase, venous lactate, creatinine, bilirubin, procalcitonin, and C-reactive protein; and counts of lymphocytes and platelets).*
Rivera-Izquierdo M, Valero-Ubierna MDC 2020	Lymphocytes HR=1.00 (95% CI: 0.99, 1.00) Neutrophils HR=1.00 (95% CI: 0.99, 1.01) Haemoglobin HR=1.00 (95% CI: 0.88, 1.13) D-Dimer HR=1.00 (95% CI: 0.99, 1.00) Ferritin HR=1.00 (95% CI: 1.00, 1.00) C-reactive protein HR=1.00 (95% CI: 1.00, 1.00) Procalcitonin HR=1.04 (95% CI: 1.00, 1.08) *(Comment from review authors: HRs were adjusted for age expressed as increments in the hazard of death per unit increase in the variable. However, these units were not reported.)*
Zhang L, Yan X 2020	Total white blood cell count C-index=0.625 (95% CI: 0.571, 0.676) Absolute lymphocyte count C-index=0.872 (95% CI: 0.832, 0.906) Absolute neutrophil count C-index=0.773 (95% CI: 0.725, 0.817) Platelet count C-index=0.781 (95% CI: 0.734, 0.824) Haemoglobin C-index=0.583 (95% CI: 0.528, 0.635) D-dimer C-index=0.883 (95% CI: 0.842, 0.916) *(Comment from review authors: Similarly to the AUC, C-index=1 corresponds to the best model prediction, and C-index=0.5 represents a random prediction. Source: https://square.github.io/pysurvival/metrics/c_index.html; Accessed 30/08/2020)*
Studies assessing the risk for intensive care requirement in all COVID-19 patients	
Bhargava A, Fukushima EA 2020	Leukopenia OR=0.81 (95% CI: 0.31, 2.12), p=0.67 Lymphopenia OR=1.47 (95% CI: 0.82, 2.64), p=0.20 Thrombocytopenia OR=1.17 (95% CI: 0.56, 2.42), p=0.68 Elevated C-reactive protein OR=4.20 (95% CI: 0.51, 34.94), p=0.15 Elevated procalcitonin OR=4.29 (95% CI: 1.41, 12.99), p=0.006 *(Comment from review authors: Thresholds were not specified)*
Cai SH, Liao W 2020	Absolute lymphocyte count OR=0.684 (95% CI: 0.350, 1.338), p=0.267 Absolute neutrophil count OR=0.979 (95% CI: 0.725, 1.322), p=0.889 Platelet count OR=0.997 (95% CI: 0.990, 1.004), p=0.398 Haemoglobin OR=1.006 (95% CI: 0.981, 1.032), p=0.630 Lactate dehydrogenase OR=1.001 (95% CI: 0.994, 1.008), p=0.756 Creatine kinase OR=1.002 (95% CI: 1.000, 1.005), p=0.097

	(Comment from review authors: Thresholds were not specified. Data of 96 confirmed COVID-19 cases.)
Cecconi M, Piovani D 2020	Procalcitonin ≥0.5 ng/mL HR=2.86 (95% CI: 1.74, 4.69), p<0.001 Interleukin-6 ≥200 pg/mL HR=1.31 (95% CI: 1.00, 1.73), p=0.049 Ferritin ≥ 336.2 ng/mL HR=2.49 (95% CI: 1.23, 5.04), p=0.012 C-reactive protein ≥5 mg/dL HR=3.63 (95% CI: 1.90, 6.92), p=0.010 *(Comment from review authors: Univariable Cox PH Model)*
Chen J, Tangkai Q 2020	Total white blood cell count $x10^9$/L OR=1.28 (95% CI: 1.08, 1.52), p=0.004 Absolute lymphocyte count $x10^9$/L OR=0.24 (95% CI: 0.08, 0.75), p=0.010 CD4+ lymphocyte count per 100 cells/μL OR=0.45 (95% CI: 0.31, 0.64), p<0.001 C-reactive protein mg/L OR=1.04 (95% CI: 1.02, 1.05), p=0.67 Lactate dehydrogenase (U/L) OR=1.01 (95% CI: 1.00, 1.02), p<0.001 *(Comment from review authors: Univariate logistic regression referring to increase or decrease of risk for mortality by each unit of the given parameters)*
Galloway JB, Norton S 2020	Absolute lymphocyte count $x10^9$/L HR=0.59 (95% CI: 0.30, 1.13), p=0.113 Absolute neutrophil count $x10^9$/L HR=1.09 (95% CI: 1.05, 1.13), p<0.001 C-reactive protein mg/L HR= 1.05 (95% CI: 1.03, 1.06), p<0.001 (Comment by review authors: HRs were adjusted for age and sex.)
Omrani-Nava V, Maleki I 2020	Lymphopenia OR=1.48 (95% CI: 0.23, 9.51), p=0.676 Thrombocytopenia OR=1.79 (95% CI: 0.12, 25.65), p=0.667 CRP (positive) OR=2.83 (95% CI 0.48, 16.54), p=0.245 *(Comment from review authors: data from 93 confirmed COVID-19 patients and 186 healthy controls.)*
Studies assessing the risk for mortality among critically ill COVID-19 patients	
Cummings MJ, Darryl Abrams 2020	Interleukin-6 pg/mL HR=1.11 (95% CI: 1.02, 1.20) (per decile increase) D-dimer μg/mL HR=1.10 (95% CI: 1.01, 1.19) (per decile increase) *(Comment from review authors: HRs were adjusted to initial severity of the disease.)*
Li J, Li M 2020	Platelet count OR=0.998 (95% CI: 0.978, 0.999), p=0.012 D-dimer OR=1.112 (95% CI: 0.951, 1.301), p=0.185 Lactate dehydrogenase OR=1.004 (95% CI: 1.000, 1.008), p=0.073 *Comment from review authors: ORs were adjusted for age, and cardiovascular disease acute respiratory distress syndrome)*

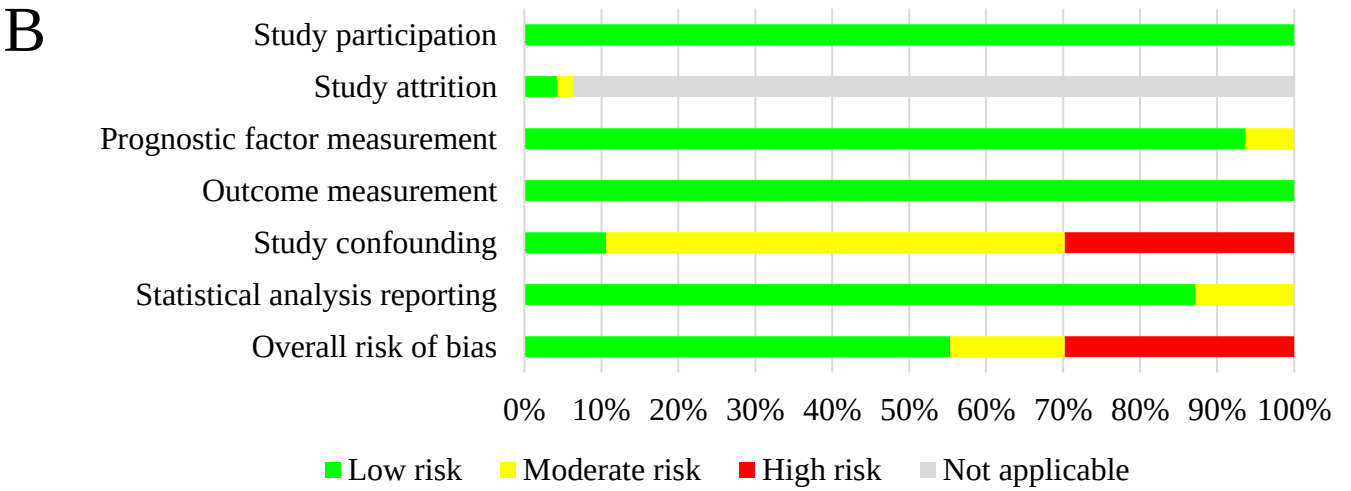
Supplementary Table 4: Results of studies included in the qualitative synthesis
CI: confidence interval; HR: hazard ratio; IQR: interquartile range OR: odds ratio, SD: standard deviation

A

n.a. Not applicable
+ Low risk
? Moderate risk
– High risk

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding [1]	Statistical analysis reporting [2]	Overall risk of bias	Included in meta-analyses
Asghar MS, Kazmi, SJH	+	n.a.	+	+	-	+	-	Yes
Al-Samkari H, Leaf RK	+	n.a.	+	+	-	+	-	Yes
Barman HA, Atici A	+	n.a.	+	+	?	+	+	Yes
Bazzan M, Montaruli B	+	?	+	+	-	+	-	Yes
Bonetti G, Manelli F	+	n.a.	+	+	?	+	+	Yes
Borobia A, Carcas A	+	n.a.	+	+	-	+	-	Yes
Cao J, Tu WJ	+	n.a.	+	+	-	+	-	Yes
Chen L, Yu J	+	n.a.	+	+	?	+	+	Yes
Chen R, Liang W	+	n.a.	+	+	?	+	+	Yes
Chen R, Sang L	+	n.a.	+	+	?	+	+	Yes
Chen X, Zhao B	+	n.a.	+	+	-	+	-	No
Ciceri F, Castagna A	+	n.a.	+	+	?	+	+	Yes
De Biasi S, Meschiari M	+	n.a.	+	+	?	+	+	Yes
Fan JL, Wang H	+	n.a.	+	+	?	+	+	Yes
Galloway JB, Norton S	+	n.a.	+	+	?	?	?	No
Gan J, Li J	+	n.a.	+	+	+	+	+	Yes
Giacomelli A, Ridolfo AL	+	+	+	+	-	+	-	Yes
Javanian M, Bayani M	+	n.a.	+	+	?	+	+	Yes
Li D, Chen Y	+	n.a.	+	+	-	+	-	Yes
Li K, Chen D	+	n.a.	+	+	?	+	+	Yes
Li L, Yang L	+	n.a.	+	+	?	+	+	No
Li Q, Cao Y	+	n.a.	+	+	-	+	-	Yes
Li Y, Peng S	+	n.a.	?	+	?	+	?	No
Liu Y, Sun W	+	n.a	+	+	?	?	?	No
Long H, Nie L	+	n.a.	+	+	-	+	-	Yes
Luo M, Liu J	+	n.a.	+	+	?	+	+	Yes
Mikami T, Miyashita H	+	n.a.	+	+	?	+	+	Yes
Omrani-Nava V, Maleki I	+	n.a.	+	+	-	?	-	No
Price-Haywood EG, Burton J	+	n.a.	+	+	?	?	?	No
Rivera-Izquierdo M, Valero-Ubierna MDC	+	n.a.	+	+	?	?	?	No
Ruan Q, Yang K	+	n.a.	?	+	-	+	-	Yes
Salacup G, Bryan K	+	n.a.	+	+	+	+	+	Yes
Satici C, Demirkol MA	+	n.a.	+	+	+	+	+	Yes
Shahriarirad R, Khodamoradi Z	+	n.a.	?	+	?	+	?	Yes
Violi F, Cangemi R	+	n.a.	+	+	?	+	+	Yes
Wang D, Yin Y	+	n.a.	+	+	-	+	-	Yes
Wang K, Zuo P (training cohort)	+	+	+	+	?	+	+	Yes
Wang K, Zuo P (validation cohort)	+	n.a.	+	+	?	+	+	Yes
Xu B, Fan CY	+	n.a.	+	+	?	+	+	Yes
Yang H, Yang LC	+	n.a.	+	+	?	+	+	Yes
Yao Q, Wang P	+	n.a.	+	+	?	+	+	Yes
Ye W, Chen G	+	n.a.	+	+	+	+	+	Yes
Yu C, Lei Q	+	n.a.	+	+	+	+	+	Yes
Zhang L, Yan X	+	n.a.	+	+	?	?	?	No
Zhao L, Zhang YP	+	n.a.	+	+	-	+	-	Yes
Zhao X, Wang K	+	+	+	+	?	+	+	Yes
Zhou F, Yu T	+	n.a.	+	+	?	+	+	Yes

B



Supplementary Figure 1: Risk of bias assessment on study level [A] and across studies [B] deceased and discharged patients with COVID-19

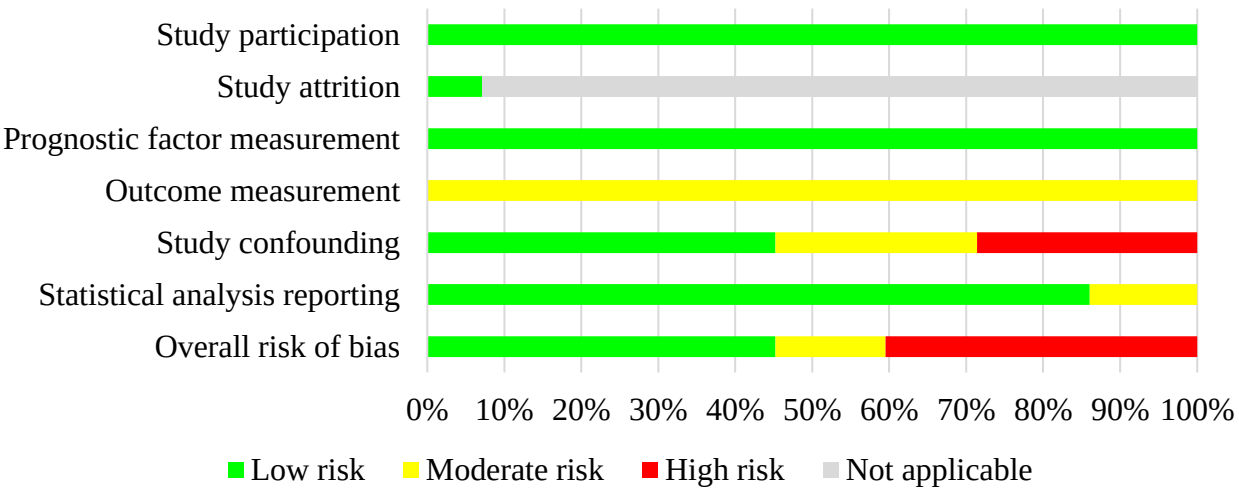
1: Assessed confounding factors are age, hypertension, heart failure and diabetes 2: As we analyzed raw data in the meta-analyses, statistical approaches of individual studies do no imply risk for this domain

A

n.a. Not applicable
+ Low risk
? Moderate risk
– High risk

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding [1]	Statistical analysis reporting [2]	Overall risk of bias	Included in meta-analyses
Aggarwal S, Garcia-Telles N	+	n.a.	+	?	+	+	+	Yes
Al-Samkari H, Leaf RK	+	n.a.	+	?	+	+	+	Yes
Asghar MS, Kazmi, SJH	+	n.a.	+	?	?	+	?	Yes
Bhargava A, Fukushima EA	+	n.a.	+	?	?	?	-	No
Burian E, Jungman F	+	n.a.	+	?	?	+	?	Yes
Cai SH, Liao W	+	n.a.	+	?	-	?	-	No
Cecconi M, Piovani D	+	n.a.	+	?	?	?	-	No
Chan SSW, Dheepa C	+	n.a.	+	?	-	+	-	Yes
Chen J, Tangkai Q	+	n.a.	+	?	?	?	-	No
Chen R, Sang L	+	n.a.	+	?	+	+	+	Yes
Cugno M, Meroni PL	+	n.a.	+	?	-	+	-	Yes
D'Alessandro M, Cameli P	+	n.a.	+	?	-	+	-	Yes
Du RH, Liu LM	+	n.a.	+	?	+	+	+	Yes
Fan BE, Chong VCL	+	n.a.	+	?	-	+	-	Yes
Feng Y, Ling Y	+	n.a.	+	?	+	+	+	Yes
Galloway JB, Norton S	+	n.a.	+	?	?	?	-	No
Goshua G, Pine AB	+	n.a.	+	?	+	+	+	Yes
Hong KS, Lee KH	+	n.a.	+	?	+	+	+	Yes
Huang C, Wang Y	+	+	+	?	+	+	+	Yes
Ihle-Hansen H, Berge T	+	n.a.	+	?	?	+	?	Yes
Israelsen SB, Kristiansen KT	+	n.a.	+	?	+	+	+	Yes
Khamis F, Al-Zakwani I	+	n.a.	+	?	+	+	+	Yes
Lagi F, Piccica M	+	n.a.	+	?	?	+	?	Yes
Li H, Xiang X	+	n.a.	+	?	-	+	-	Yes
Liu R, Wang Y	+	n.a.	+	?	+	+	+	Yes
Liu Y, Yang Y	+	n.a.	+	?	?	+	?	Yes
McElvaney OJ, McEvoy NL	+	n.a.	+	?	+	+	+	Yes
Murk J, Biggelar R	+	n.a.	+	?	+	+	+	Yes
Omrani-Nava V, Maleki I	+	n.a.	+	?	?	?	-	No
Ortiz-Bizuela E, Villanueva-Reza M	+	+	+	?	+	+	+	Yes
Petrilli CM, Jones SA	+	+	+	?	+	+	+	Yes
Romana PF, Fabio DZ	+	n.a.	+	?	?	+	?	Yes
Suleyman G, Fadel RA	+	n.a.	+	?	+	+	+	Yes
Sun DQ, Wang TY	+	n.a.	+	?	+	+	+	Yes
Urra JM, Cabrera CM	+	n.a.	+	?	+	+	+	Yes
Wang DW, Hu B	+	n.a.	+	?	-	+	-	Yes
Wang F, Hou H	+	n.a.	++	?	-	+	-	Yes
Wang R, Pan M	+	n.a.	+	?	-	+	-	Yes
Wu J, Huang J	+	n.a.	+	?	+	+	+	Yes
Yang L, Liu J	+	n.a.	+	?	-	+	-	Yes
Zeng Z, Ma YAC	+	n.a.	+	?	-	+	-	Yes
Zhou Y, Fu B	+	n.a.	+	?	-	+	-	Yes

B



Supplementary Figure 2: Risk of bias assessment on study level [A] and across studies [B] comparing patients with and without intensive care requirement

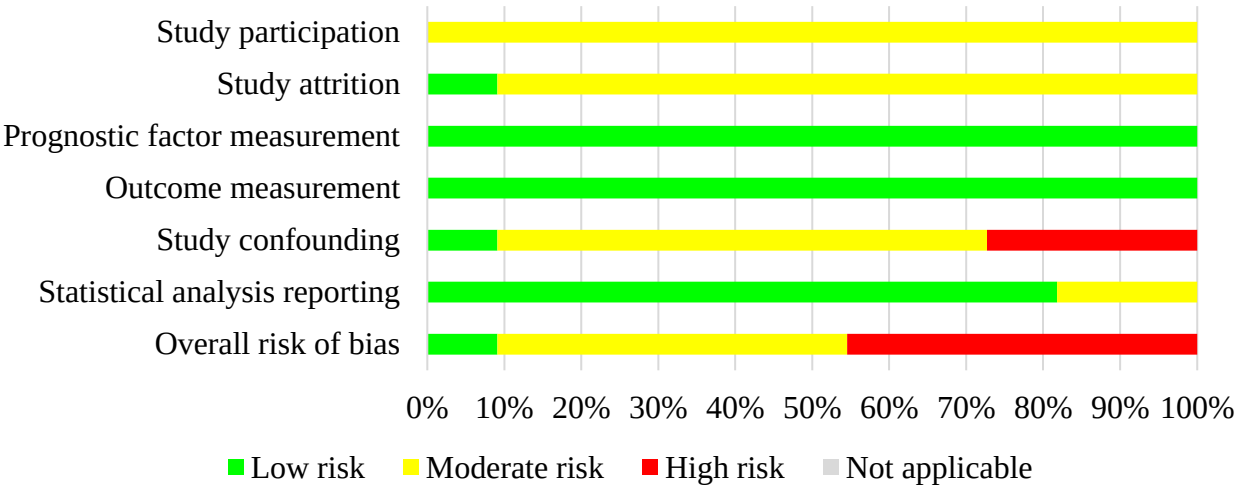
1: Assessed confounding factors are age, hypertension, heart failure and diabetes 2: As we analyzed raw data in the meta-analyses, statistical approaches of individual studies do no imply risk for this domain

A

n.a. Not applicable
+ Low risk
? Moderate risk
– High risk

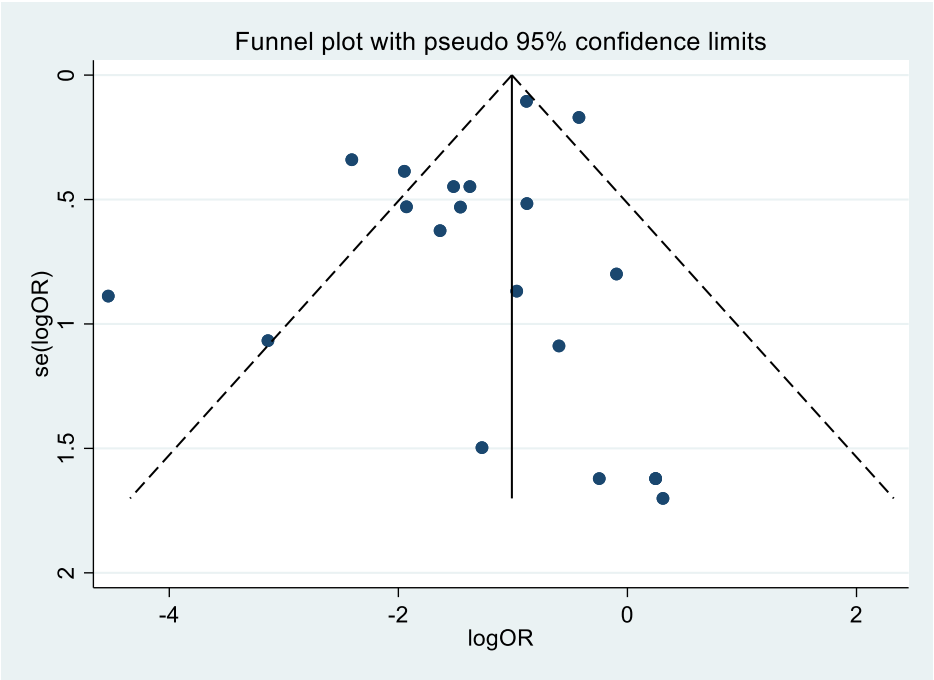
	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding [1]	Statistical analysis reporting [2]	Overall risk of bias	Included in meta-analyses
Auld S, Caridi-Scheible M	?	n.a.	+	+	?	+	?	Yes
Bhatraju KP, Ghassemieh BJ	?	n.a.	+	+	?	+	?	Yes
Borobia A, Carcas A	?	n.a.	+	+	-	+	-	Yes
Cen Y, Chen X	?	n.a.	+	+	?	+	?	Yes
Cummings MJ, Darryl Abrams	?	+	+	+	?	?	-	No
Fan H, Zhang L	?	n.a.	+	+	-	+	-	Yes
He XW, Lai JS	?	n.a.	+	+	?	+	?	Yes
Huang W, Li C	?	n.a.	+	+	+	+	+	Yes
Li J, Li M	?	n.a.	+	+	?	?	-	No
Xu J, Yang X	?	n.a.	+	+	?	+	?	Yes
Zou X, Li S	?	n.a.	+	+	-	+	-	Yes

B

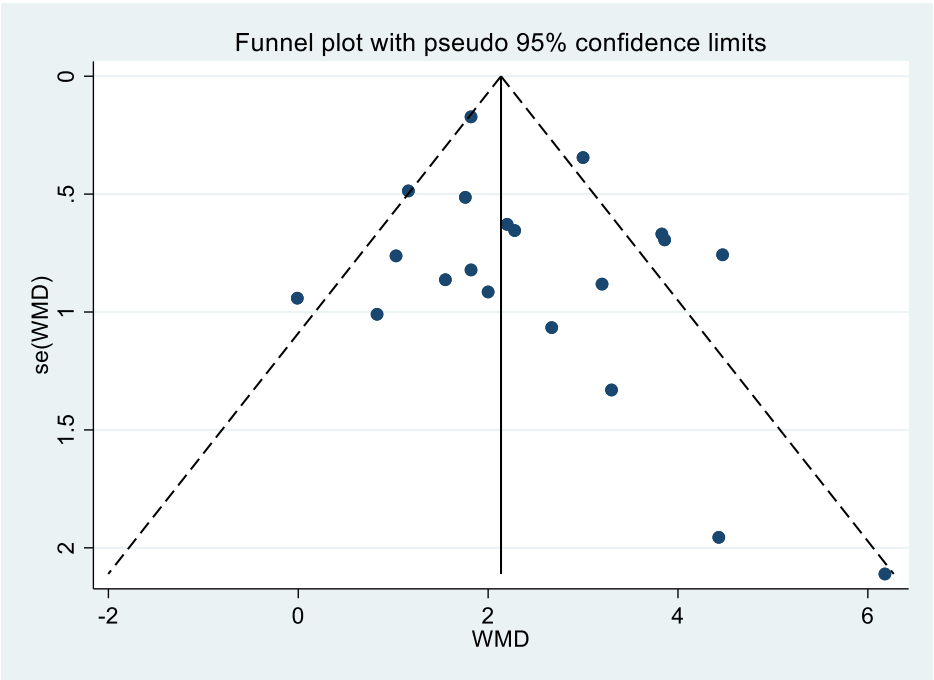


Supplementary Figure 3: Risk of bias assessment on study level [A] and across studies [B] comparing deceased and discharged critically ill patients with COVID-19

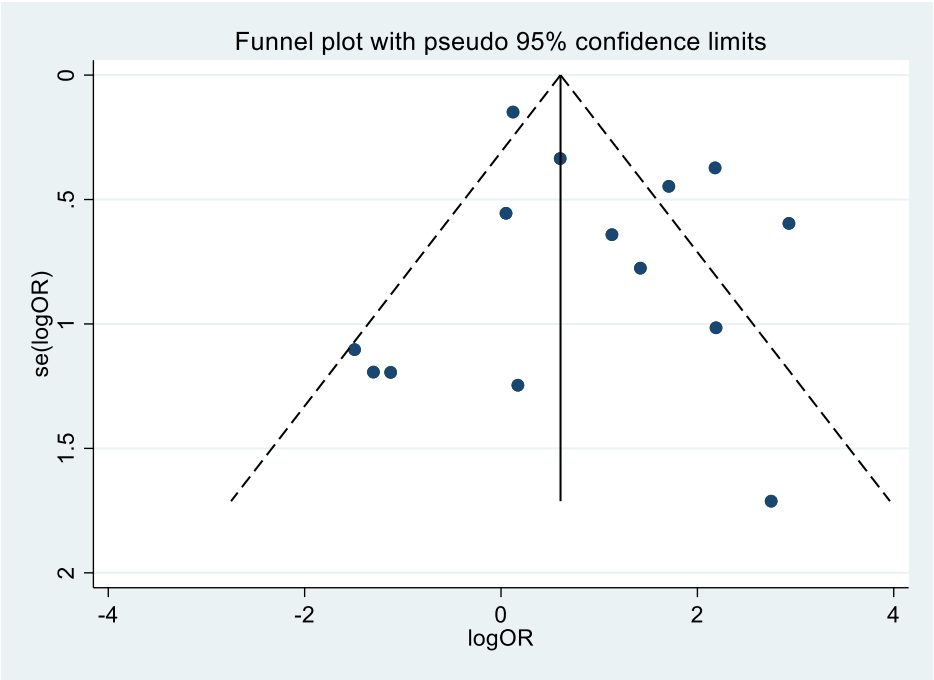
1: Assessed confounding factors are age, hypertension, heart failure and diabetes 2: As we analyzed raw data in the meta-analyses, statistical approaches of individual studies do no imply risk for this domain



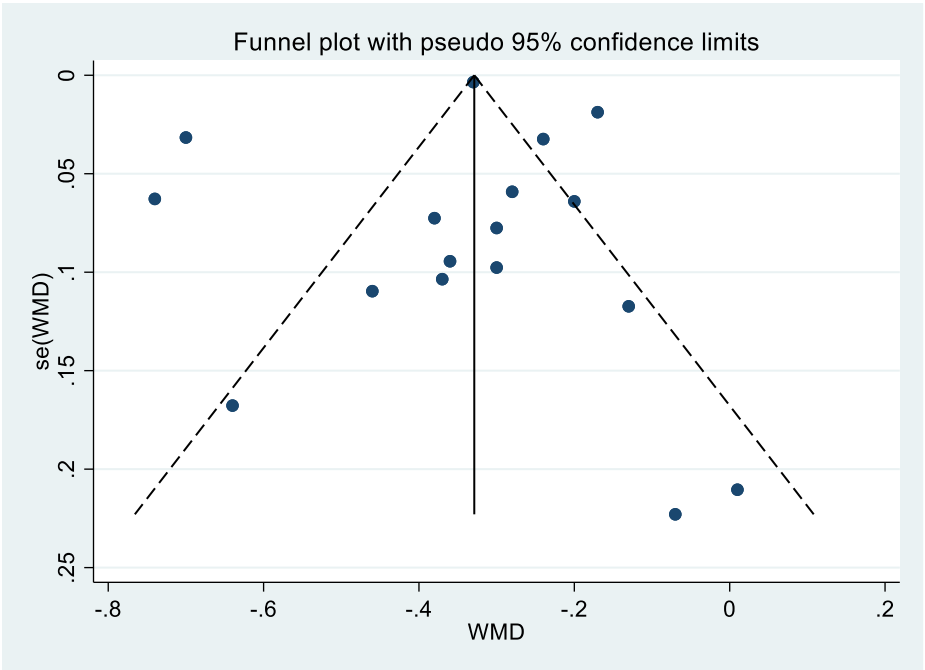
Supplementary Figure 4: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline total white blood cell count. The visual assessment of the funnel plot and the Egger's test (p=0.134) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in odds ratio.



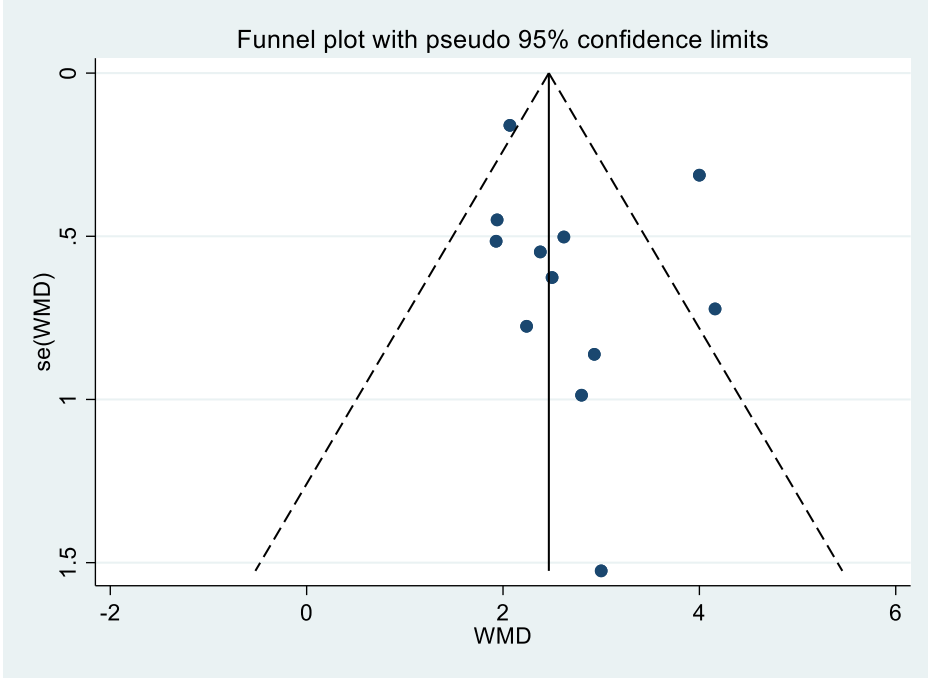
Supplementary Figure 5: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline total white blood cell count. The visual assessment of the funnel plot and the Egger's test (p=0.196) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



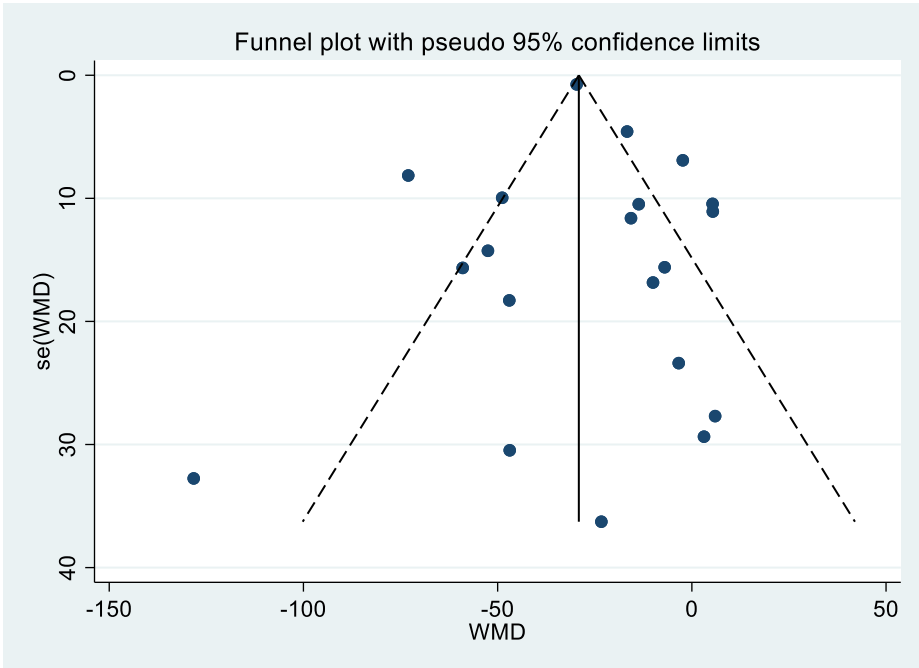
Supplementary Figure 6: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline absolute lymphocyte count. The visual assessment of the funnel plot and the Egger's test (p=0.302) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in odds ratio.



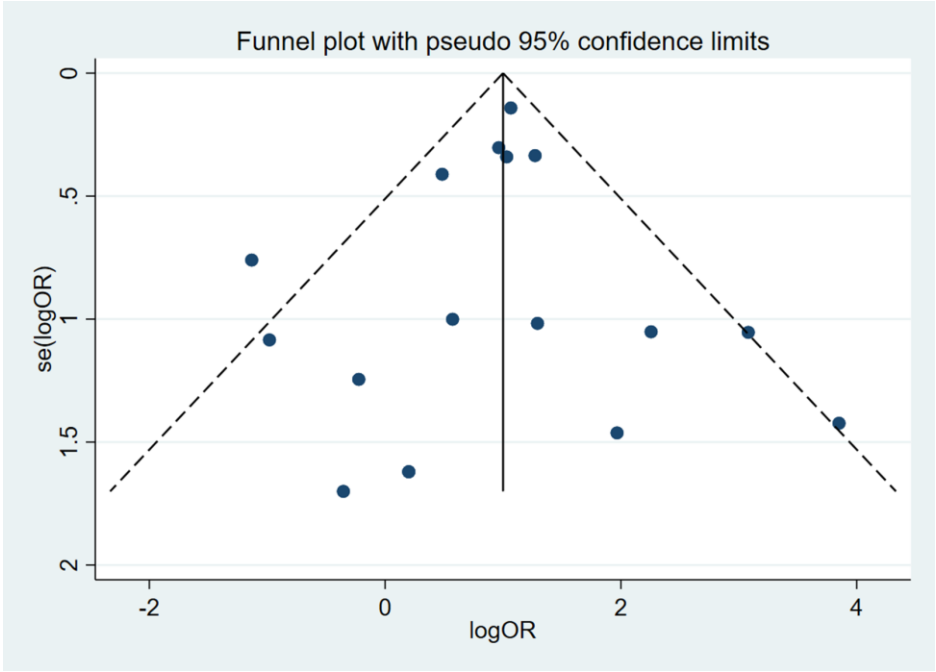
Supplementary Figure 7: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline absolute lymphocyte count. The visual assessment of the funnel plot and the Egger's test (p=0.807) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



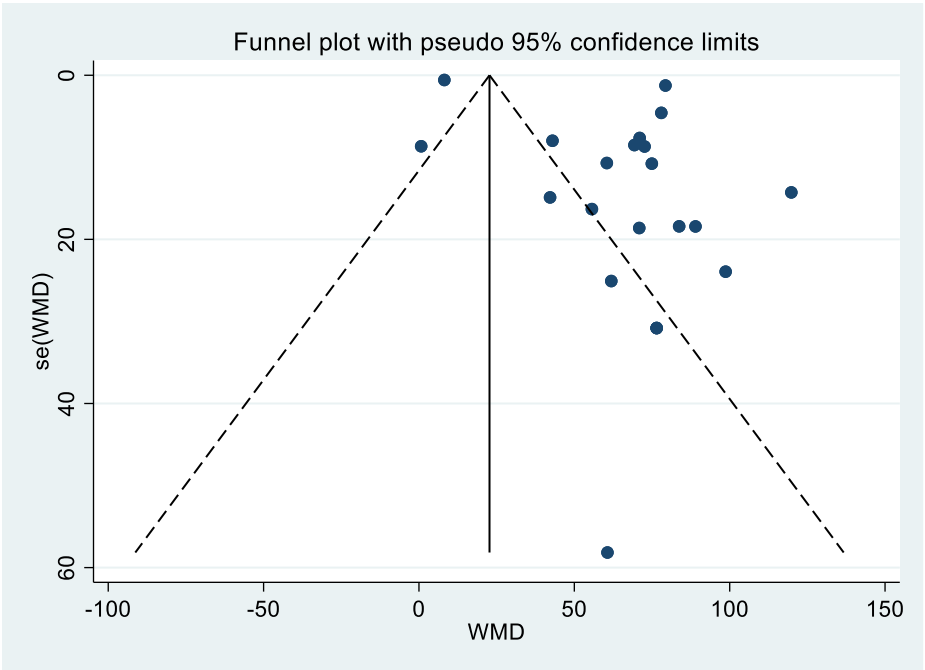
Supplementary Figure 8: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline absolute neutrophil count The visual assessment of the funnel plot and the Egger's test (p=0.345) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



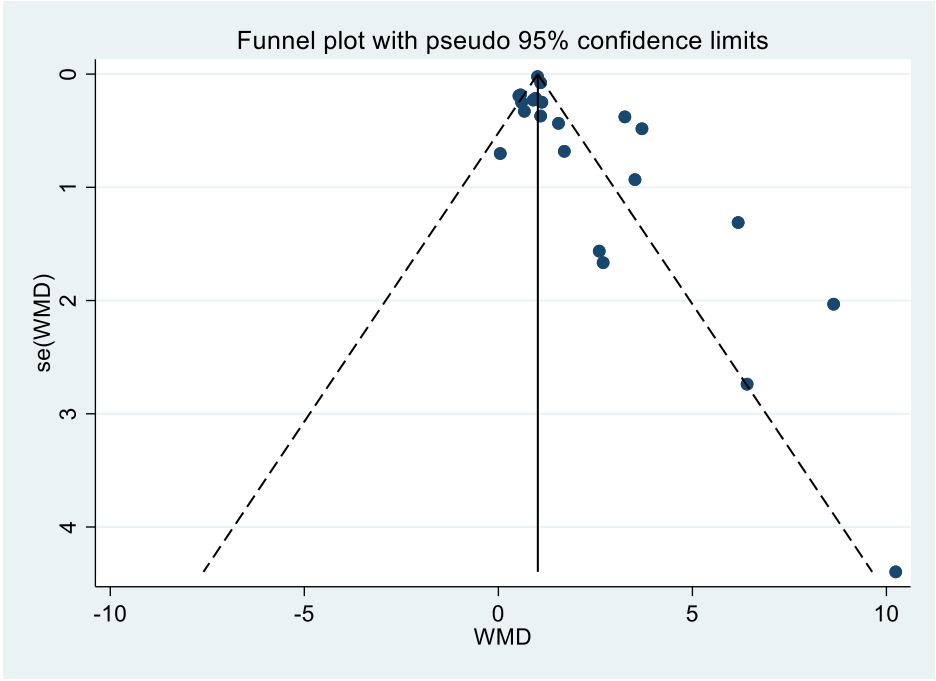
Supplementary Figure 9: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline platelet count. The visual assessment of the funnel plot and the Egger's test (p=0.569) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



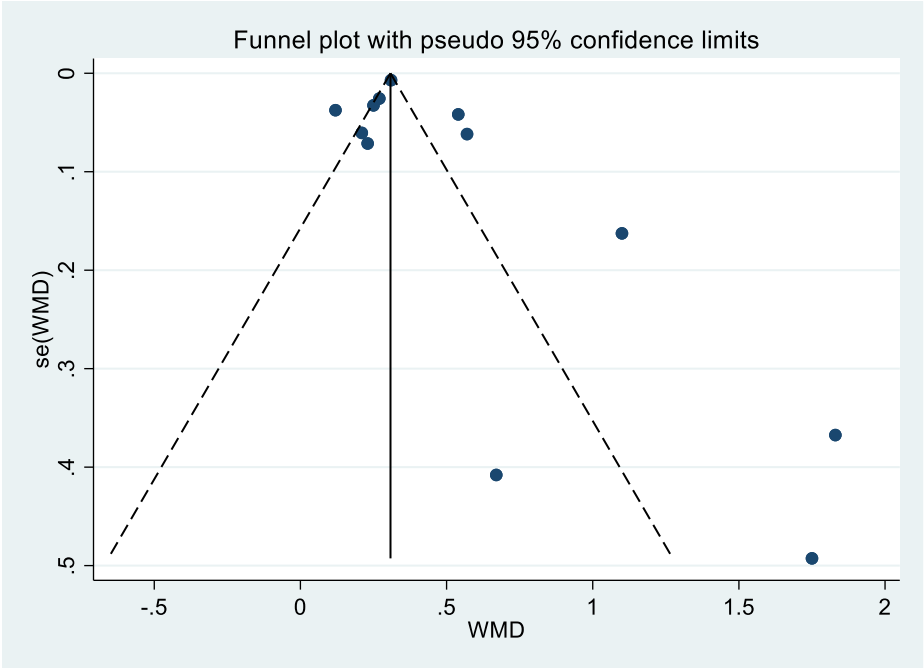
Supplementary Figure 10: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline C-reactive protein. The visual assessment of the funnel plot and the Egger's test (p=0.649) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in odds ratio.



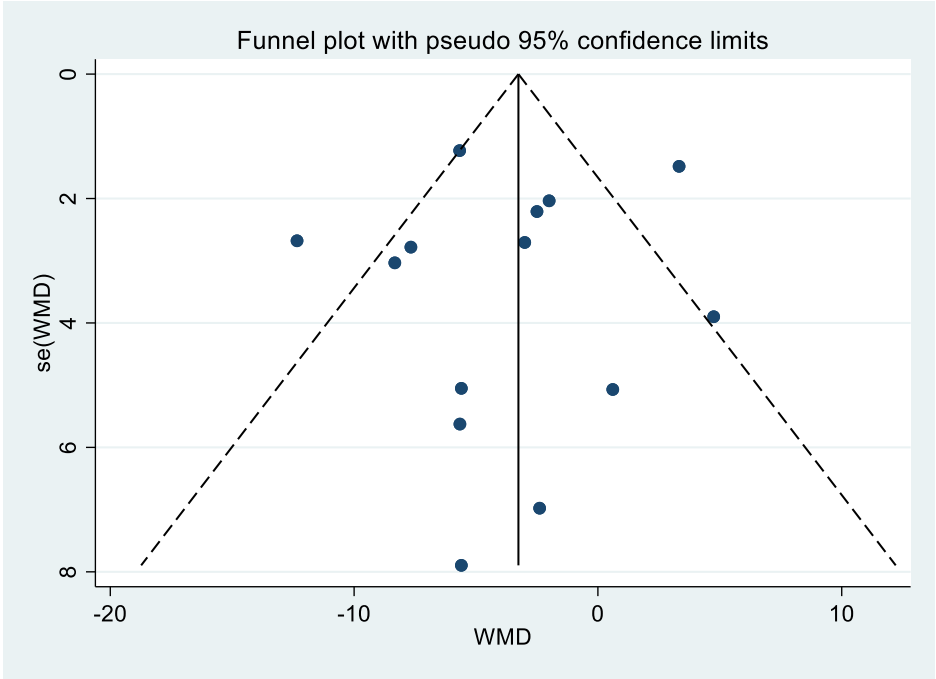
Supplementary Figure 11: Funnel plot of the studies reporting on mortality among all COVID-19 patients and C-reactive protein. The visual assessment of the funnel plot and the Egger's test (p=0.087) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



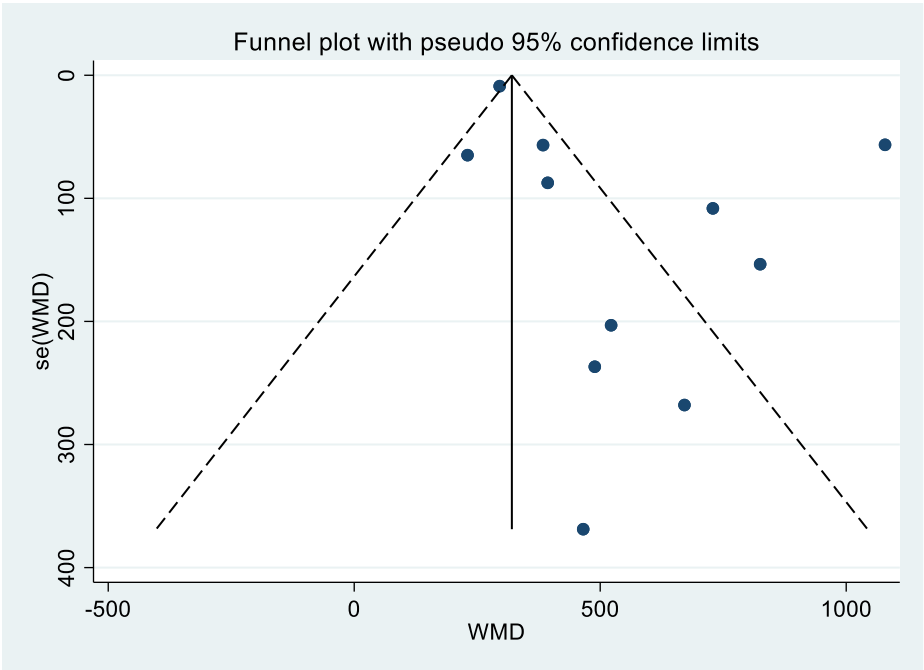
Supplementary Figure 12: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline D-dimer. The visual assessment of the funnel plot and the Egger's test (p=0.037) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



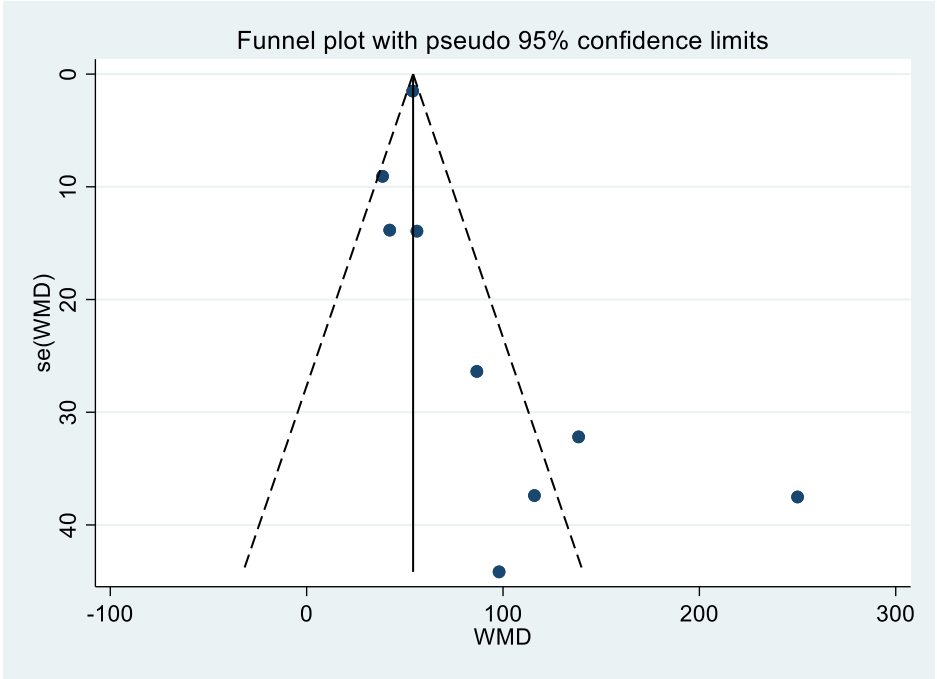
Supplementary Figure 13: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline D-dimer. The visual assessment of the funnel plot and the Egger's test (p=0.005) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in odds ratio.



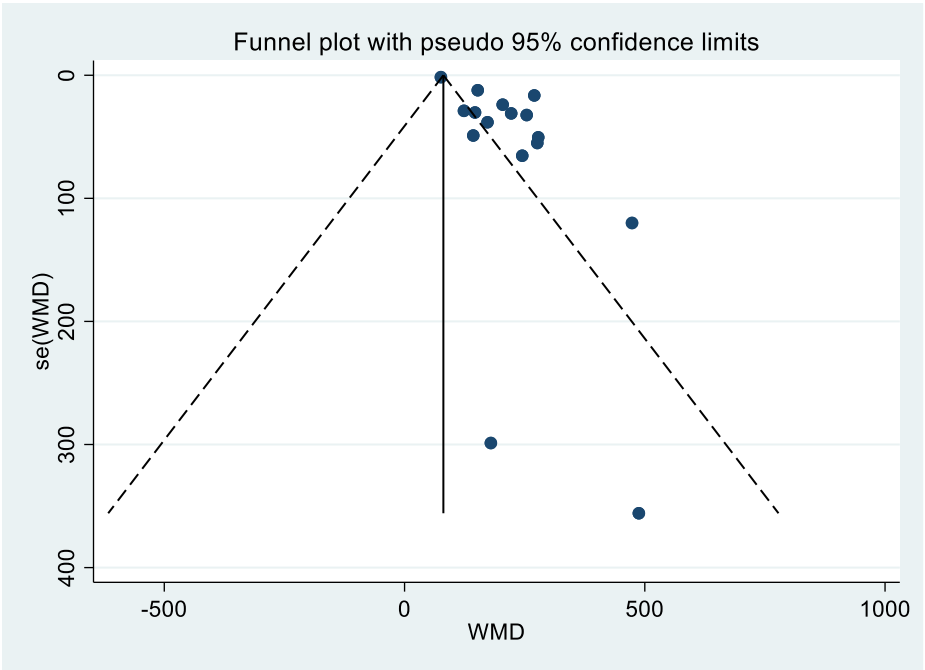
Supplementary Figure 14: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline haemoglobin. The visual assessment of the funnel plot and the Egger's test (p=0.707) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



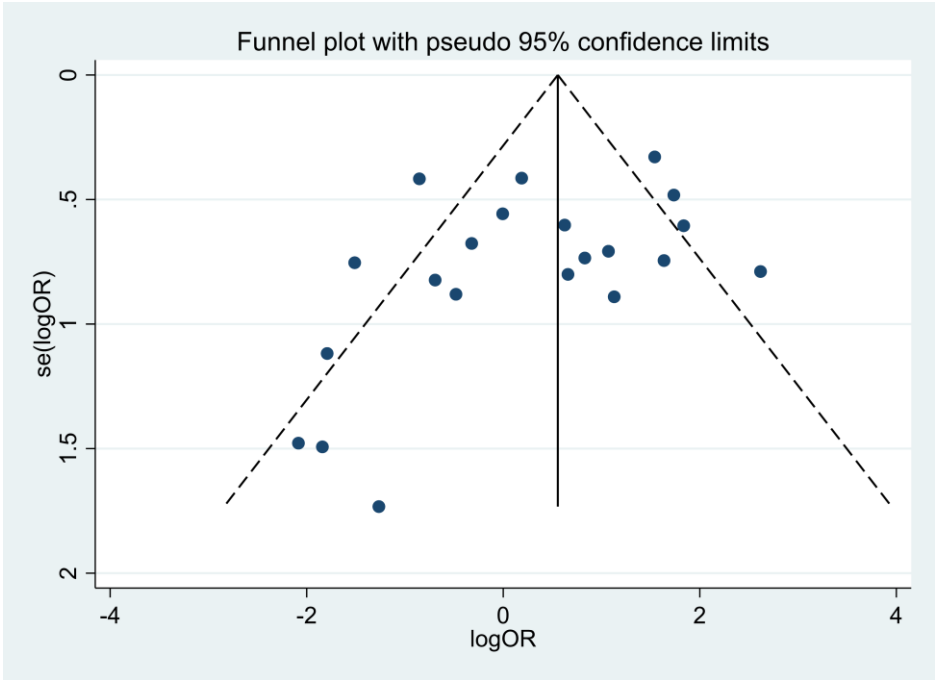
Supplementary Figure 15: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline ferritin. The visual assessment of the funnel plot and the Egger's test (p=0.103) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



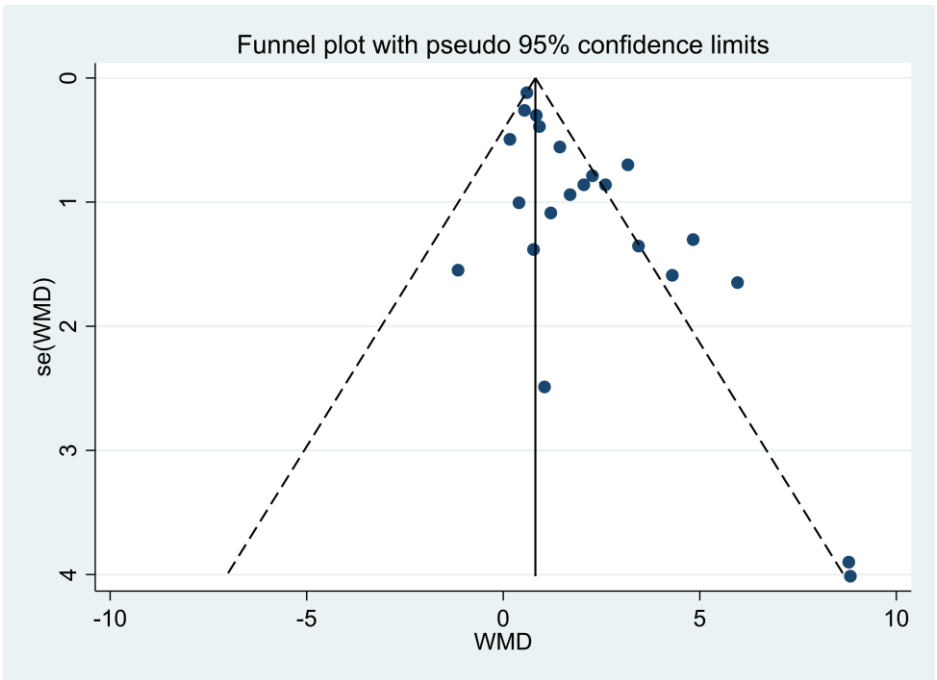
Supplementary Figure 16: Funnel plot of the studies reporting on mortality among all COVID-19 patients and creatine kinase. The visual assessment of the funnel plot and the Egger's test ($p<0.001$) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



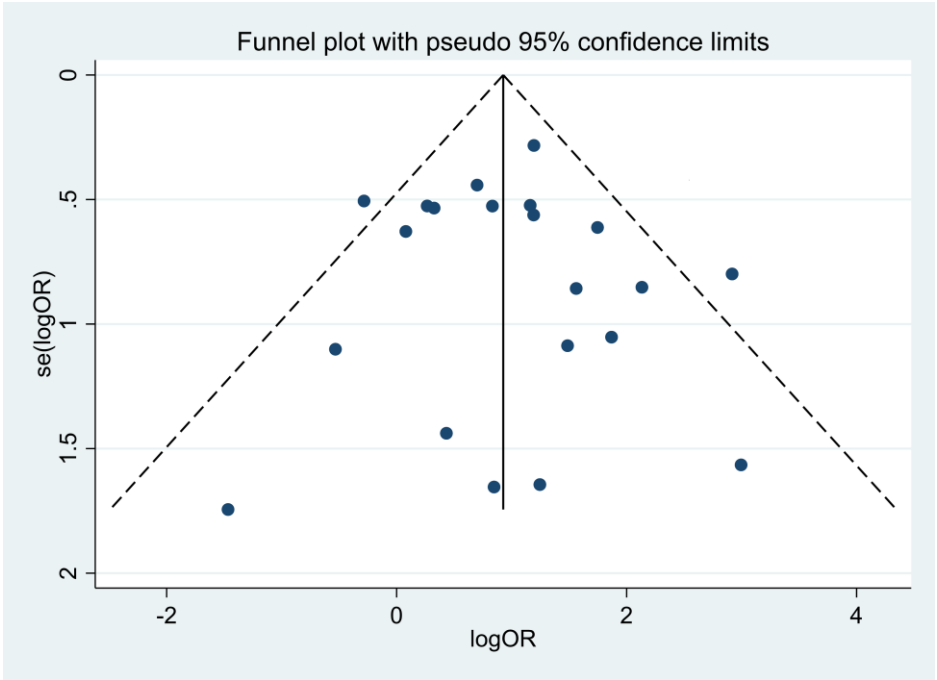
Supplementary Figure 17: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline lactate dehydrogenase. The visual assessment of the funnel plot and the Egger's test ($p<0.001$) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



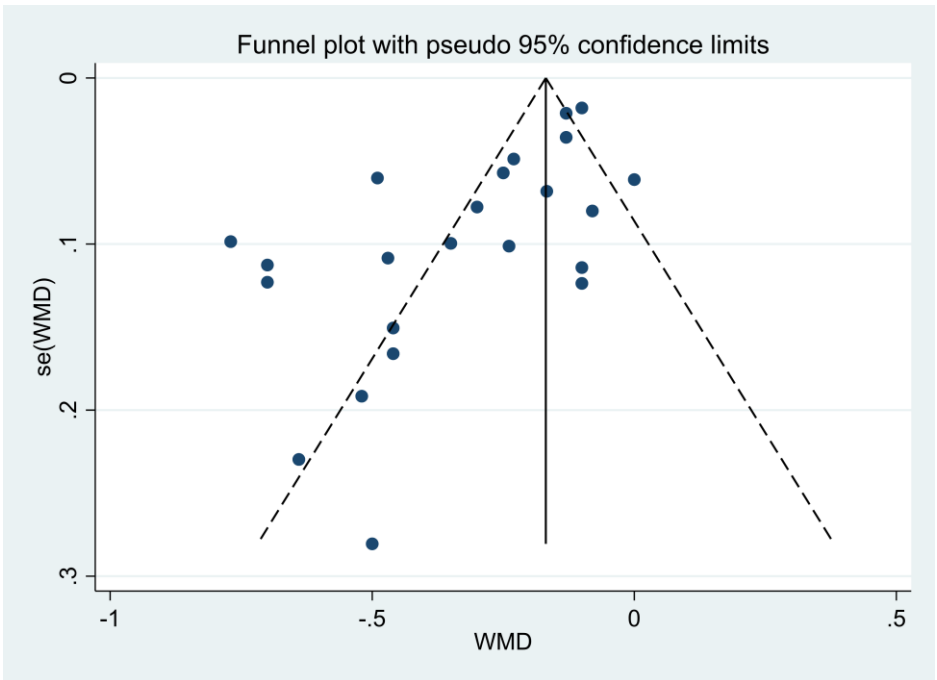
Supplementary Figure 18: Funnel plot of the studies reporting on instensive care requirement and baseline total white blood cell count. The visual assessment of the funnel plot and the Egger's test (p=0.124) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in odds ratio.



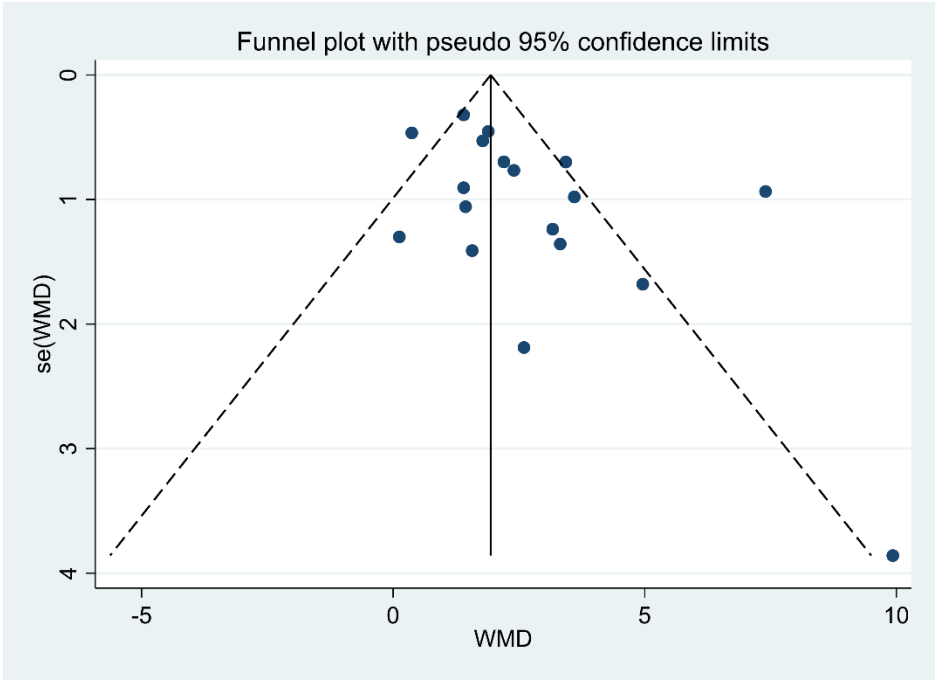
Supplementary Figure 19: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline total white blood cell count. The visual assessment of the funnel plot and the Egger's test (p<0.001) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



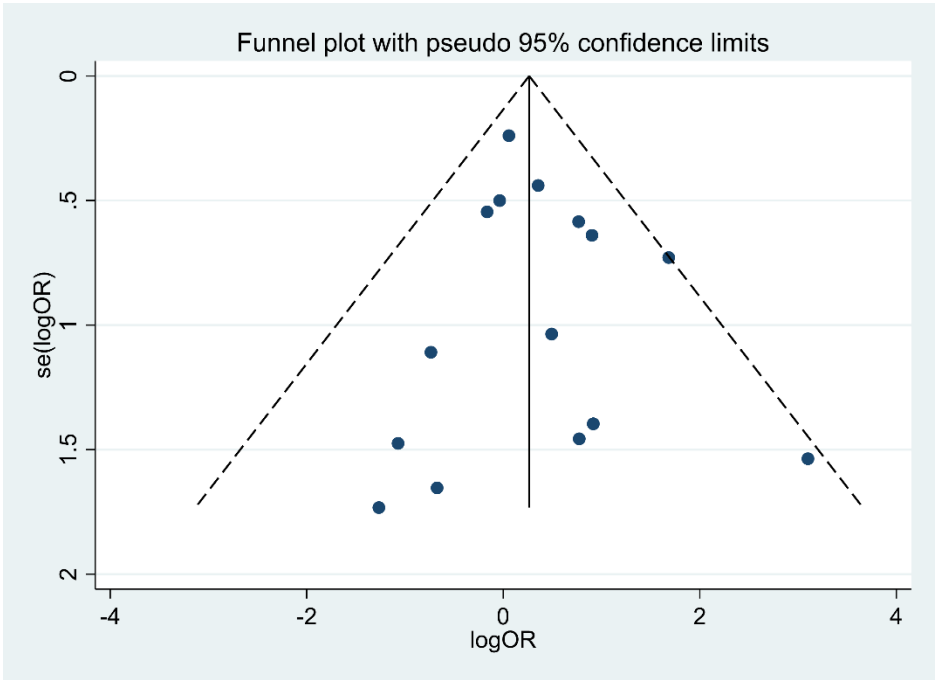
Supplementary Figure 20: Funnel plot of the studies reporting on instensive care requirement and baseline absolute lypmhocyte count. The visual assessment of the funnel plot and the Egger's test (p=0.738) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in odds ratio.



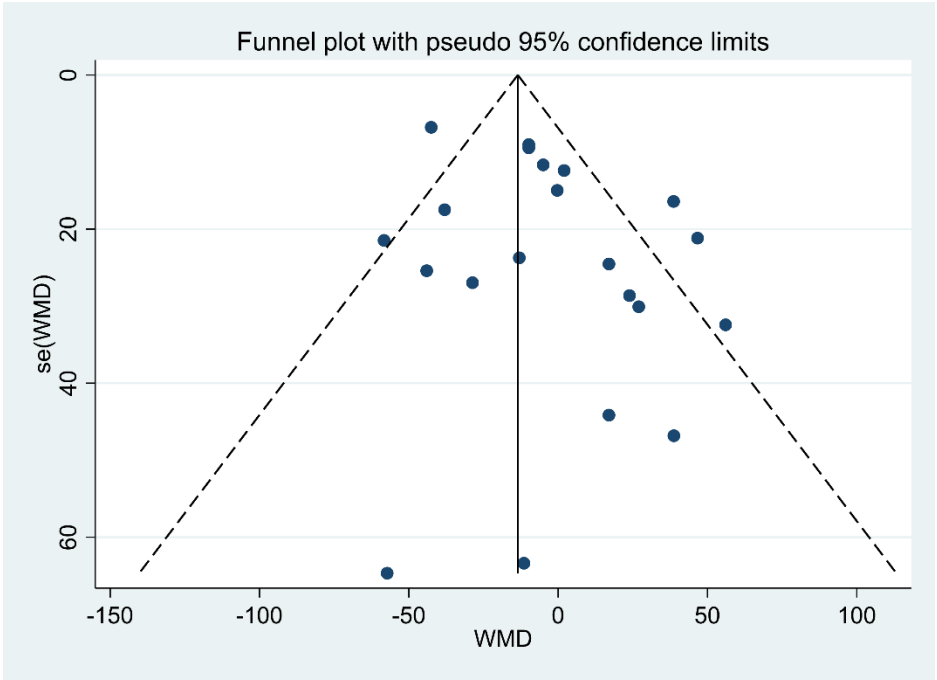
Supplementary Figure 21: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline absolute lymphocyte count. The visual assessment of the funnel plot and the Egger's test (p<0.001) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



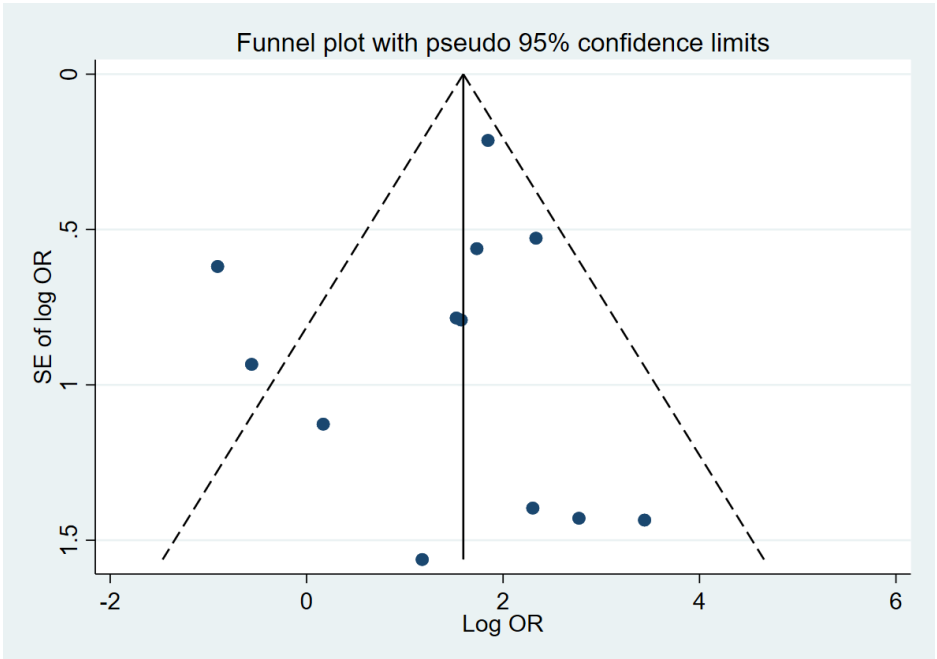
Supplementary Figure 22: Funnel plot of the studies reporting on instensive care requirement and baseline absolute neutrophil count. The visual assessment of the funnel plot and the Egger's test (p=0.037) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference .



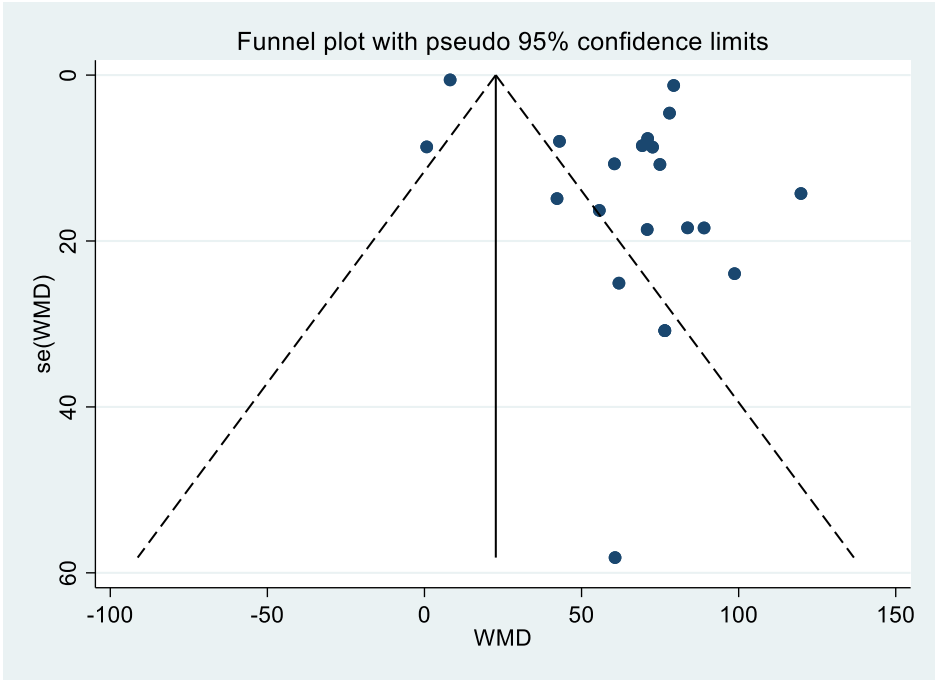
Supplementary Figure 23: Funnel plot of the studies reporting on mortality among all COVID-19 patients and platelet count. The visual assessment of the funnel plot and the Egger's test (p=0.410) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in odds ratios.



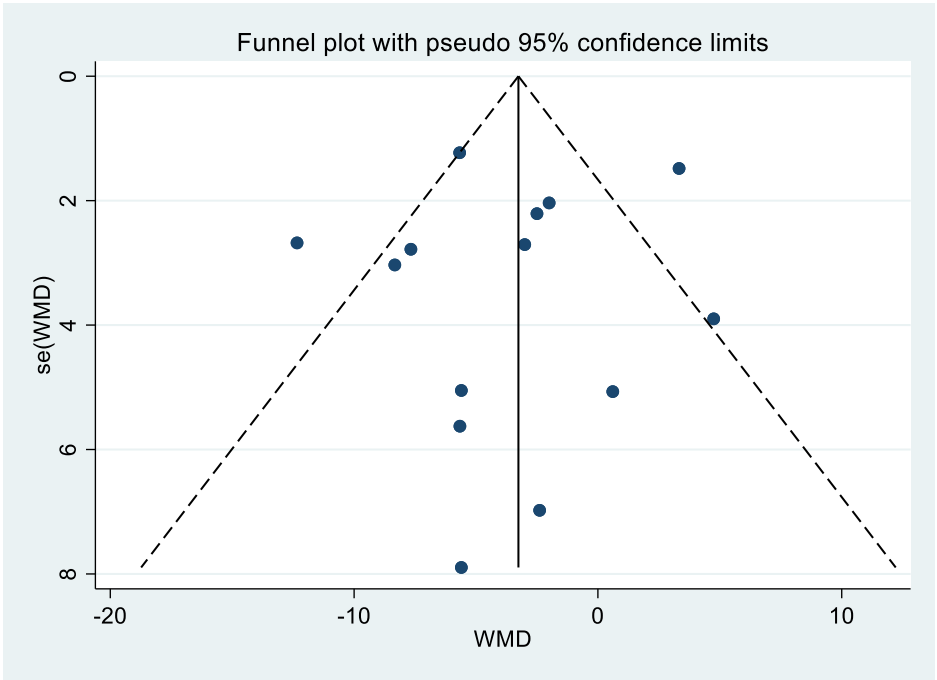
Supplementary Figure 24: Funnel plot of the studies reporting on instensive care requirement and baseline absolute platelet count. The visual assessment of the funnel plot and the Egger's test (p=0.075) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



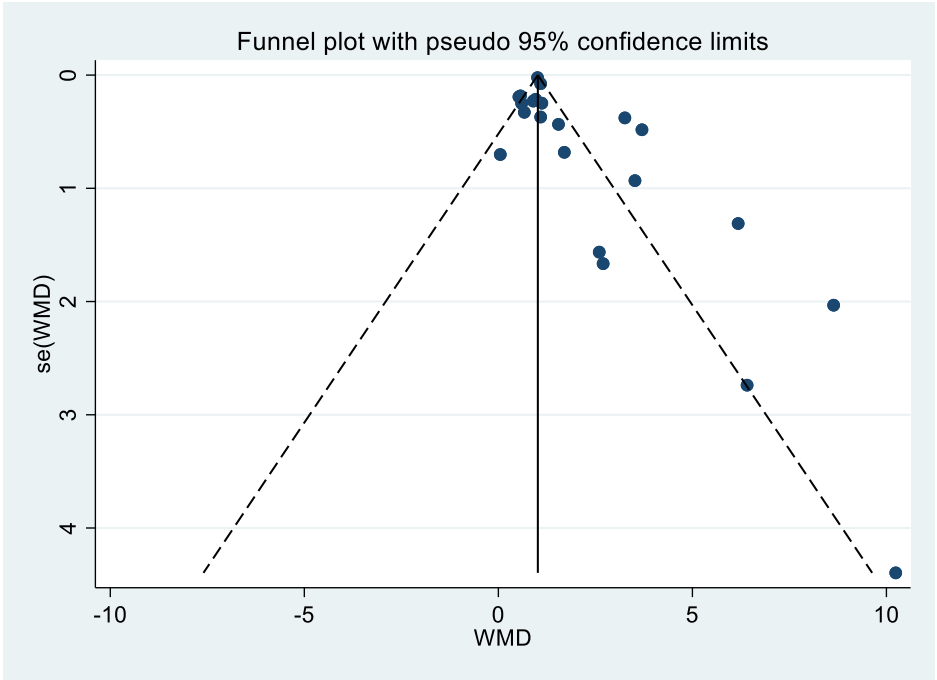
Supplementary Figure 25: Funnel plot of the studies reporting on mortality among all COVID-19 patients and baseline C-reactive protein. The visual assessment of the funnel plot and the Egger's test (p=0.474) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in odds ratios.



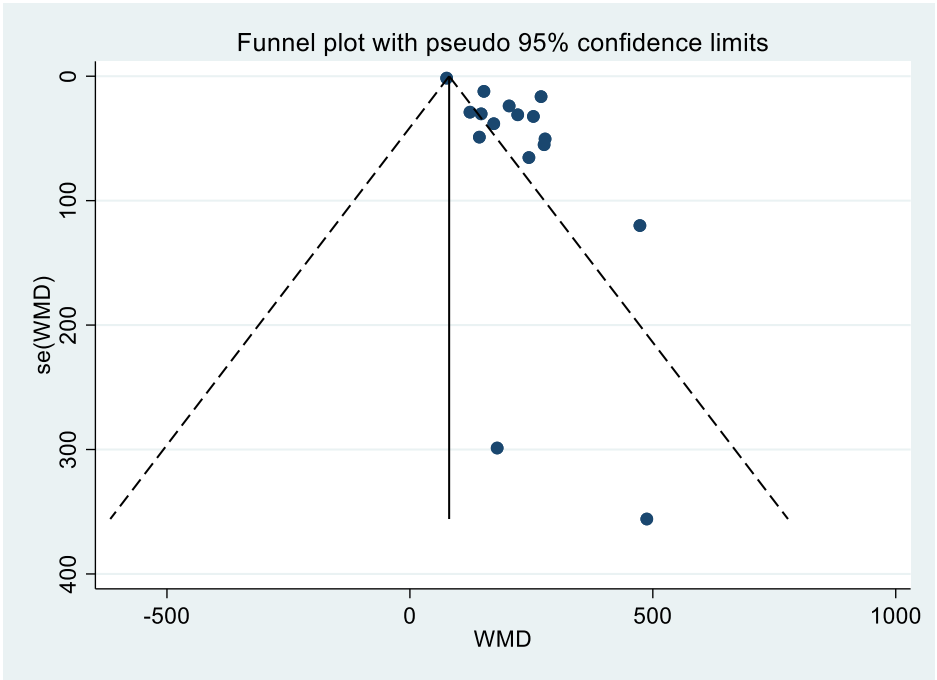
Supplementary Figure 26: Funnel plot of the studies reporting on instensive care requirement and baseline C-reactive protein. The visual assessment of the funnel plot and the Egger's test (p=0.059) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference .



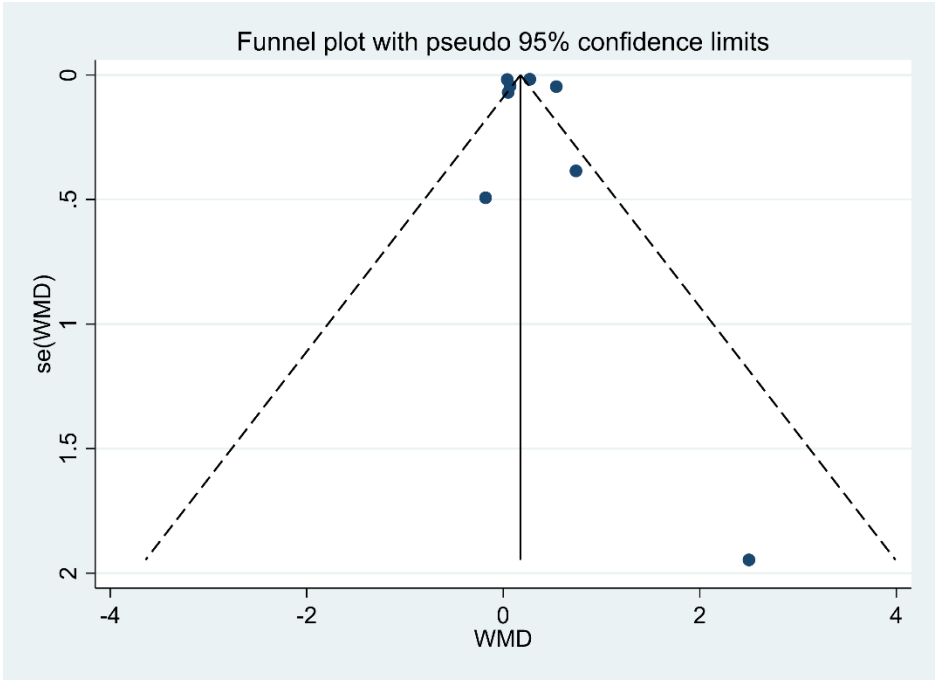
Supplementary Figure 27: Funnel plot of the studies reporting on instensive care requirement and baseline heamoglobin. The visual assessment of the funnel plot and the Egger's test (p=0.230) did indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference .



Supplementary Figure 28: Funnel plot of the studies reporting on instensive care requirement and baseline D-Dimer. The visual assessment of the funnel plot and the Egger's test (p=0.007) indicate asymmetry and therefore small study effect is likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference .



Supplementary Figure 29: Funnel plot of the studies reporting on instensive care requirement and baseline lactate dehydrogenase. The visual assessment of the funnel plot and the Egger's test (p=0.141) did indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.



Supplementary Figure 30: Funnel plot of the studies reporting on instensive care requirement and baseline procalcitonin. The visual assessment of the funnel plot and the Egger's test (p=0.735) did not indicate asymmetry and therefore small study effect is not likely to be present. Each dot represents a comparison. The y-axis is the standard error of the effect estimate. Larger studies with higher power are placed towards the top and lower powered studies are placed towards the bottom. The x-axis shows the result for the studies expressed in weighted mean difference.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4–5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Suppl. Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl. Figure 1–3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2-3 Suppl. Table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 5–7 Suppl. Table 2–3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Suppl. Figure 4–30
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 7–9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 1

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Early prediction of acute necrotizing pancreatitis by artificial intelligence: a prospective cohort-analysis of 2387 cases

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Pancreatic necrosis is a consistent prognostic factor in acute pancreatitis (AP). However, the clinical scores currently in use are either too complicated or require data that are unavailable on admission or lack sufficient predictive value. We therefore aimed to develop a tool to aid in necrosis prediction. The XGBoost machine learning algorithm processed data from 2387 patients with AP. The confidence of the model was estimated by a bootstrapping method and interpreted via the 10th and the 90th percentiles of the prediction scores. Shapley Additive exPlanations (SHAP) values were calculated to quantify the contribution of each variable provided. Finally, the model was implemented as an online application using the Streamlit Python-based framework. The XGBoost classifier provided an

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AUC value of 0.757. Glucose, C-reactive protein, alkaline phosphatase, gender and total white blood cell count have the most impact on prediction based on the SHAP values. The relationship between the size of the training dataset and model performance shows that prediction performance can be improved. This study combines necrosis prediction and artificial intelligence. The predictive potential of this model is comparable to the current clinical scoring systems and has several advantages over them.

Acute pancreatitis (AP) affects about 34 per 100,000 people per year, and it is the most frequent gastrointestinal disease requiring acute hospitalization[1,2]. The overall mortality is around 3%[3,4]; however, in about 10–20% of AP cases, acute necrotizing pancreatitis (ANP) develops, thus further increasing the risk of morbidity and mortality[5,6]. The overall mortality of ANP is approximately 15–20%, of which there is a further twofold increase in a third of ANP cases where the necrotic tissue becomes infected[7,8].

Early appraisal of severity and prognosis is crucial in AP, particularly on clinical admission, to identify patients at risk of developing life-threatening complications. In these cases, close monitoring and early intervention may prevent organ dysfunction and a fatal outcome[9,10].

It has long been known that necrosis is a consistent prognostic factor in AP[9]. The diagnosis of this local complication strongly relies on contrast-enhanced computer tomography (CECT) because it has a much higher sensitivity to detect ANP than ultrasonography[7]. Despite being the gold standard method for diagnosing ANP, CECT has many disadvantages: (1) ANP usually becomes apparent only 72 h after the onset of symptoms; (2) early and inappropriate CECT may prolong hospitalization; and (3) it is not accessible in every case[11]. There is therefore a need for other methods to supplement ANP assessment.

As the underlying pathophysiology of AP becomes more and more familiar by the accumulation of scientific data, several potential therapeutic targets have been identified[12,13]. Since some of these specific therapies may be available soon, prompt initiation of treatment after early identification of ANP could be even more important.

Since ANP is associated with life-threatening complications and increased mortality and it is the principal determinant of the incidence of secondary infection in AP[14], researchers have endeavored to find an accurate clinical scoring system or biomarker that can predict ANP, the severe disease course or mortality itself. As regards ANP, these systems are either too complicated or require data that is unavailable in the initial stage of hospitalization or lack sufficient sensitivity and specificity. They are therefore rarely used in everyday clinical practice.

As artificial intelligence (AI) can overcome the limitations provided by the complexity of the data and time-dependent variables, the number of AI tools is increasing in medicine[15]. AI applications in pancreatic diseases are also evolving quickly[16]. Four AI models aimed to predict the severity of AP on clinical admission, all of which seems to outperform the conventional prediction scores[17–19]. Despite their promising preliminary results, these AI tools are limited by the overlap between the patient group used for model preparation and internal validation and the relatively low patient number.

This study has two main goals: first, to overcome these limitations and build an AI model that provides an accurate prediction for ANP development; and, second, to create an online tool from the model that could aid physicians in the early prognosis of AP.

Methods

This study was reported following the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement[20]. Ethics approval was obtained from the Hungarian Medical Research Council's Scientific and Research Ethics Committee (22254-1/2012/EKU, 17787-8/2020/EÜIG). Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the Helsinki Declaration.

Data source and eligibility criteria. The analyzed dataset was collected by the Hungarian Pancreatic Study Group between 2012 and 2019. There were 2461 adult patients enrolled in the patient registry from 30 centers across 13 countries (Appendix A). All patients fulfilled two out of three AP diagnostic criteria based on the revised Atlanta classification[21]. Data were collected by physicians and trained clinical administrators on admission and each day during the whole hospital stay and were stored both on paper and electronically. Relevant clinical data underwent a four-level quality check system before analysis.

In all cases deemed eligible a CECT was performed during hospitalization to assess pancreatic necrosis formation. Exclusion criteria were as follows: (1) no pancreas imaging had been performed; and (2) the mere suspicion of necrosis formation by imaging, which was not confirmed later by CECT.

Groups, outcomes, and predictors analyzed. Eligible participants were divided into two groups: (1) pancreatic necrosis formation was confirmed by a radiologist by CECT during hospitalization; and (2) absence of necrosis development. The dataset was analyzed and compared accordingly.

ANP was defined as lack of parenchymal enhancement or findings of peripancreatic necrosis such as an acute necrotic collection on CECT[22]. Other local (acute peripancreatic fluid collection and pseudocyst) and systemic (new-onset diabetes, heart failure, renal failure, and respiratory failure) complications and disease severity were defined based on the revised Atlanta classification[21]. Data on in-hospital mortality, length of hospital stay, and etiology of AP were also collected.

The assessed predictors of ANP were gender, age, body mass index (BMI), and laboratory parameters measured in the first 24 h of clinical admission. The following were evaluated: alanine transaminase, albumin, amylase,

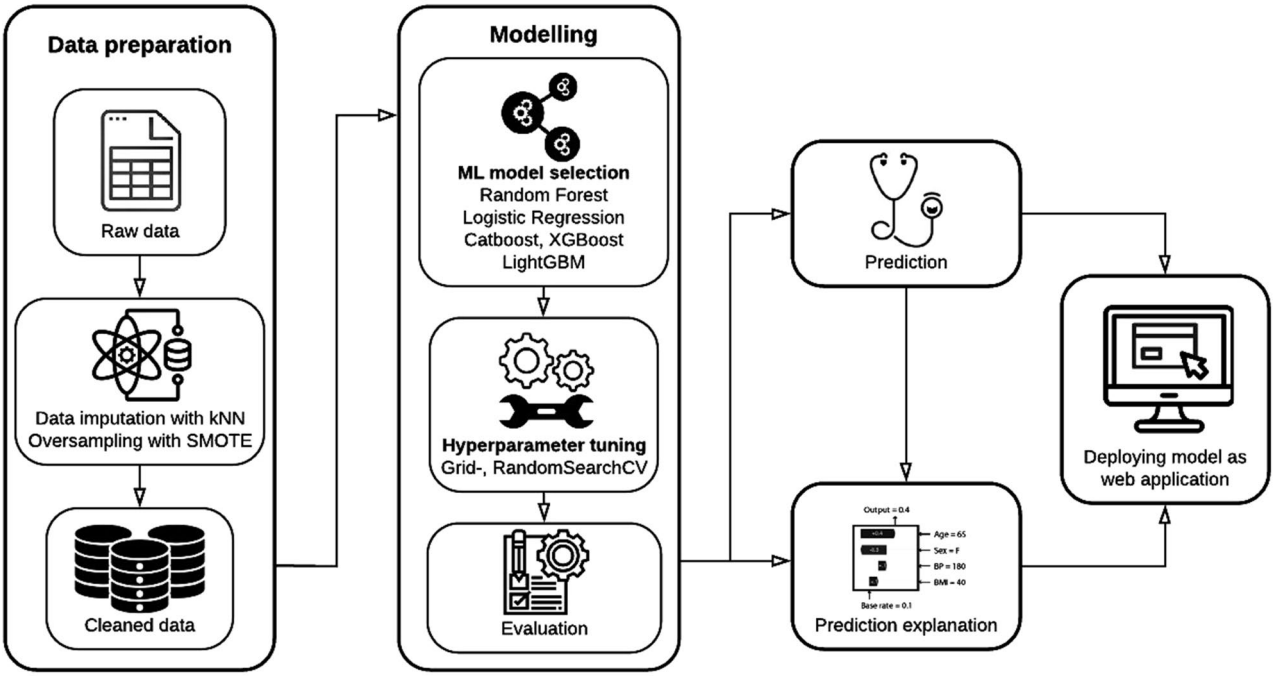

Figure 1. Flowchart representing the process of developing the model.

alkaline phosphatase (ALP), aspartate transaminase, blood urea nitrogen, calcium, C-reactive protein (CRP), creatinine, direct bilirubin, gamma-glutamyl transferase (GGT), glucose, estimated glomerular filtration rate (eGFR), glycated hemoglobin (HbA1c), hematocrit, hemoglobin, lactate dehydrogenase (LDH), lipase, potassium, procalcitonin, red blood cell count, sodium, thrombocyte, total bilirubin, total cholesterol, total protein, total white blood cell count (WBC), and triglyceride.

Predictive modelling. The process of predictive modelling is depicted in Fig. 1. Thirty-one variables have been used for modelling. Data quality is provided in Appendix A. Missing data were handled with a k-nearest-neighbor-based data imputer algorithm (KNNImputer)[23]. The SMOTE algorithm[24] was used to deal with the imbalance in class distribution (number of patients with and without ANP).

Random Forest, Logistic Regression, Catboost, XGBoost, and LightGBM were tested for modelling to identify the best performing machine learning algorithm[25–28]. The catboost, xgboost, lightgbm, and scikit-learn Python packages were applied. The optimal model was chosen based on the receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) value after performing four-fold cross-validation. The confidence of the best performing model was estimated with a bootstrapping method, namely by re-sampling the training dataset and training a hundred independent copies of the model on these datasets. The confidence of the model prediction was interpreted with the aid of the 10th and the 90th percentiles of the prediction scores.

Shapley Additive exPlanations (SHAP) values were calculated[29] to locally explain the model prediction and to quantify the contribution of each variable provided. Finally, the model was deployed as an online application using the Streamlit Python-based framework.

Other statistical analyses. The presence of sampling bias was tested by assessing the representativeness between the cohort analyzed and the whole cohort (Appendix A). The prediction parameters were also compared between patients with and without ANP with the Kolmogorov–Smirnov test and the Chi-squared test. ANP was tested as a risk factor for mortality, severe AP, and local and systemic complications by calculating risk ratios (RR) with the corresponding 95% confidence interval (CI).

Ethics approval. Ethics approval was obtained from the Hungarian Medical Research Council's Scientific and Research Ethics Committee (22254-1/2012/EKU, 17787-8/2020/EÜIG). The study was conducted in accordance with the Helsinki Declaration.

Consent to participate. Written informed consent was obtained from all participants before enrolment.

Consent for publication. The corresponding author accepts responsibility for releasing this material on behalf of all co-authors.

Variable	Value (n = 2387)
Age in years, median (IQR)	57 (44–69)
Male, n (%)	1357 (56.85%)
BMI, median (IQR)	27.14 (23.88–31.25)
Etiology, n (%)	
Biliary	955 (40.01%)
Alcoholic	484 (20.28%)
Hypertriglyceridaemia	81 (3.39%)
Biliary and alcoholic	39 (1.63%)
Biliary and hypertriglyceridaemia	13 (0.54%)
Alcoholic and hypertriglyceridaemia	58 (2.43%)
Post-ERCP	67 (2.81%)
Idiopathic	432 (18.10%)
Other	258 (10.81%)
Revised Atlanta classification	
Mild, n (%)	1714 (71.81%)
Moderate, n (%)	551 (23.08%)
Severe, n (%)	122 (5.11%)
Mortality, n (%)	66 (2.76%)
Length of stay in days, median (IQR)	8 (6–12)
Patients with local complication, n (%)	623 (26.19%)
APFC, n (%)	510 (21.37%)
Pseudocyst, n (%)	179 (7.50%)
Acute necrotic collection, n (%)	233 (9.76%)
Patients with systemic complication, n (%)	202 (8.46%)
Respiratory failure, n (%)	136 (5.70%)
Heart failure, n (%)	52 (2.18%)
Renal failure, n (%)	83 (3.48%)
New-onset diabetes, n (%)	75 (3.14%)

Table 1. Characteristics of the analyzed study population. *APFC* acute peripancreatic fluid collection, *BMI* body mass index, *ERCP* endoscopic retrograde cholangiopancreatography, *IQR* interquartile range.

Results

Characteristics of the cohort analyzed. 2387 of the 2461 patients with AP proved to be eligible for the analysis. Characteristics of this population are summarized in Table 1. In 9.76% of the cases, ANP was confirmed. There was a statistically significant difference between patients with and without ANP as regards age, gender, and BMI (Appendix B Supplementary Figs. 16–18). A detailed analysis of the results as regards other biomarkers can be found in Appendix B.

ANP was associated with a significantly higher risk for mortality, severe disease course, and all the investigated local and systemic complications (Fig. 2). ANP was also associated with longer hospitalization (9.13 ± 6.21 days vs. 20.78 ± 19.70 days, $p < 0.001$).

Model selection and model performance. After an evaluation of the machine learning algorithms, an XGBoost classifier was identified as the best performing model with an AUC value of 0.757 (standard deviation: 0.012) on cross-validation (Fig. 3). The relationship between the size of the data set and the model performance is depicted in Fig. 4. The steady increase of AUC values implies that our model has not yet reached its maximal prediction performance. Internal validation implies that our model has higher reliability near the endpoints of the prediction spectrum since the confidence intervals are narrower (Fig. 5).

The assessment of the impact on the model output showed that glucose, CRP, ALP, gender, and WBC have the five highest SHAP values. The most influential predictors are shown in Fig. 6 Panel A. Our assessment showed that the predictive potential depends on the number of biomarkers provided. The models built on the top k most influential predictors according to their SHAP values show an increasing performance as regards the predictive potential; however, the extent of this improvement decreases with the number of variables provided (Fig. 7).

Application. The current version of the model can be accessed at http://necro-app.org/. At least five of the available predictors must be provided to use the application. This limit was applied based on the relation between the size of the dataset and the desired accuracy[30]. The application is aided by a built-in BMI calculator and validations to filter out invalid values. The model offers a numerical probability value between 0 and 1. The higher the number, the higher the risk for ANP becomes. These numerical values are also supplied with a textual interpretation. For educational purposes, the effect of the biomarkers on prediction is also indicated (Fig. 6 Panel B).

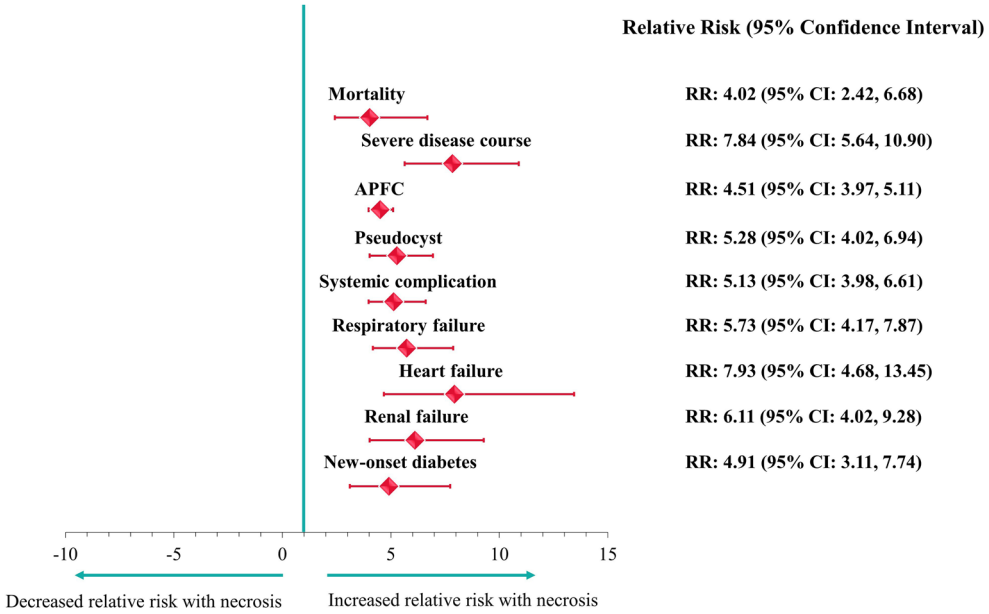

Figure 2. Association between necrosis development and other complications in acute pancreatitis.

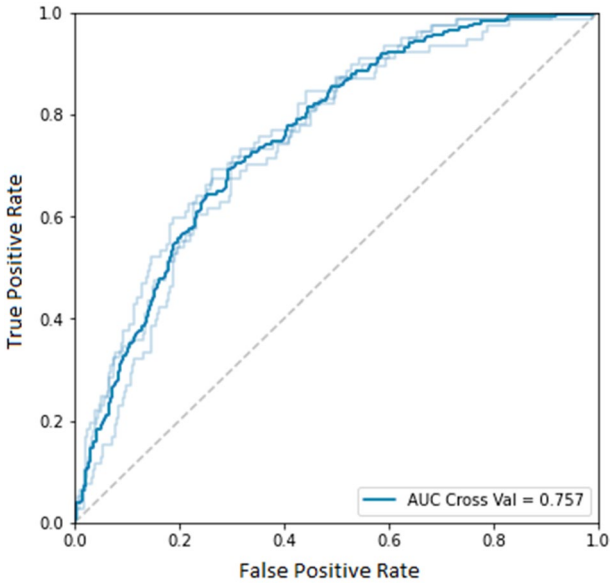

Figure 3. Receiver operating characteristic (ROC) curve for the XGBoost model.

By checking an extra field, the application assigns a confidence interval in addition to the numerical value. This adds further clarification to the predicted necrosis probability; however, it takes extra time.

Discussion

The current study describes the first AI model designed to predict ANP. In addition to creating this model, we also implemented it as an easily accessible online tool. In addition to these, ANP was extensively described in a large, prospective, multicenter, cohort study.

Our cohort in the context of previous data. With the occurrence of ANP in around one-tenth of patients, our results are comparable with previously reported data[31,32]. The importance of ANP in determining the disease course and outcome is well-known[33,34]. Schepers et al. found that 38% of the patients with ANP developed respiratory, cardiovascular or renal system failure[35]. In our cohort, necrosis was also associated with a four to eight-fold increased risk of local and systematic complications, severe disease course, and mortality. We also confirmed their observation regarding prolonged hospitalization indicating the impact of ANP on short-

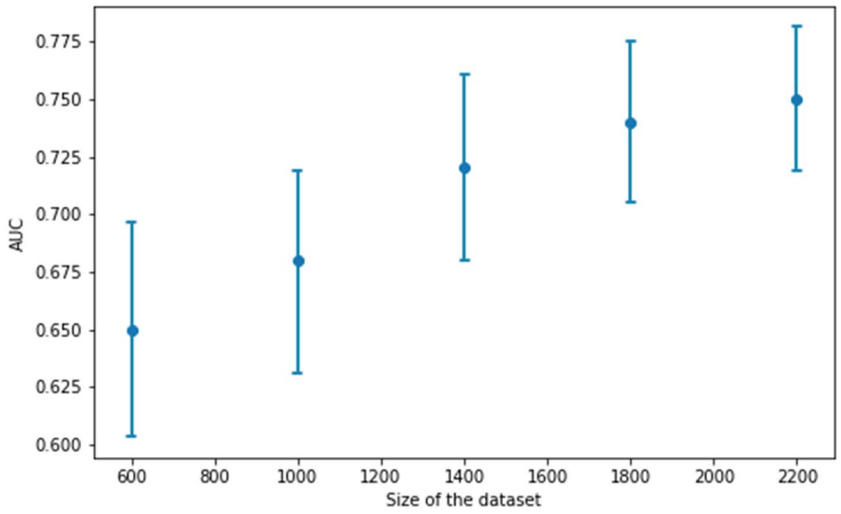

Figure 4. The relationship between the size of the data set and the model performance. The blue dot represents the area under the ROC curve value and the vertical lines show the corresponding confidence intervals.

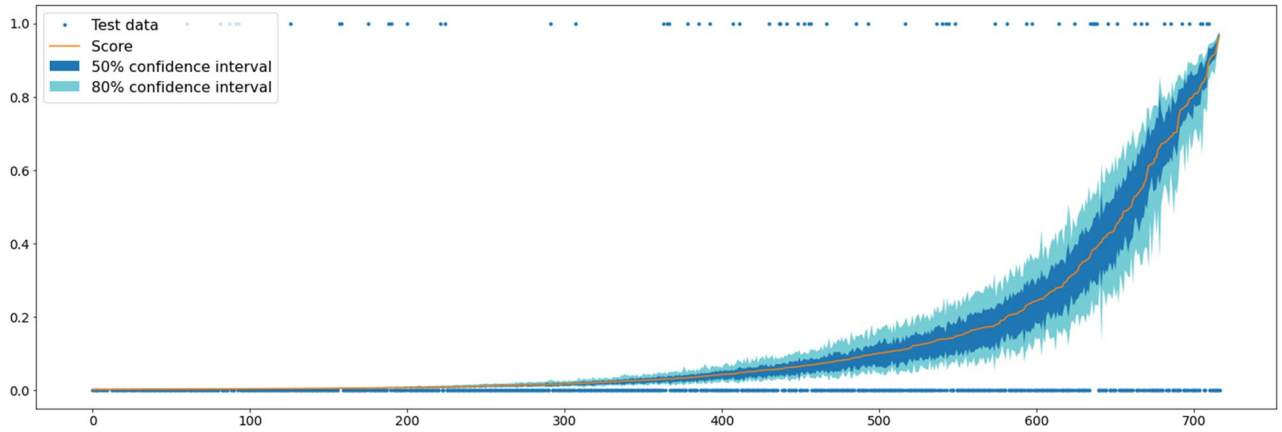

Figure 5. The predicted necrosis probabilities with the corresponding 50% (between the 25th and 50th percentiles) and 80% confidence (between the 10th and 90th percentiles).

term (i.e.: in-hospital) outcomes. However, the importance of pancreatic necrosis development also lies in the long-term complications.

Recent studies investigated this topic and shed light on long-term outcomes. A meta-analysis of long-term follow-up studies found that the pooled prevalence of exocrine pancreatic insufficiency (EPI) after ANP is between 41 and 58% depending on the extent of necrosis[36]. In a cohort study by Maatman et al., this ratio was only 19%[22]. The discrepancy in the frequency can be attributed to that. While the meta-analysis accounted for EPI during both the hospital stay and follow-up, the cohort assessed EPI after the resolution of AP. Furthermore, the retrospective nature of data has an inherent limitation, which can also explain this difference. In addition to the increased frequency of EPI, they found endocrine insufficiency in 35% of the patients with a median follow-up of 46 months. Despite the fact that our study covered the time of hospitalization, our results imply that necrosis formation increases the risk of new-onset diabetes.

Currently existing clinical scores as predictors of necrosis. Since ANP is a potent prognostic factor for the short-term severity of AP and could forecast long-term consequences, it would be ideal for identifying these patients as soon as possible. The prediction of ANP was attempted by numerous scoring systems and biomarkers[37]; however, each of them has its own limitations. The Balthazar Computer Tomography Severity Index (CTSI) possesses a higher positive predictive value for necrosis than most commonly used prediction methods[38], e.g. the Ranson score and the APACHE II score, but it is limited by the availability of CECT. It must be noted that ANP usually becomes apparent after two to three days after disease onset, and that prevents on-admission prediction in certain cases. The application of other scoring systems without mandatory CECT is restricted by their complexity. The Ranson score has eleven factors, which have to be assessed on admission and

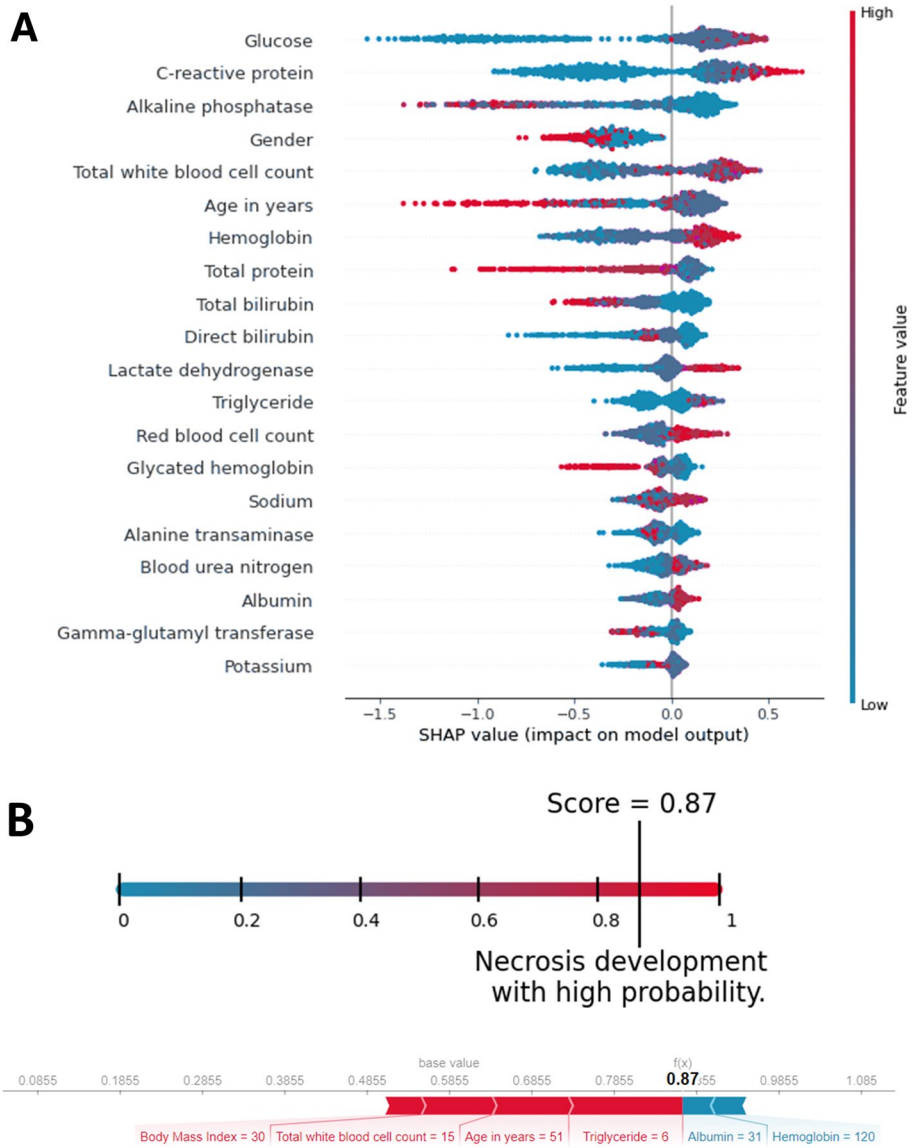

Figure 6. (**A**) The features with the highest impact on model output based on the SHAP values. The higher the predictor is on the list, the bigger the impact on model output. Each patient is represented by a dot. The x-axis represents the extent of the impact on prediction. The color of the dot shows the feature value (e.g. the red color implies higher values). (**B**) An example of prediction and its textual interpretation. The lower picture highlights the effect of individual predictors and the final necrosis probability provided by the model.

after 48 hours[39]. The APACHE II score is superior to the scores noted above in terms of flexibility and speed; however, its sensitivity and specificity are far lower[40].

Two prospective studies compared CTSI, Ranson score, and APACHE II score in predicting necrosis development[41,42]. Despite limitation in terms of patient number and the slightly different AUC values for necrosis, they concluded that the positive predictive value decreases in the following order: CTSI, Ranson score, and APACHE II. It must be emphasized that these scoring systems are strongly limited by the conversion of continuous variables to binary ones and this topic should be investigated by more mathematical models with better accuracy[42].

Artificial intelligence in the prognosis of acute pancreatitis. Artificial intelligence has appeared on the scene as a very intriguing modality of data-based decision support, and these models are extensively researched in numerous areas of medicine, including pancreaticobiliary diseases[43]. In the last decade, multiple AI algorithms have been developed in AP[16]. Most of these models were designed to predict the occurrence of a

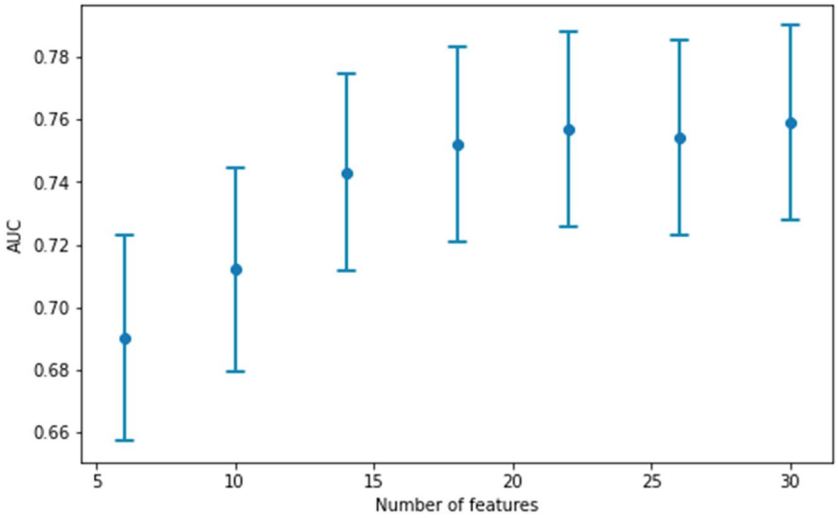

Figure 7. The models build on the *k* predictors with the highest SHAP value.

specific complication or disease severity. The most commonly used score in critical care is the APACHE II score; however, three AP severity AI models have been reported to outperform this score [17–19]. The AI model developed by Keogan et al. was compared to the CTSI and Ranson scores, both of which were found inferior in terms of predicting the severity of AP[44]. It should be noted that this study assessed the disease severity with LOH and not with the revised Atlanta classification. Despite the positive results, these prediction systems, except for the artificial neural network by Mofidi et al.[19], are limited by the overlap between the data used for model training and the validation. Furthermore, these models need another step after validation. Despite the tremendous efforts and scientific results, much of this knowledge has not been applied in everyday clinical practice[45]. In order to bring these complex models to the bedside, they need to be implemented as easy to use and broadly accessible tools[46].

The current study was not designed to predict severity but to assess the probability of necrosis formation on clinical admission. Although we had a different outcome, we aimed to overcome the limitations of most previous models and to find a way to use our AI model. As suggested by Shung et al., AI-assisted tools have to overcome many challenges[46]. First of all, we must have high-quality data. This issue was addressed in our study with a four-level data quality check system. The second main challenge is ongoing data maintenance. Our model was constructed such that the new data could be incorporated after validation. Since the predictive potential of the model shows an increasing trend, this could contribute to better accuracy. Algorithmic understanding is also a key factor. The help of physicians, who will eventually use the AI model, is crucial to confirm the performance of such a tool. Furthermore, practitioners could help in differentiating between valid prediction with actual signals and distorted predictions masked by confounding variables[46]. Our web-based application shows the weighted impact of the individual biomarkers in each decision. This tool thus meets these expectations. Consequently, the next step will be screening for these confounding factors while continuously incorporating new data and monitoring the feasibility of the bedside application of this model.

Strengths and limitations. Our study has multiple strengths and some limitations. Although the predictive potential of this model is similar to that of currently available predictive scoring systems, it has multiple advantages over them. It provides risk assessment with any five of the predictors in our study, which are commonly assessed in daily practice. Therefore, this better reflects everyday clinical practice. To the best of our knowledge, this is the first AI model to strive to predict the development of ANP on clinical admission. We designed our model on a much larger population, as compared to the already existing prognostic AI models in AP, and there was no overlap between the original and validation population. Furthermore, we placed great emphasis on the interpretation of the model for physicians and its implementation by creating an online application. Nevertheless, in addition to predictive model development, ANP was extensively analyzed.

In addition to these strengths, the present study has several limitations. Firstly, as we move further from the endpoint of the prediction spectrum, the confidence of the model becomes wider, and prediction becomes less reliable. Secondly, the cross-validated AUC value of our XGBoost model is currently in the fair range[47]. Thirdly, data imputation can also introduce bias. Most of these limitations can be overcome. Based on our analyses, we could reach better predictive potential by increasing the training sample size and more data could provide more accurate imputation as well. Therefore, by using the application, making further predictions with more data, the model itself could improve.

It should be highlighted that AI models should not be considered as a substitute for human intelligence[16]. These tools, including our model, were designed to facilitate physicians' decision-making and every prediction should be interpreted in accordance with the clinical picture.

Implication for practice and research. Development of ANP is associated with several short- and long-term complications, e.g. endocrine insufficiency, but CECT is not performed solely and exclusively to confirm necrosis in AP. Therefore, by knowing the high risk for necrosis development, we can identify a group of patients who need closer follow-up. Nevertheless, this model can aid physicians when CECT is either contraindicated or not available. Also, as soon as new therapies emerge, early identification of ANP will become even more important. Further research is needed on other potential predictive factors, which could be incorporated in the current model to further improve predictions.

Conclusion

This study is the first to combine prediction of necrosis development and artificial intelligence in AP. The predictive potential of this model is comparable to the already existing clinical scoring systems and the model is expected to further improve with use. The easy-to-use web application supported by the interpretation of the prediction facilitates early, on-admission prediction of necrosis and allows continuous data maintenance and algorithmic understanding.

Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests
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Appendix A

Early prediction of acute necrotizing pancreatitis by artificial intelligence: A prospective cohort-analysis of 2387 cases

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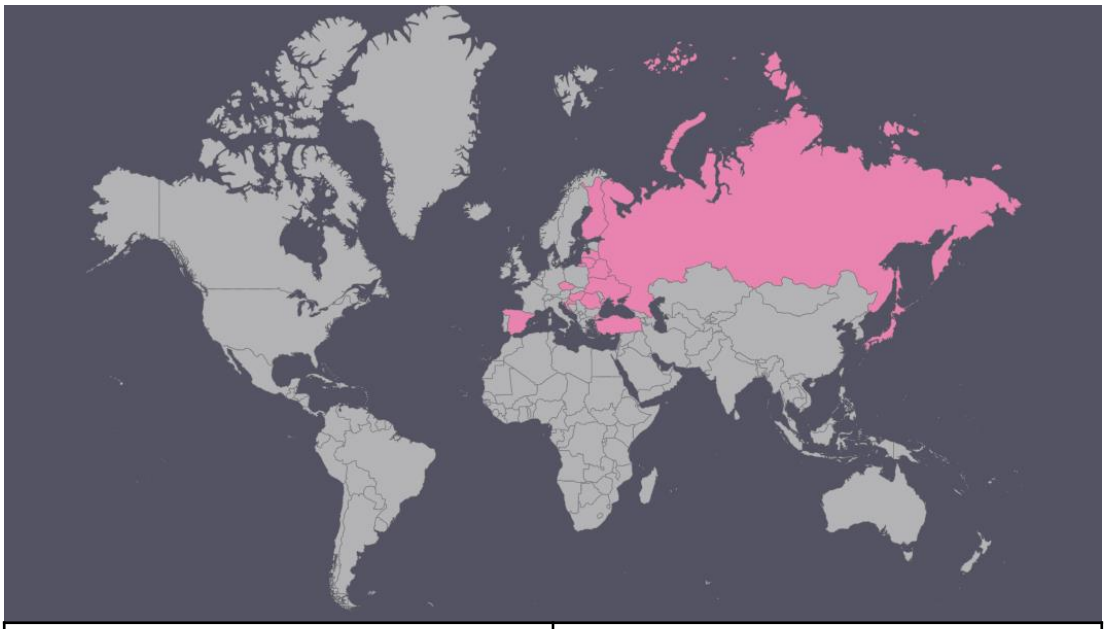
Supplementary Figure 1: Geographical distribution of patients in the whole cohort



Country	Number of patients
Belarus	8
Croatia	11
Czech Republic	11
Finland	25
Hungary	2225
Japan	2
Latvia	6
Lithuania	31
Romania	58
Russia	28
Spain	28
Turkey	20
Ukraine	8

Supplementary Table 1: List of study centres

	Centre		Centre
1	Bács-Kiskun County Hospital, Kecskemét, Hungary	16	Dr. Réthy Pál Hospital, Békéscsaba, Hungary
2	Bajcsy-Zsilinszky Hospital and Clinic, Budapest, Hungary	17	First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
3	Bogomolets National Medical University, Kiev, Ukraine	18	Gastroenterology, Hepatology and Nutritional Centre, Pauls Stradins Clinical University Hospital, Riga, Latvia
4	Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital, Miskolc, Hungary	19	General Surgery, Consorci Sanitari del Garraf, Sant Pere de Ribes, Barcelona, Spain
5	Buda Hospital of the Hospitaller Order of Saint John of God, Budapest, Hungary	20	Gomel Regional Clinical Hospital, Gomel, Belarus
6	Central Military Emergency Hospital "Dr Carol Davila", Bucharest, Romania	21	Heim Pál National Pediatric Institute, Budapest, Hungary
7	Centrum péče o zažívací trakt, Vítkovická nemocnice a.s., Ostrava, Czech Republic	22	Hospital of Bezmialem Vakif University, School of Medicine, Istanbul, Turkey
8	Clinical Hospital Center Rijeka, Rijeka, Croatia	23	Keio University, Tokyo, Japan
9	County Emergency Clinical Hospital of Targu Mures Hospital, University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Romania	24	Markusovszky University Teaching Hospital, Szombathely, Hungary
10	Csongrád County Health Center, Makó, Hungary	25	Military Hospital, Budapest, Hungary
11	Department of Internal Medicine, University of Debrecen, Debrecen, Hungary	26	Pándy Kálmán Hospital of Békés County, Gyula, Hungary
12	Department of Internal Medicine, University of Szeged, Szeged, Hungary	27	Saint Luke Clinical Hospital, St. Petersburg, Russia
13	Department of Surgery, University of Debrecen	28	Second Department of Internal Medicine, Semmelweis University, Budapest, Hungary
14	Department of Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland	29	Szent György University Teaching Hospital of Fejér County, Székesfehérvár, Hungary
15	Dr. Bugyi István Hospital, Szentes, Hungary	30	Vilnius University Hospital, Vilnius, Lithuania

Supplementary Table 2: Data quality in the analyzed population regarding epidemiology, etiology, and disease outcomes

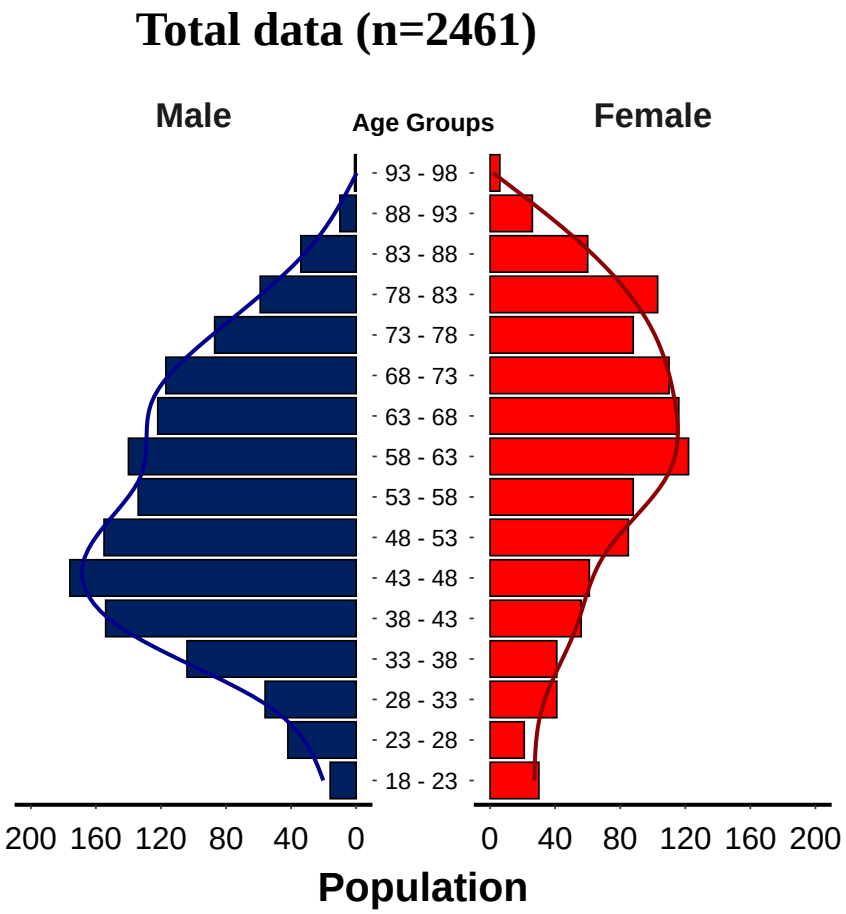
EPIDEMIOLOGY, ETIOLOGY	OVERALL	UPLOADED DATA	%
Age	2387	2387	100%
Gender	2387	2387	100%
Etiology	2387	2387	100%
Total	***7161***	***7161***	***100%***

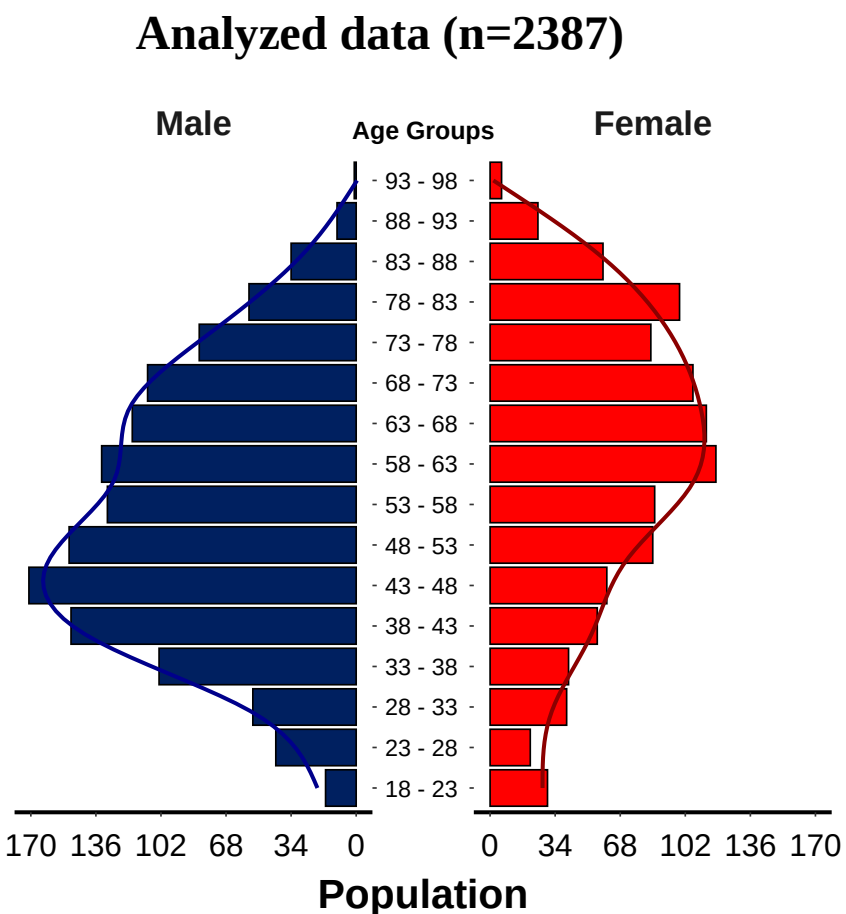
OUTCOMES	OVERALL	UPLOADED DATA	%
Local pancreatic complications	2387	2379	99.7%
Acute peripancreatic fluid collection	2387	2380	99.7%
Pancreatic pseudocyst	2387	2380	99.7%
Pancreatic necrosis	2387	2387	100%
Diabetes mellitus as complication	2387	2387	100%
Systemic complication	2387	2379	99.7%
Renal failure	2387	2379	99.7%
Heart failure	2387	2379	99.7%
Respiratory failure	2387	2378	99.6%
Length of hospitalization	2387	2387	100%
Severity (mild/moderate/severe)	2387	2387	100%
Mortality	2387	2387	100%
Total	***28644***	***28589***	***99.8%***

Supplementary Table 3: Data quality in the analyzed population regarding laboratory parameters

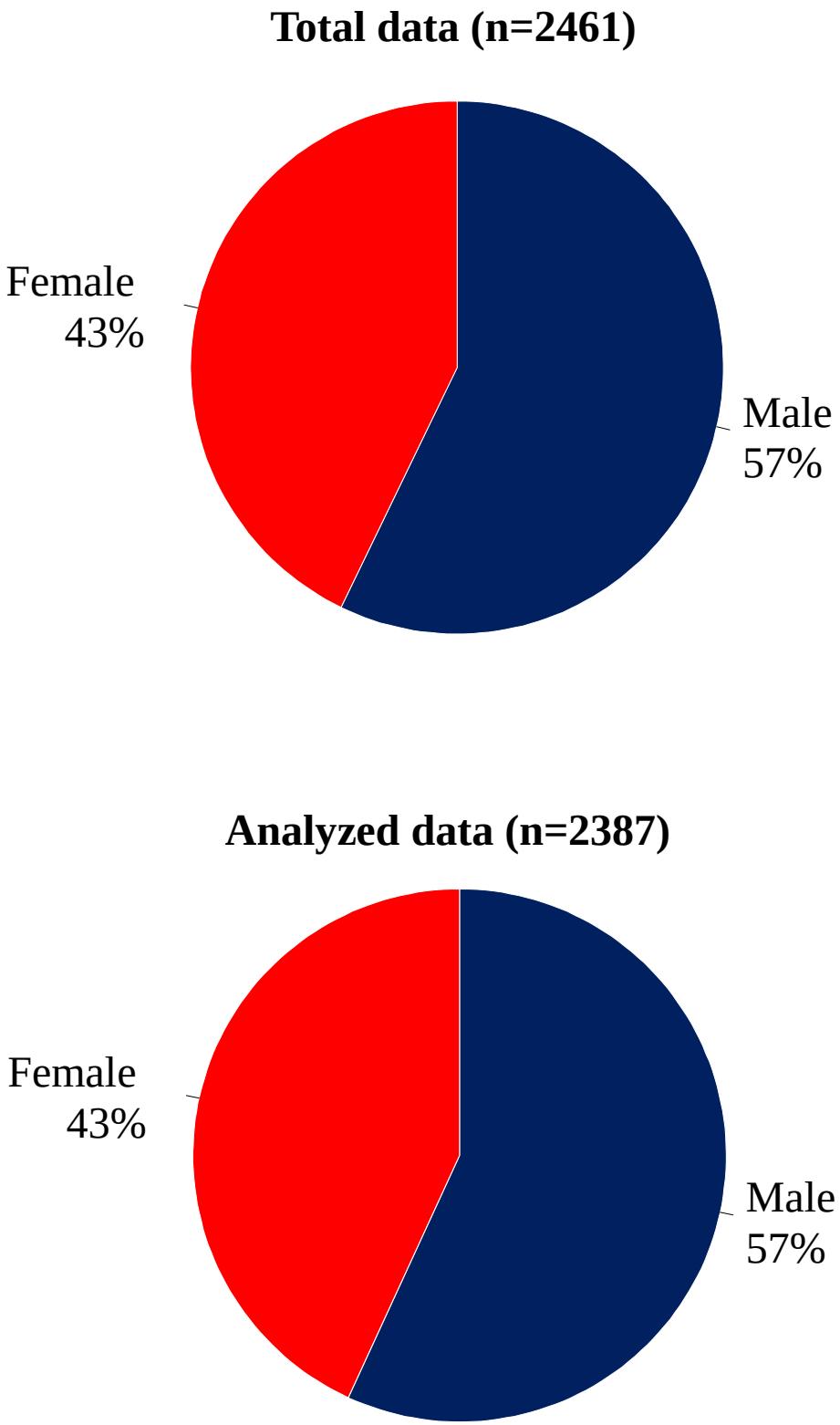
LABORATORY PARAMETERS ON ADMISSION	OVERALL	UPLOADED DATA	%
Amylase	2387	2332	97.7%
Lipase	2387	1916	80.3%
Triglyceride (TG)	2387	1377	57.7%
Total cholesterol	2387	1257	52.7%
C-reactive protein (CRP)	2387	2223	93.1%
Procalcitonin (PCT)	2387	889	37.2%
Total white blood cell count (WBC)	2387	2322	97.3%
Red blood cell count (RBC)	2387	1901	79.6%
Hematocrit	2387	1908	79.9%
Hemoglobin	2387	1884	78.9%
Thrombocyte	2387	1902	79.7%
Glucose	2387	2155	90.3%
Glycated hemoglobin (HbA1c)	2387	729	30.5%
Aspartate transaminase (ASAT)	2387	1730	72.5%
Alanine transaminase (ALAT)	2387	1692	70.9%
Gamma-glutamyl transferase (γGT)	2387	2106	88.2%
Alkaline phosphatase (ALP)	2387	2109	88.4%
Lactate dehydrogenase (LDH)	2387	1650	69.1%
Total bilirubin	2387	2159	90.4%
Direct bilirubin	2387	1205	50.5%
Potassium	2387	1825	76.5%
Sodium	2387	1817	76.1%
Calcium	2387	1552	65.0%
Albumin	2387	1059	44.4%
Total protein	2387	900	37.7%
Estimated glomerular filtration rate (eGFR)	2387	2190	91.7%
Creatinine	2387	2234	93.6%
Blood urea nitrogen (BUN)	2387	2181	91.4%
Total	***66836***	***49204***	***73.6%***

Supplementary Figure 2: Representativity analysis regarding age distribution showed no difference between the whole cohort and the analyzed population (t-test, p=0.738)

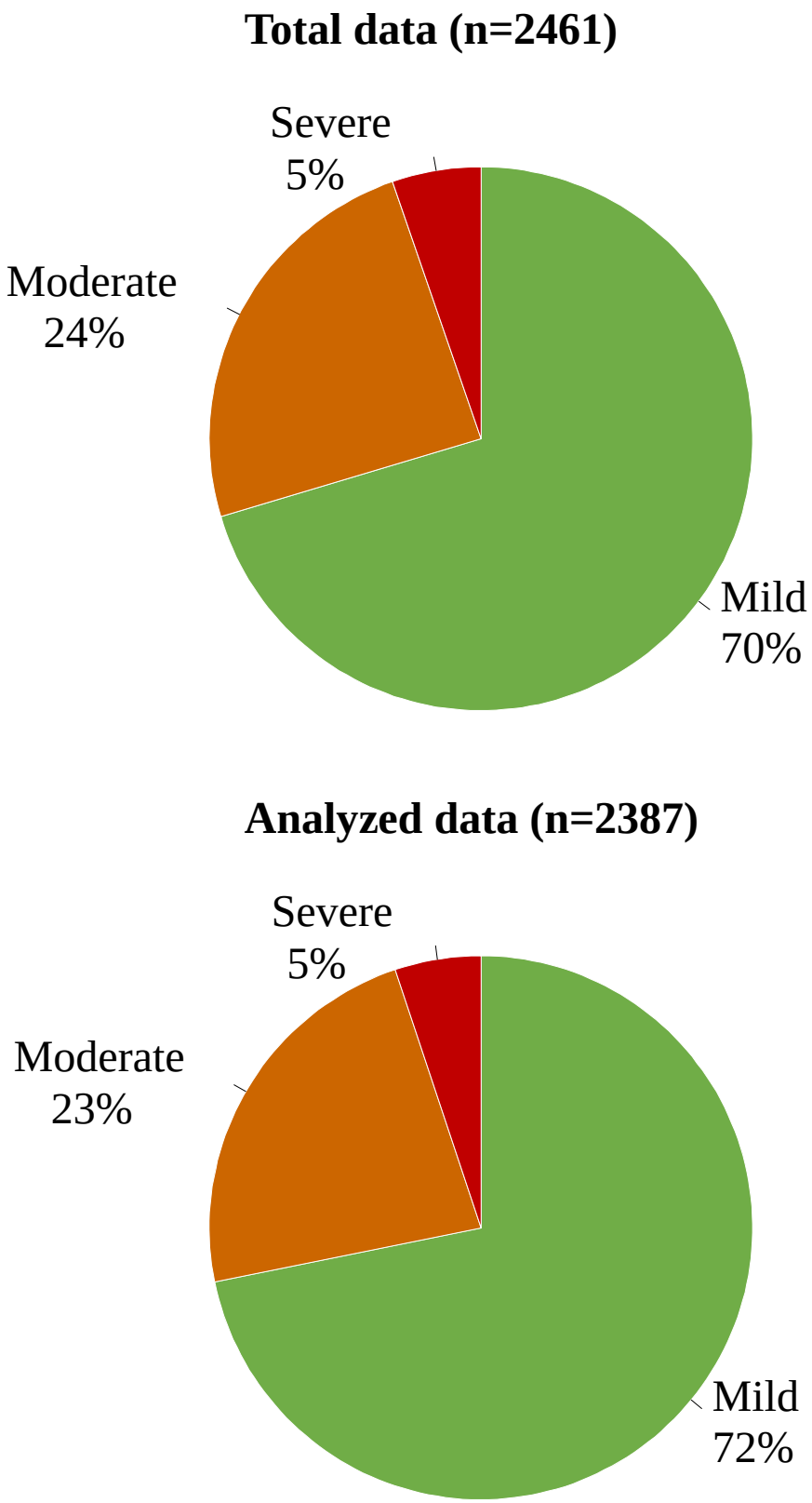




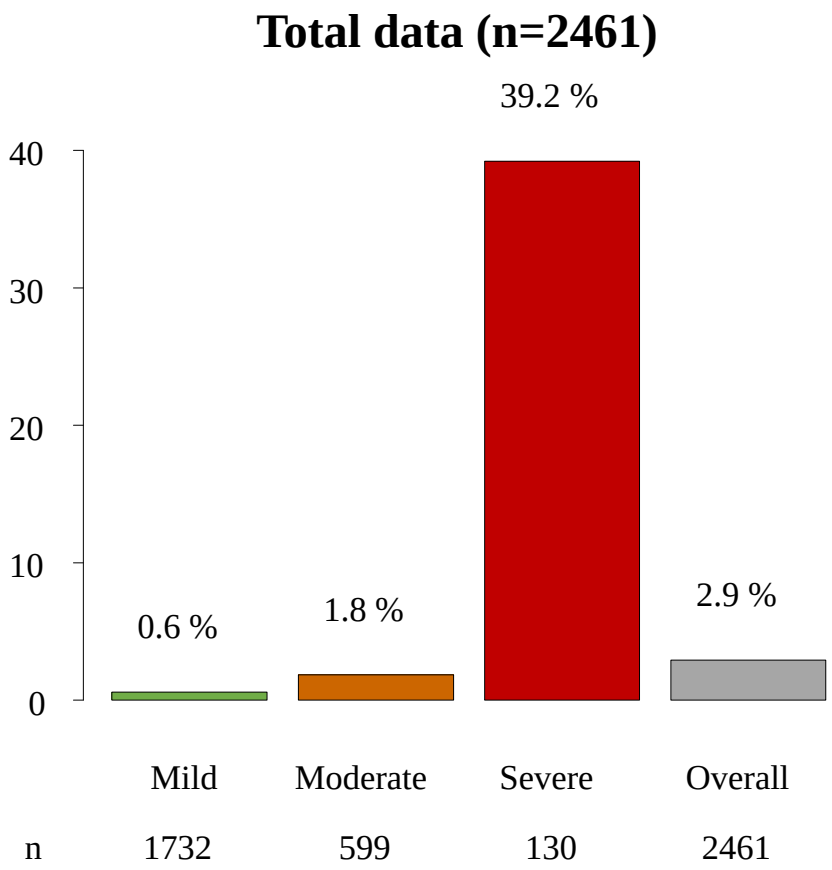
Supplementary Figure 3: Representativity analysis regarding gender distribution showed no difference between the whole cohort and the analyzed population (Chi^2 test, p=0.750)

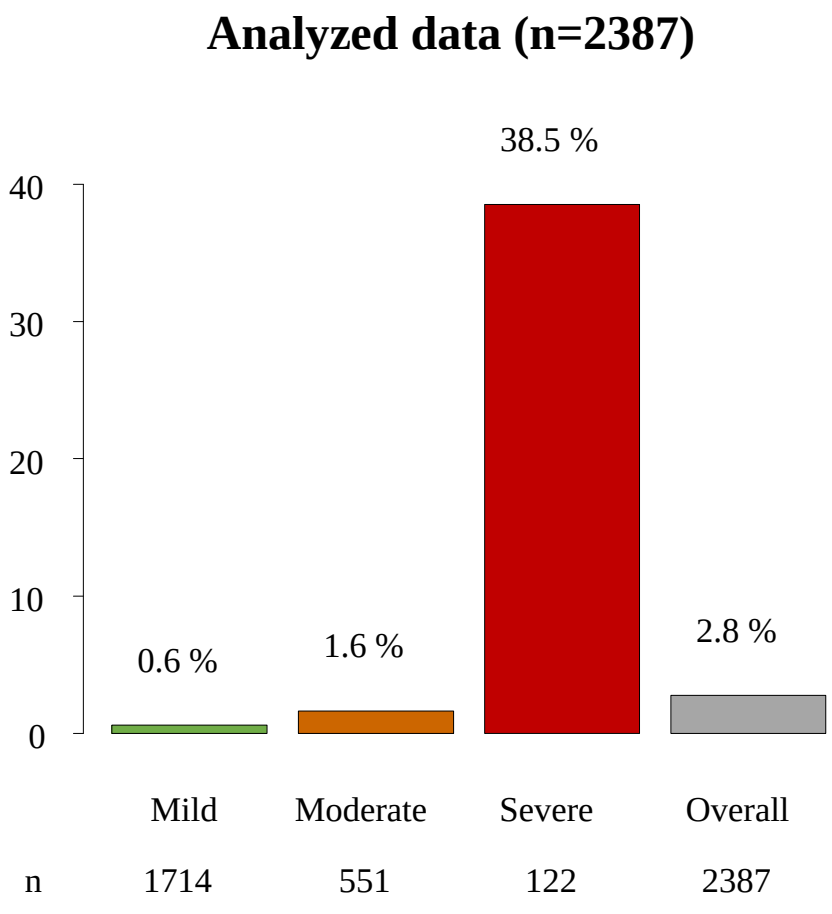


Supplementary Figure 4: Representativity analysis regarding disease severity showed no difference between the whole cohort and the analyzed population (Chi^2 test, p=0.305)

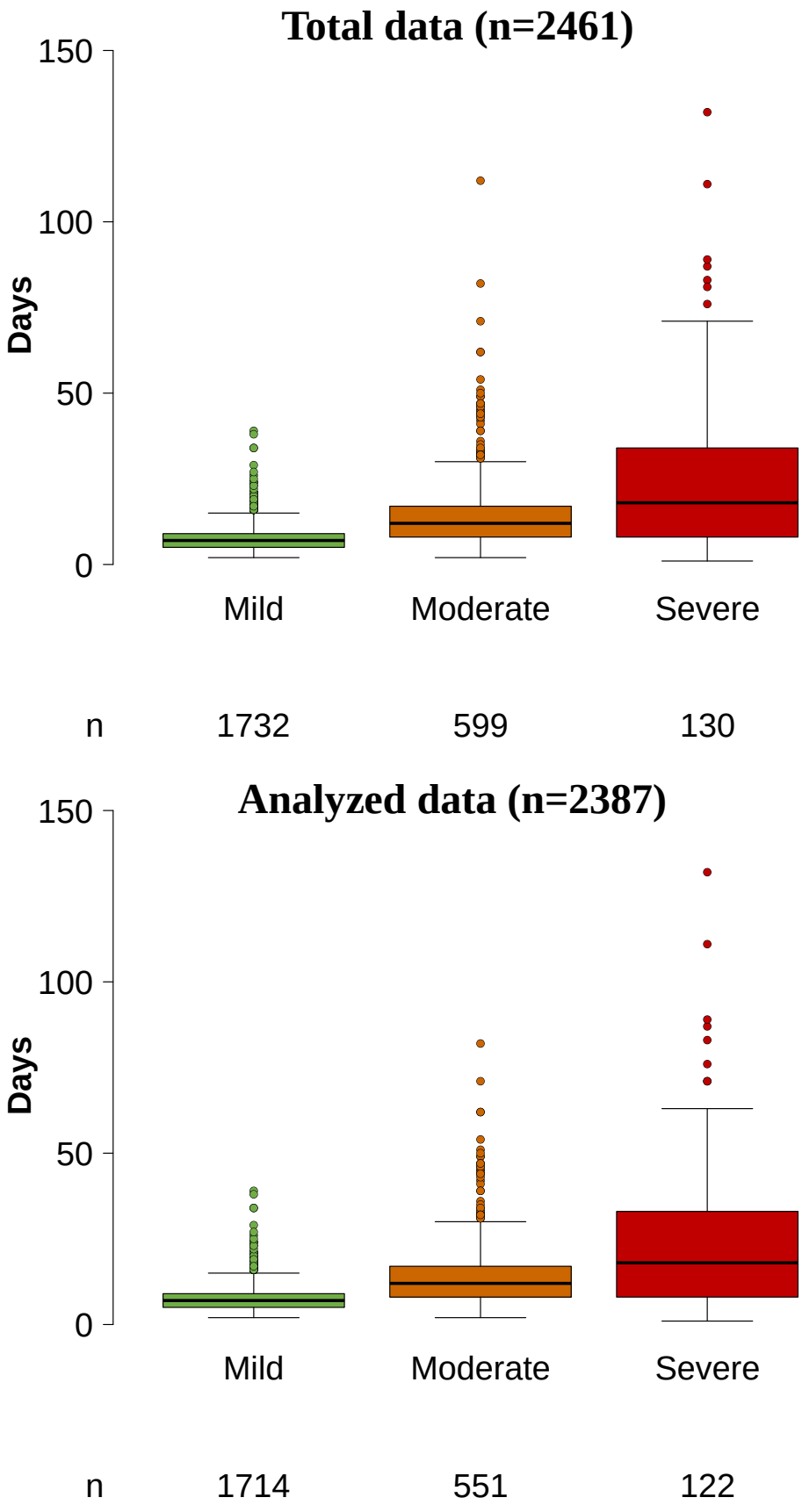


Supplementary Figure 5: Representativity analysis regarding mortality showed no difference between the whole cohort and the analyzed population (Chi² test, p=0.641)

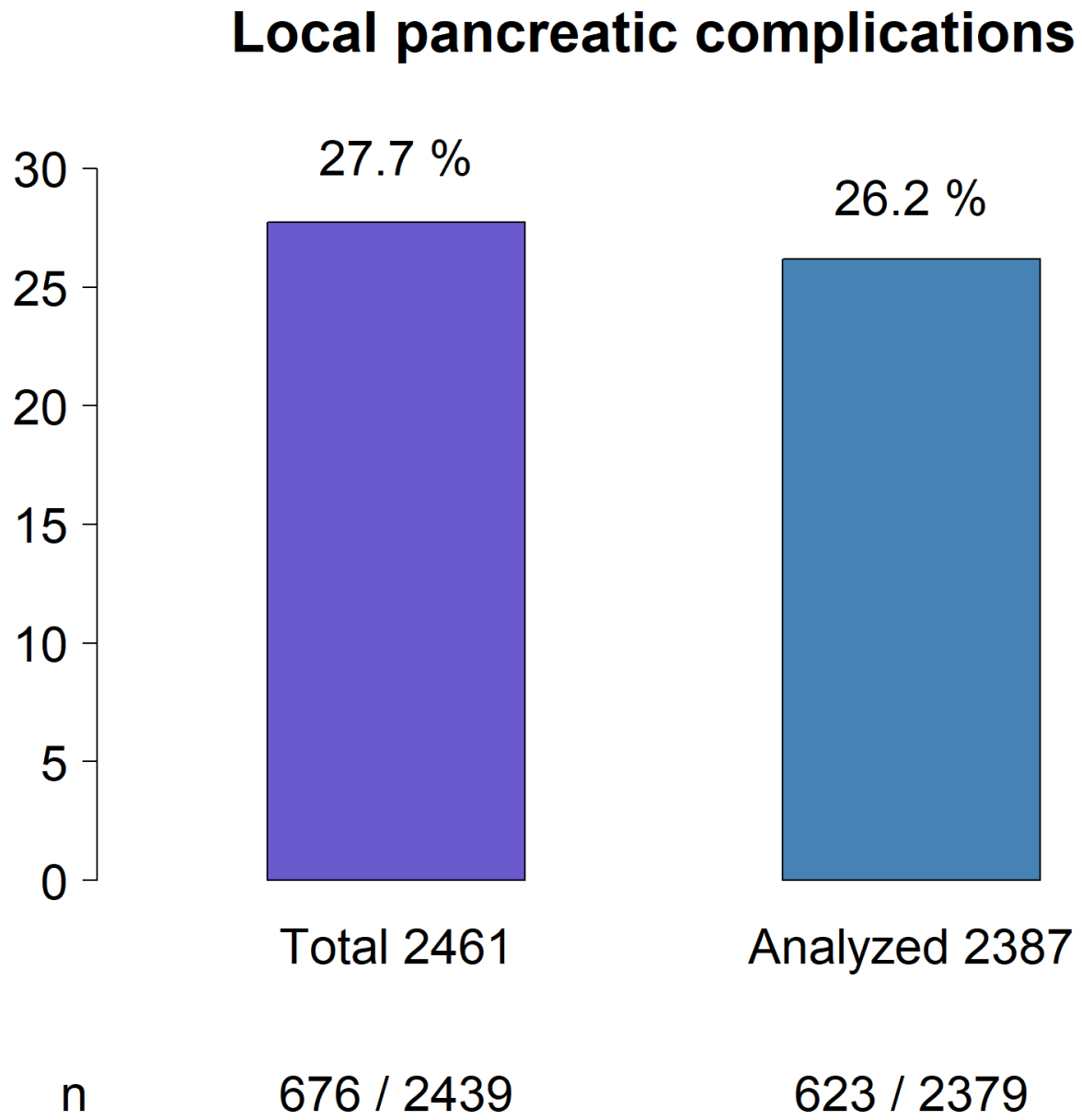




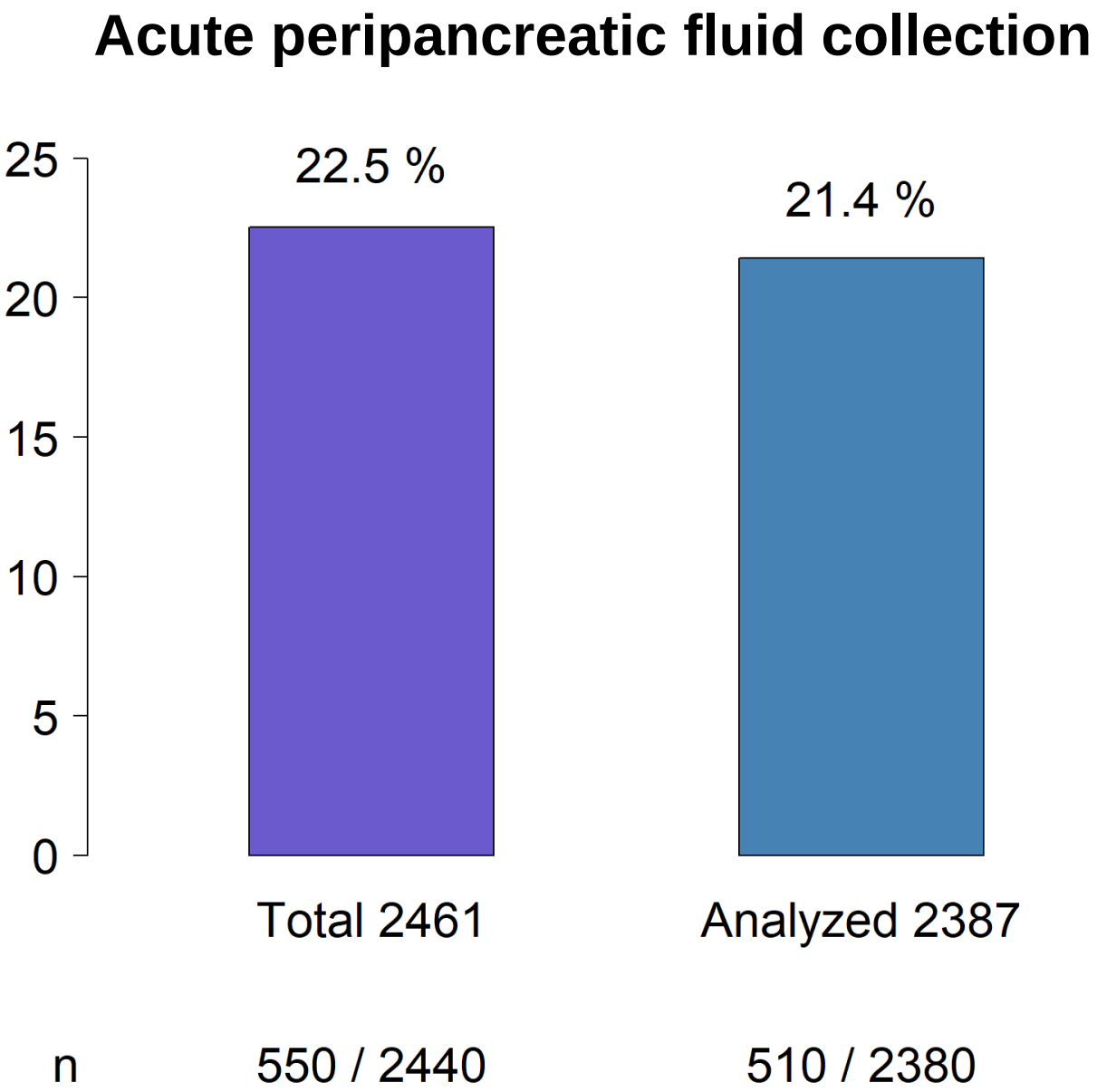
Supplementary Figure 6: Representativity analysis regarding length of hospitalization showed no difference between the whole cohort and the analyzed population (Mann-Whitney test, p=0.641)



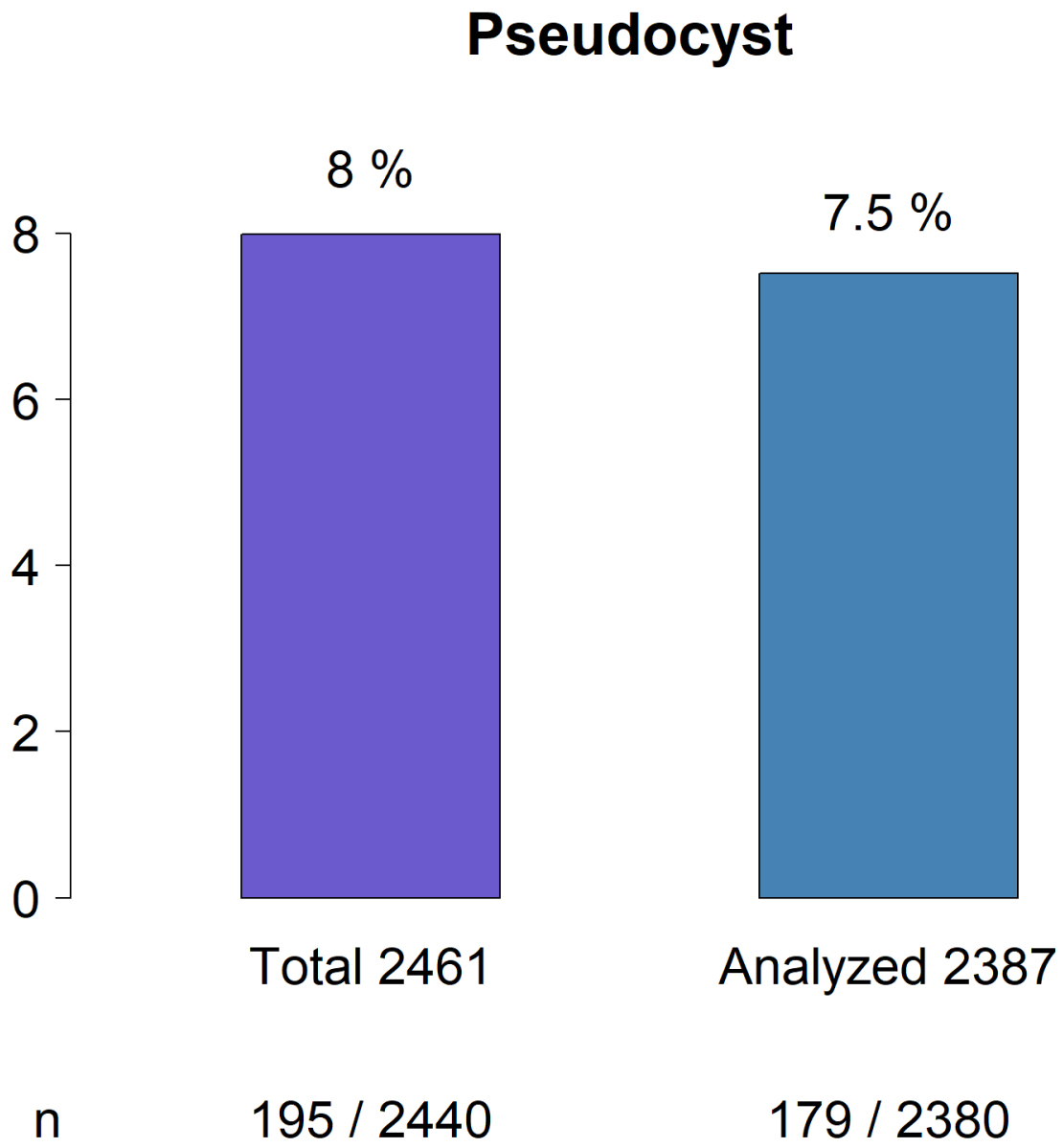
Supplementary Figure 7: Representativity analysis regarding local pancreatic complications showed no difference between the whole cohort and the analyzed population (Chi^2 test, p=0.096)



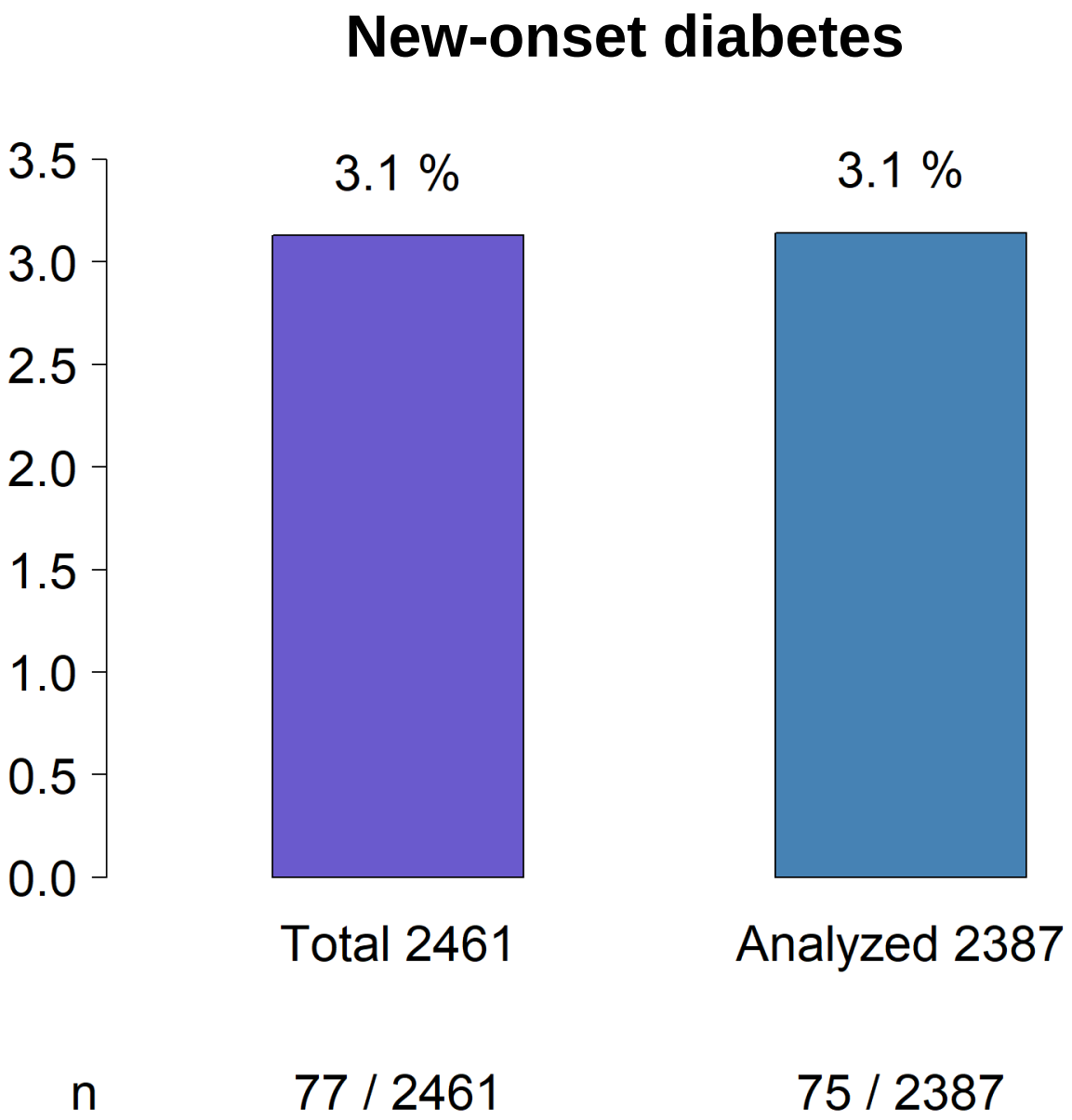
Supplementary Figure 8: Representativity analysis regarding acute peripancreatic fluid collection showed no difference between the whole cohort and the analyzed population (Chi^2 test, p=0.194)



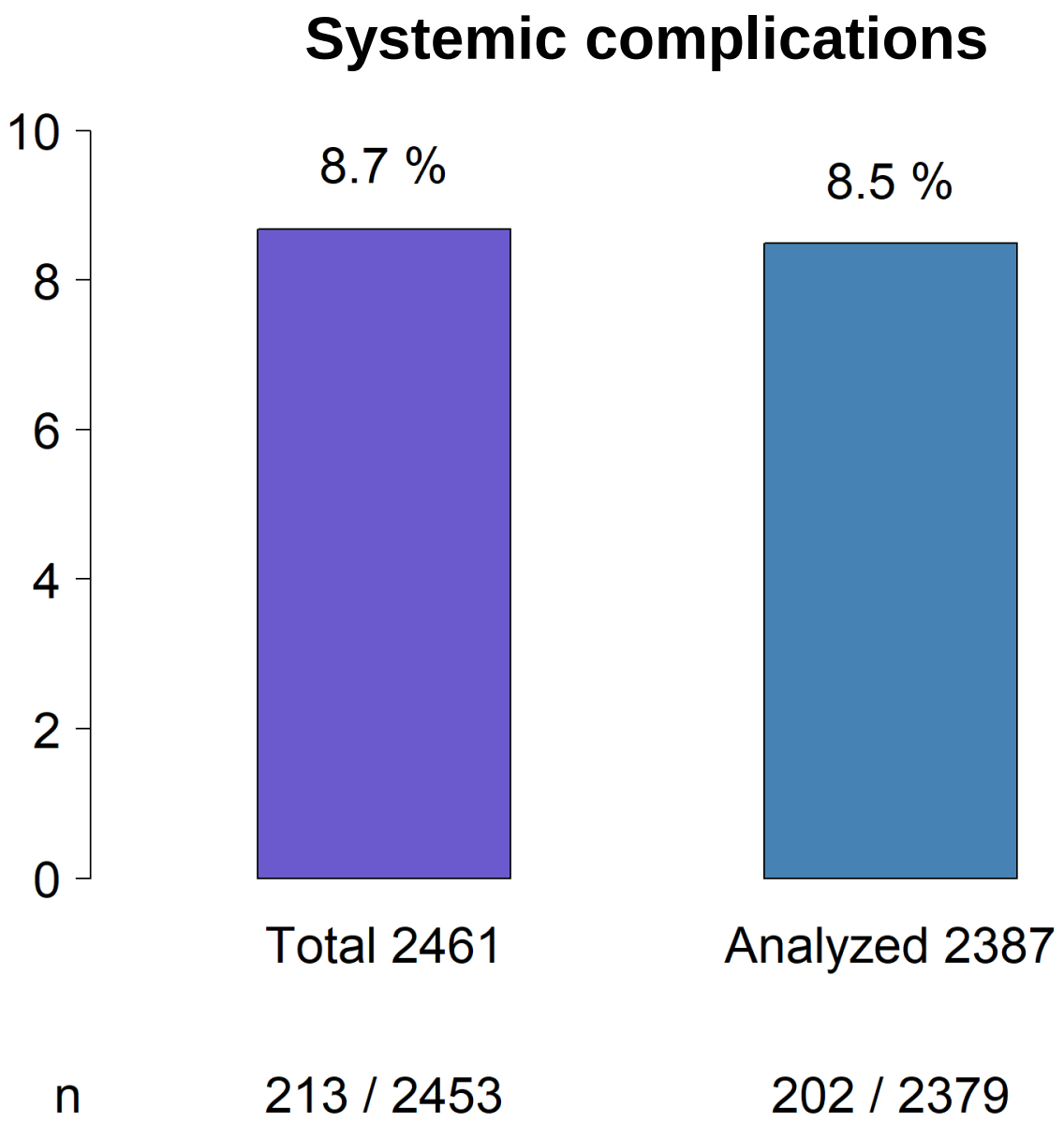
Supplementary Figure 9: Representativity analysis regarding pseudocyst showed no difference between the whole cohort and the analyzed population (Chi² test, p=0.397)



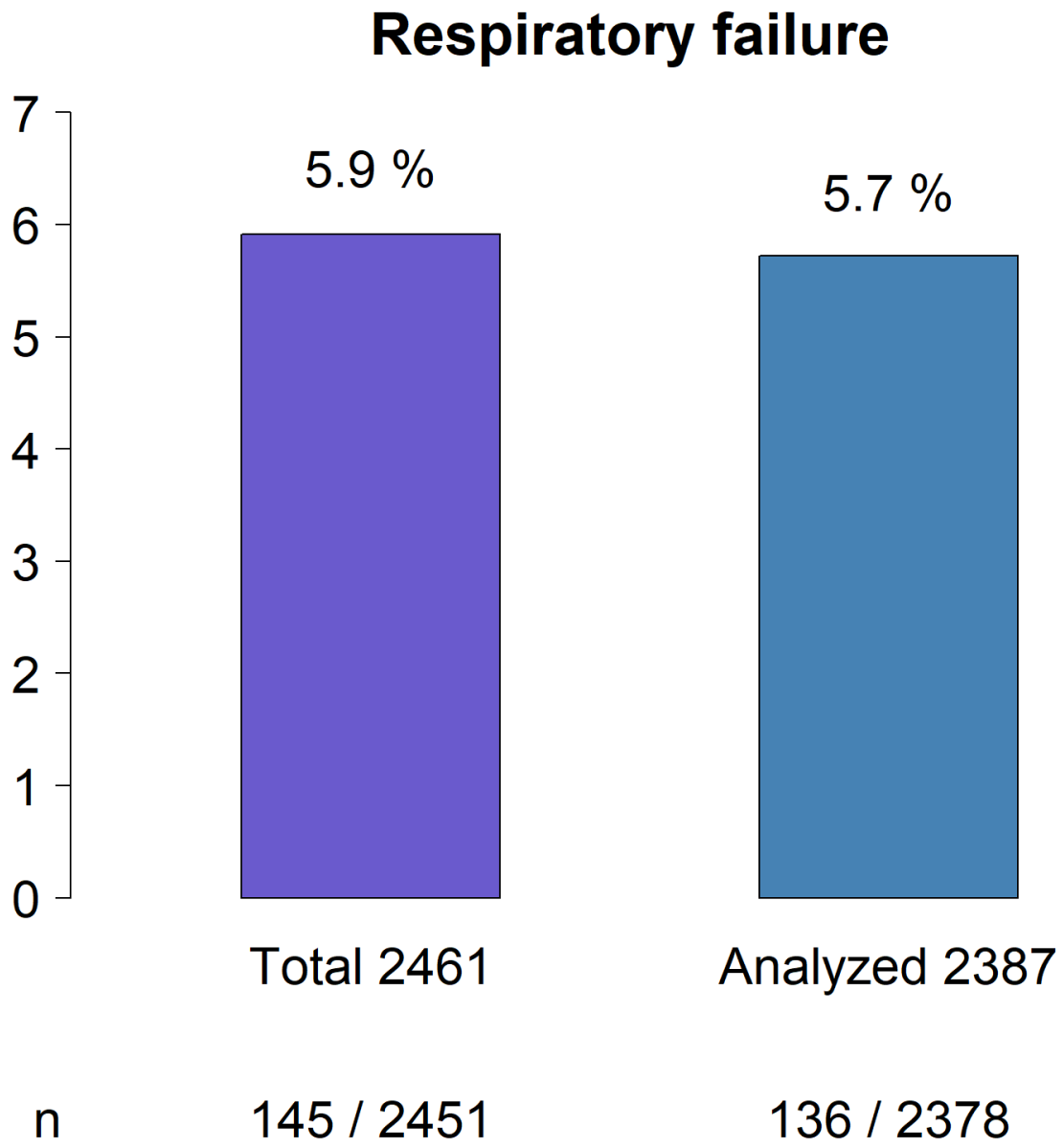
Supplementary Figure 10: Representativity analysis regarding new-onset diabetes showed no difference between the whole cohort and the analyzed population (Chi^2 test, p=0.970)



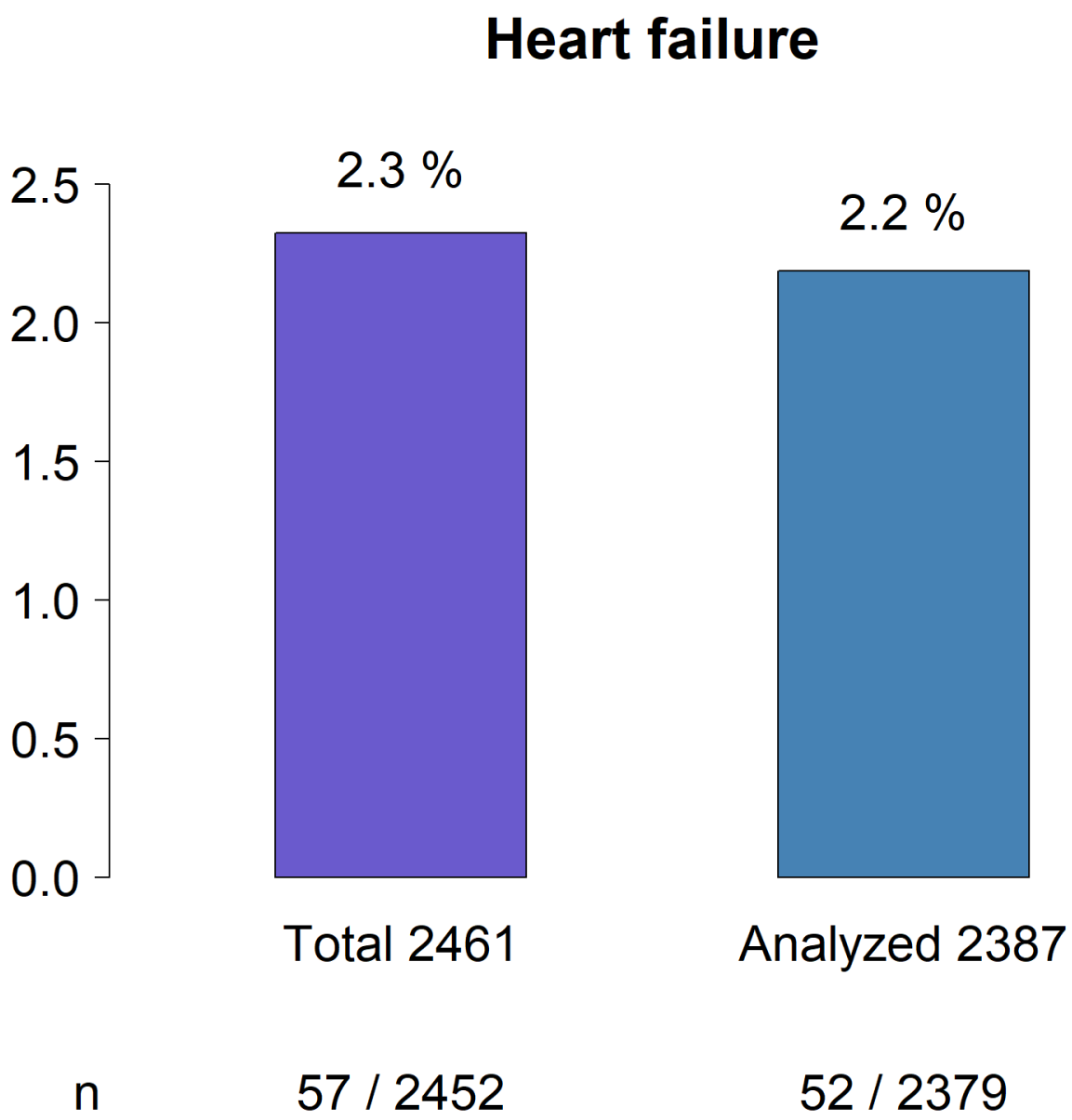
Supplementary Figure 11: Representativity analysis regarding systemic complications showed no difference between the whole cohort and the analyzed population (Chi^2 test, p=0.739)



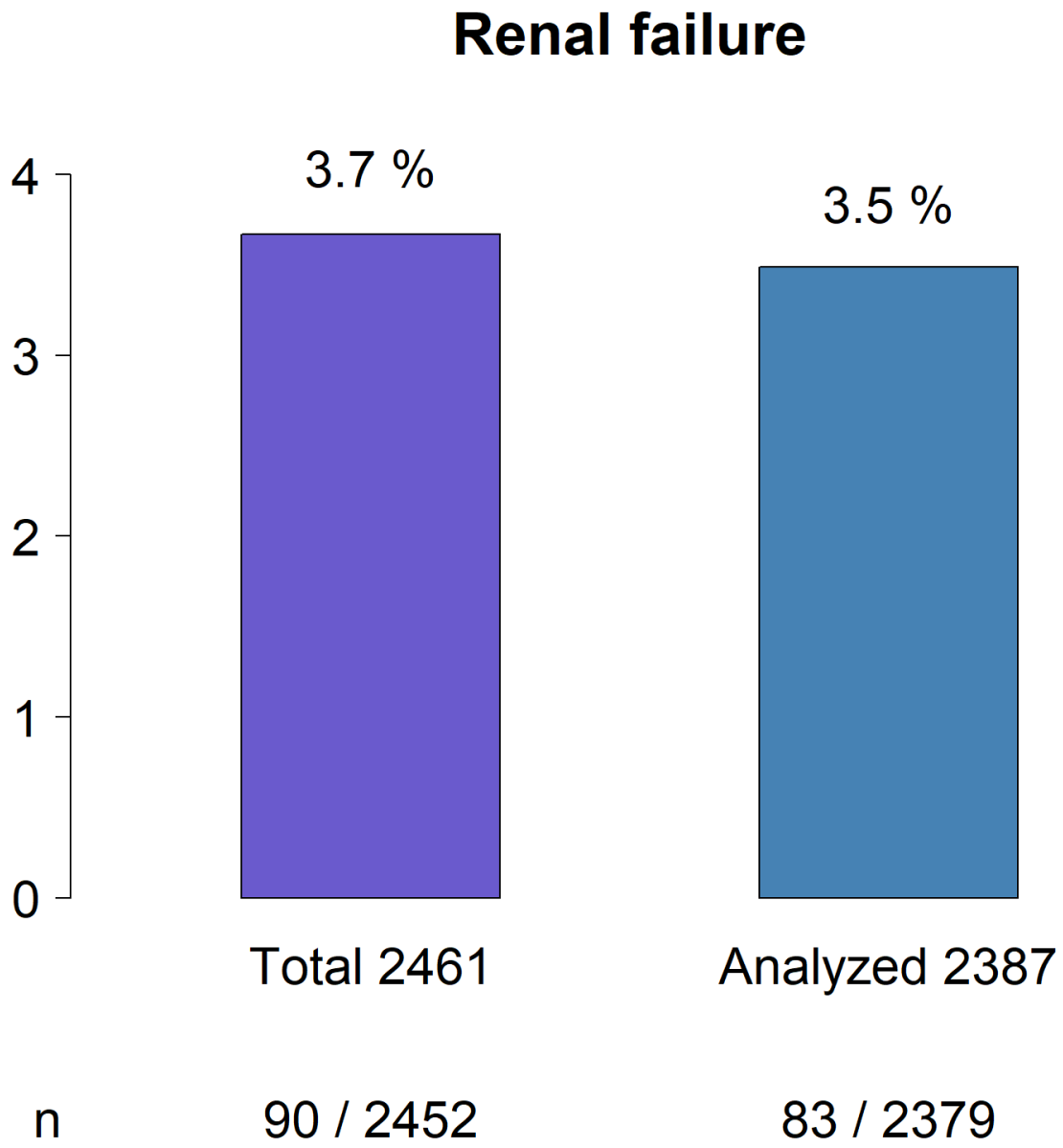
Supplementary Figure 12: Representativity analysis regarding respiratory failure showed no difference between the whole cohort and the analyzed population (Chi^2 test, p=0.684)



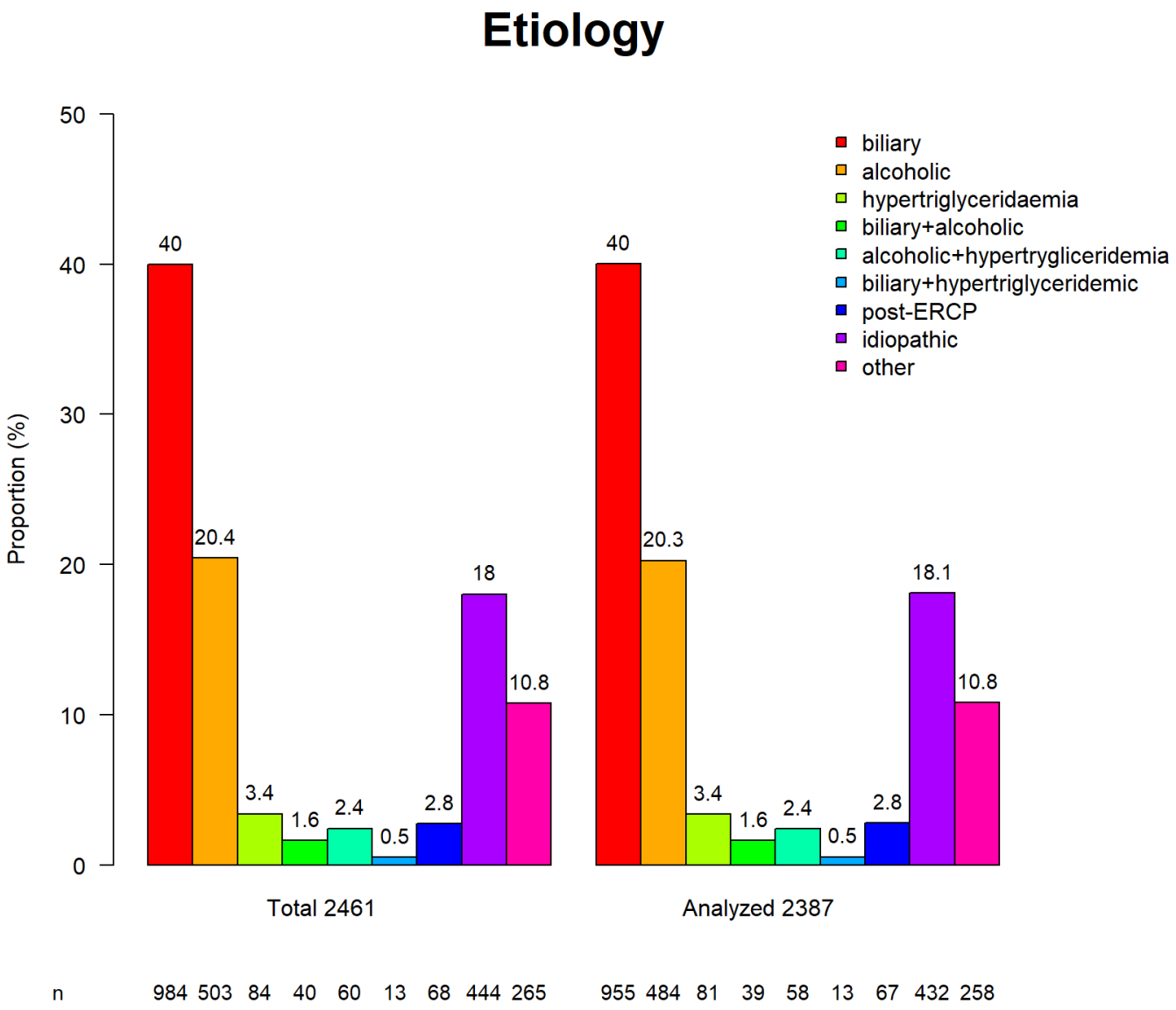
Supplementary Figure 13: Representativity analysis regarding heart failure showed no difference between the whole cohort and the analyzed population (Chi² test, p=0.653)



Supplementary Figure 14: Representativity analysis regarding renal failure showed no difference between the whole cohort and the analyzed population (Chi² test, p=0.638)



Supplementary Figure 15: Representativity analysis regarding etiology showed no difference between the whole cohort and the analyzed population (Chi² test, p=1.0)



Appendix B

Early prediction of acute necrotizing pancreatitis by artificial intelligence: A prospective cohort-analysis of 2387 cases

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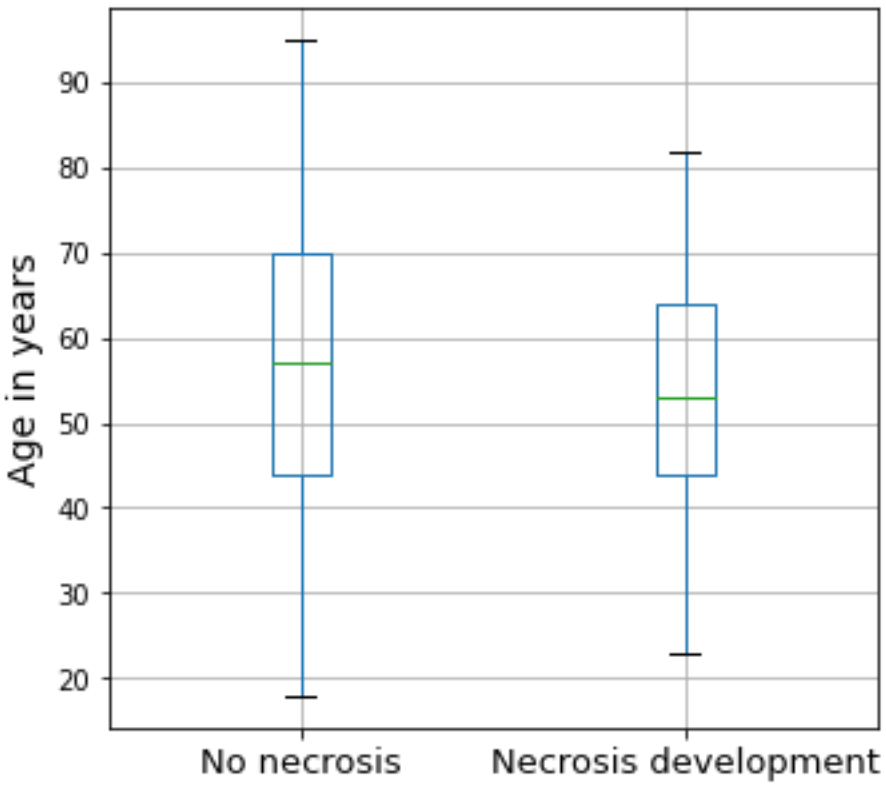
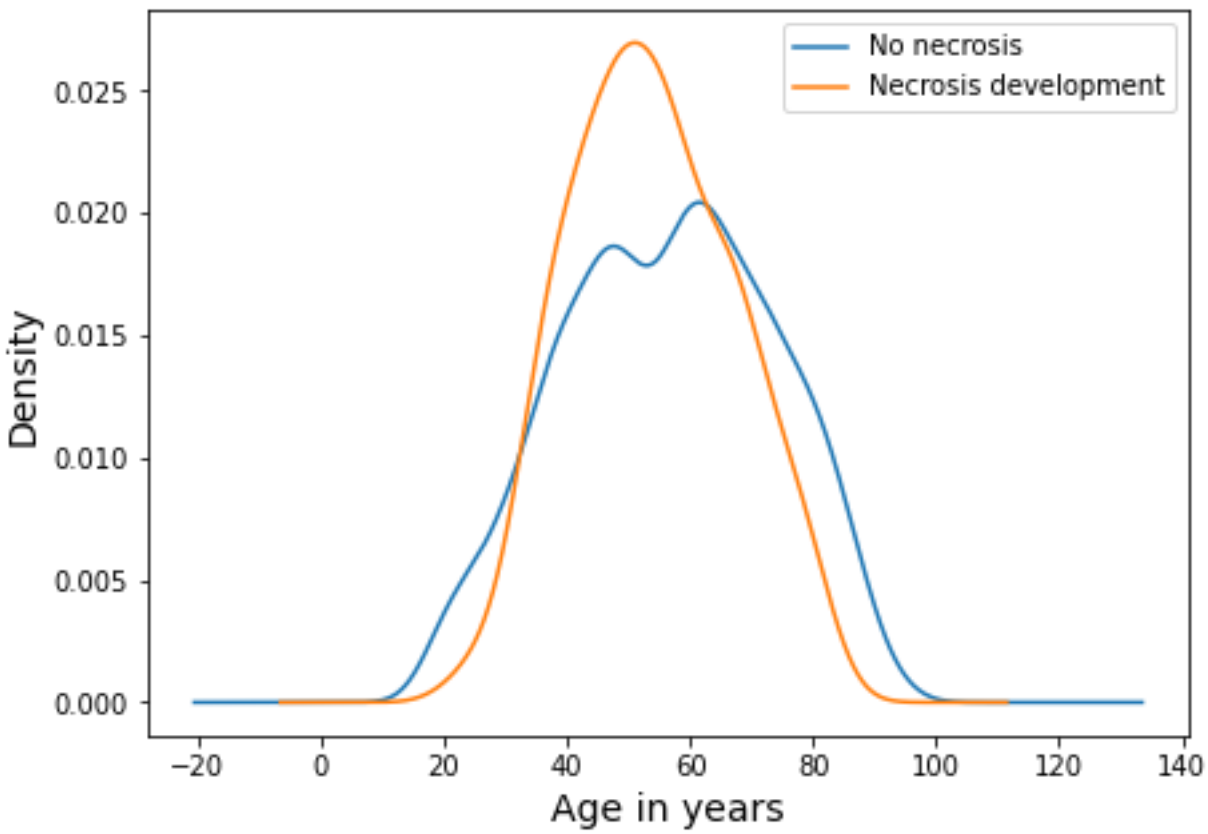
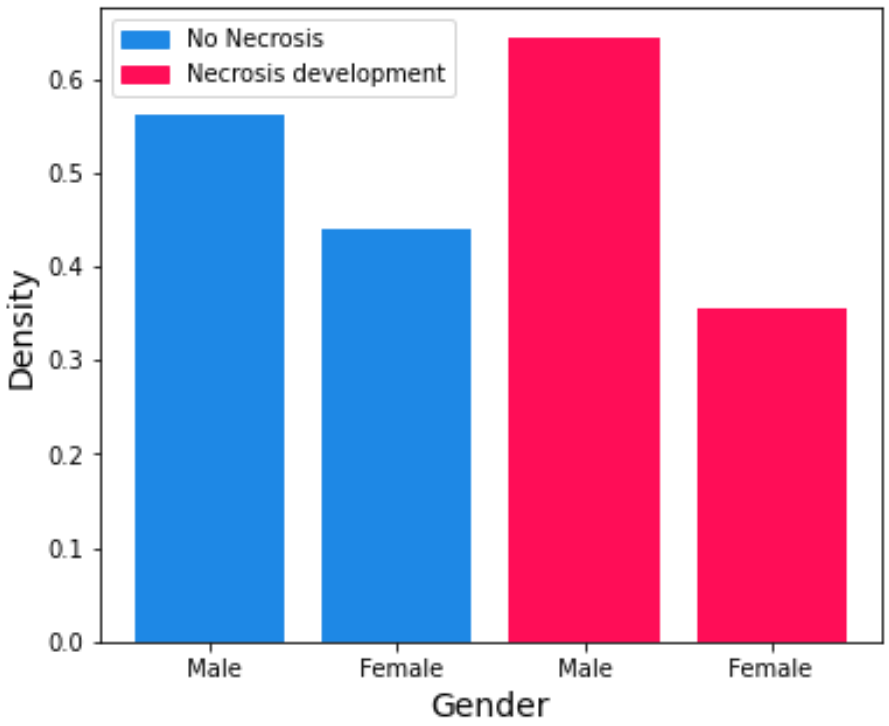
Supplementary Figure 16: The comparison in terms of age showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



n=2154 **n=233**

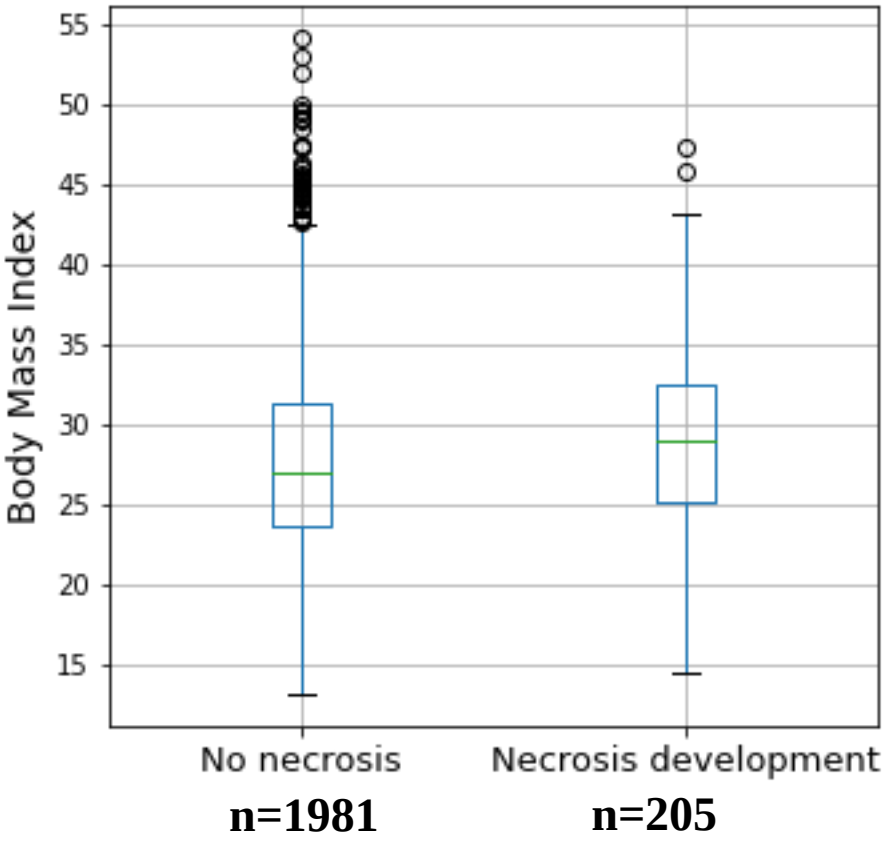


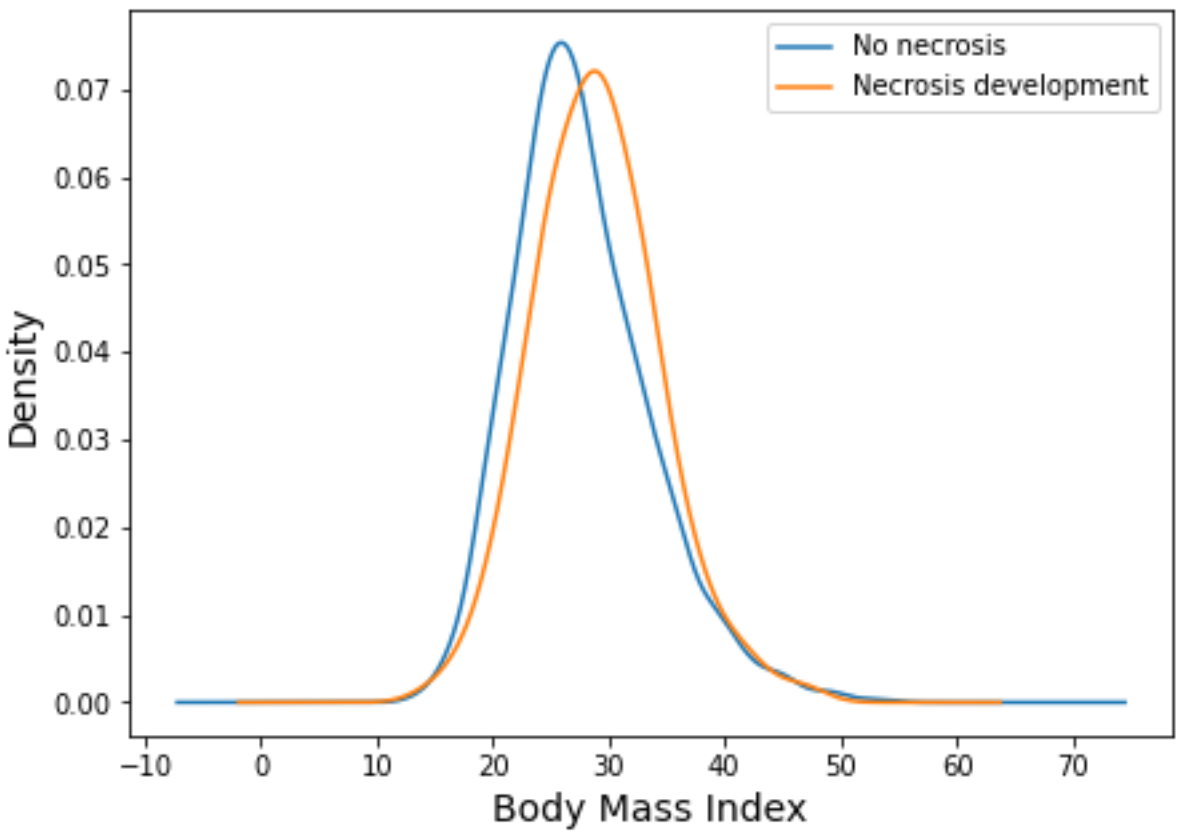
Supplementary Figure 17: The comparison in terms of gender distribution showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Chi2 test, p=0.018).



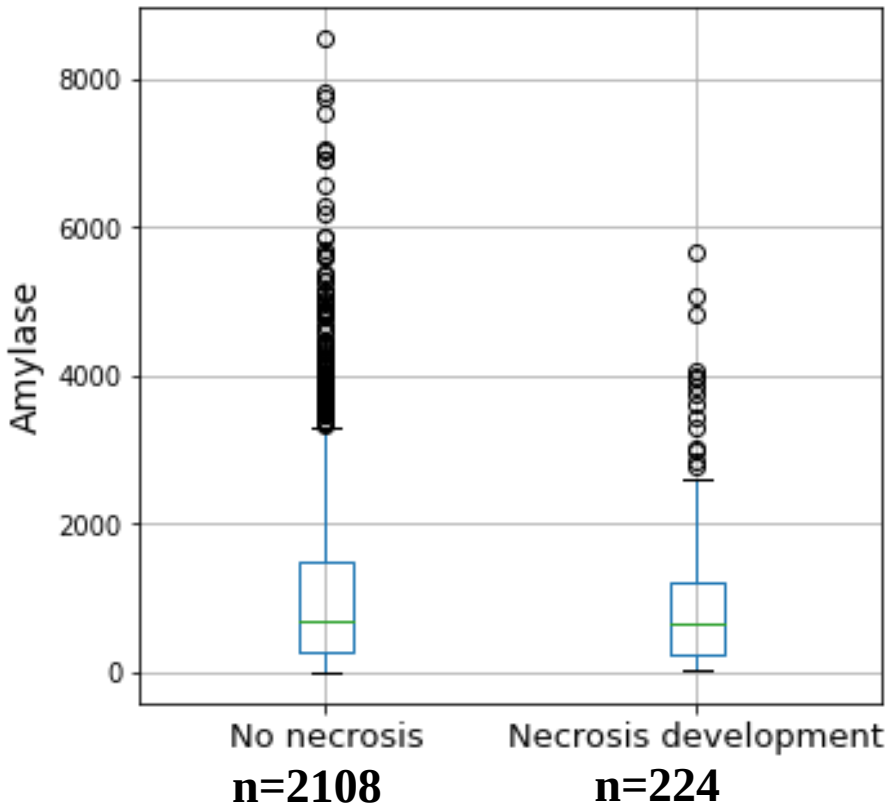
n=2154 **n=233**

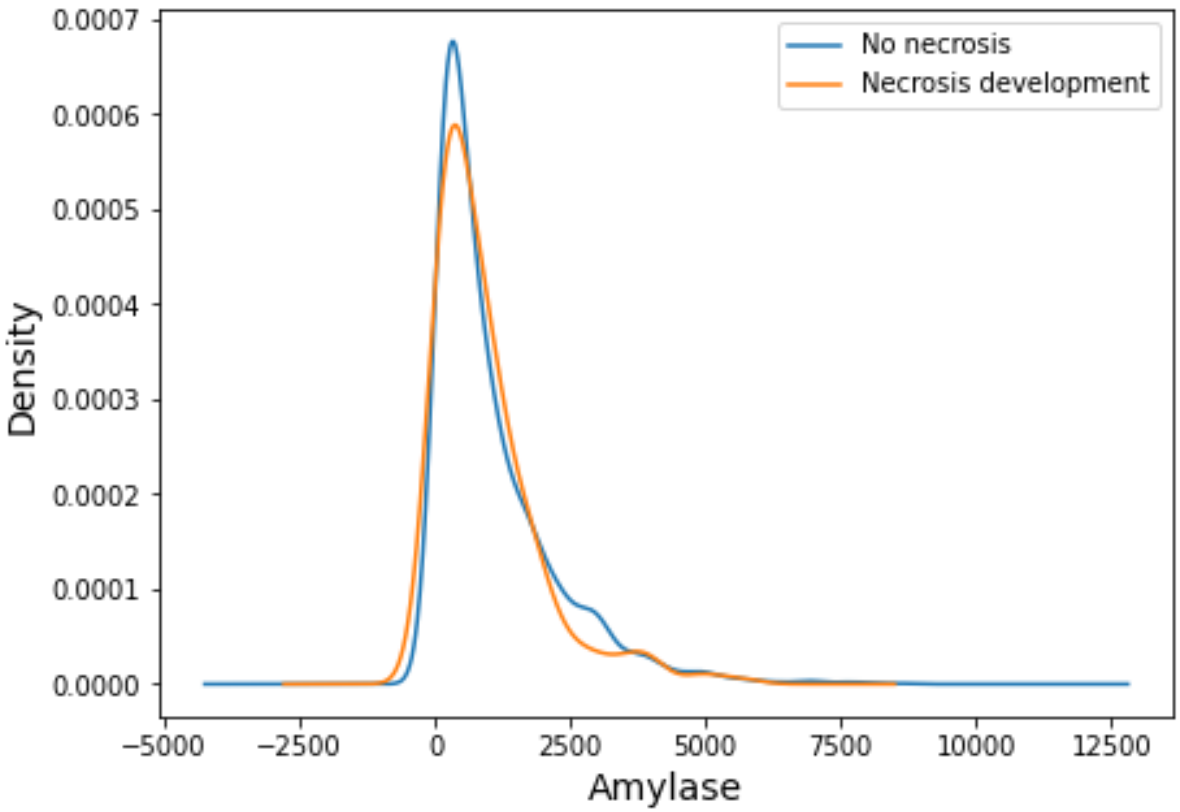
Supplementary Figure 18: The comparison in terms of body mass index showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



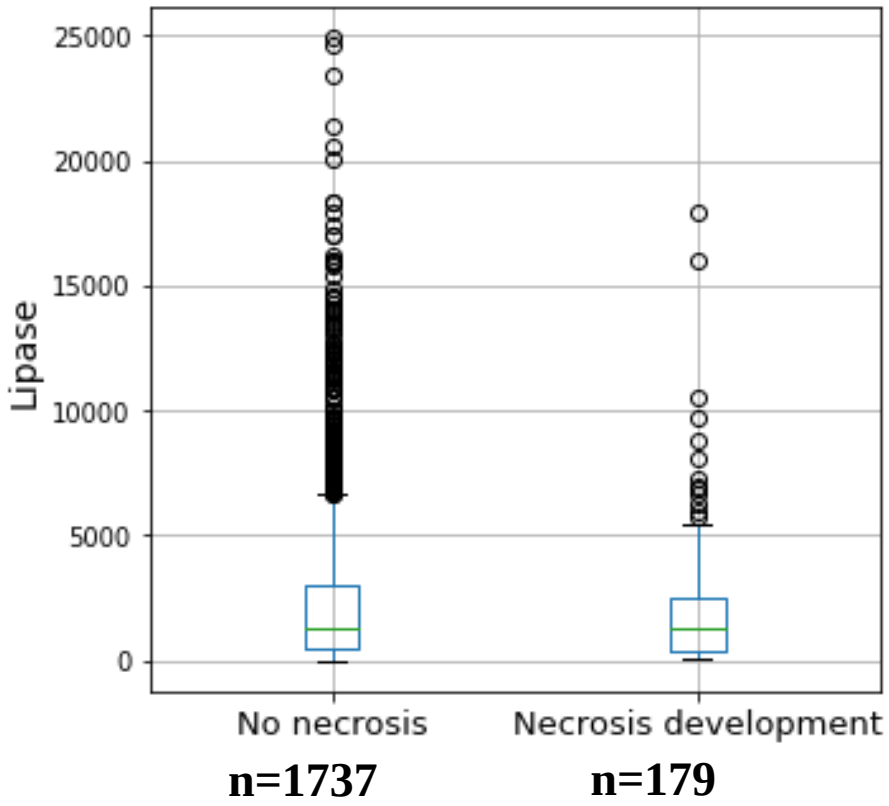


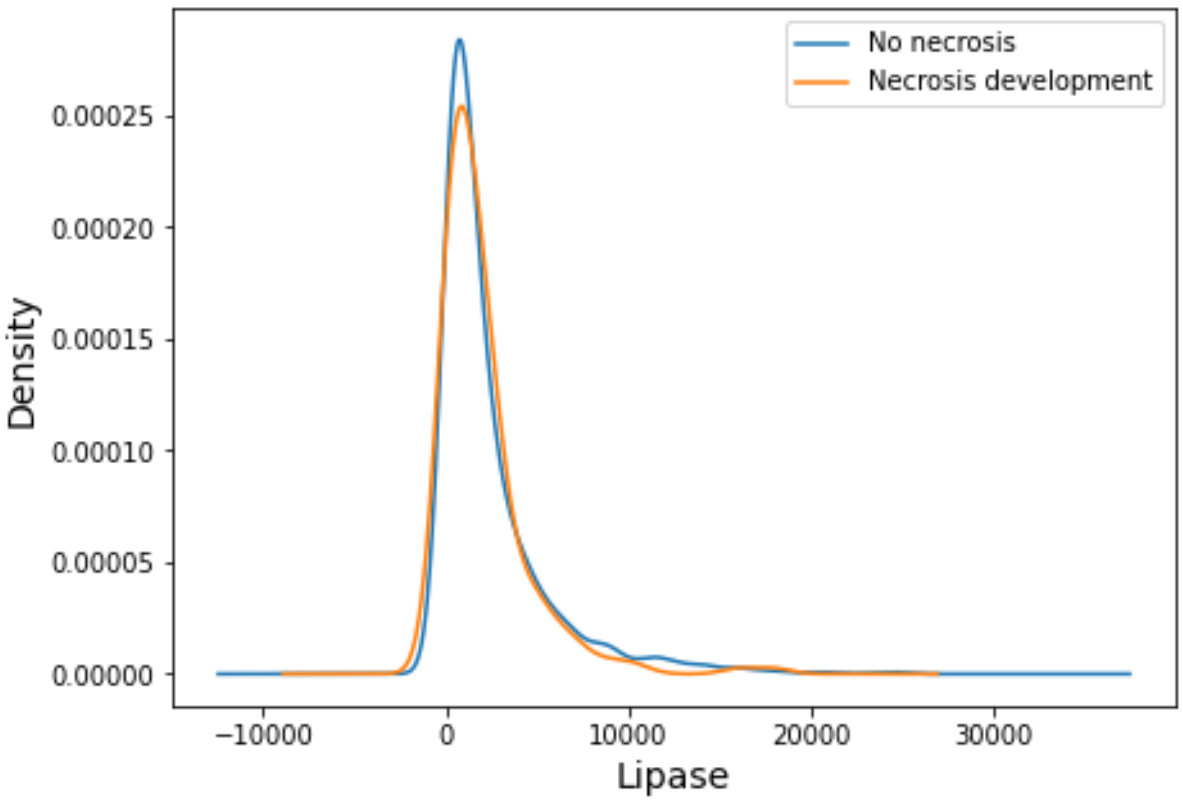
Supplementary Figure 19: The comparison in terms of amylase did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.053).



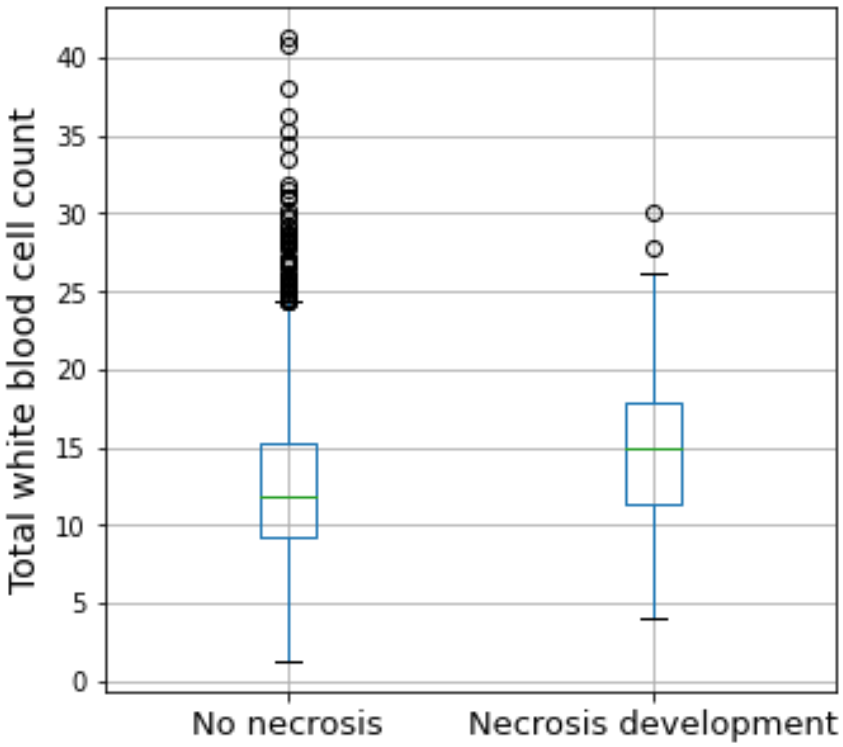


Supplementary Figure 20: The comparison in terms of lipase did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.380).

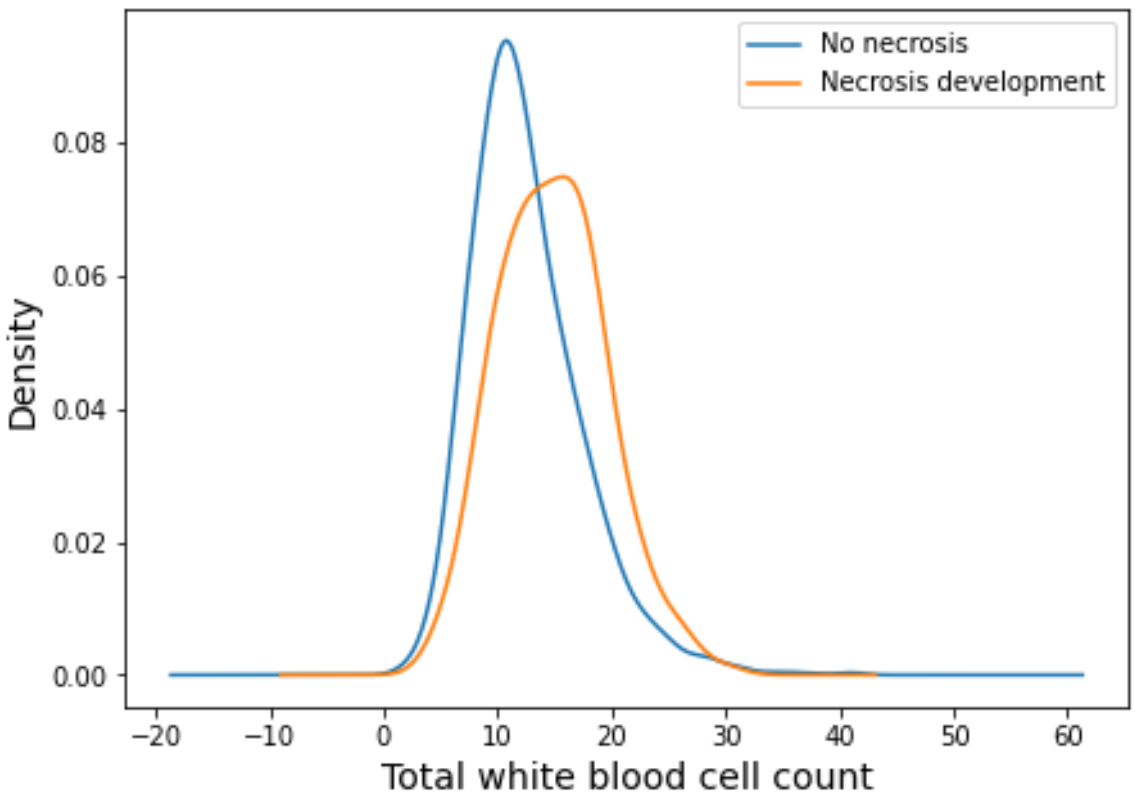




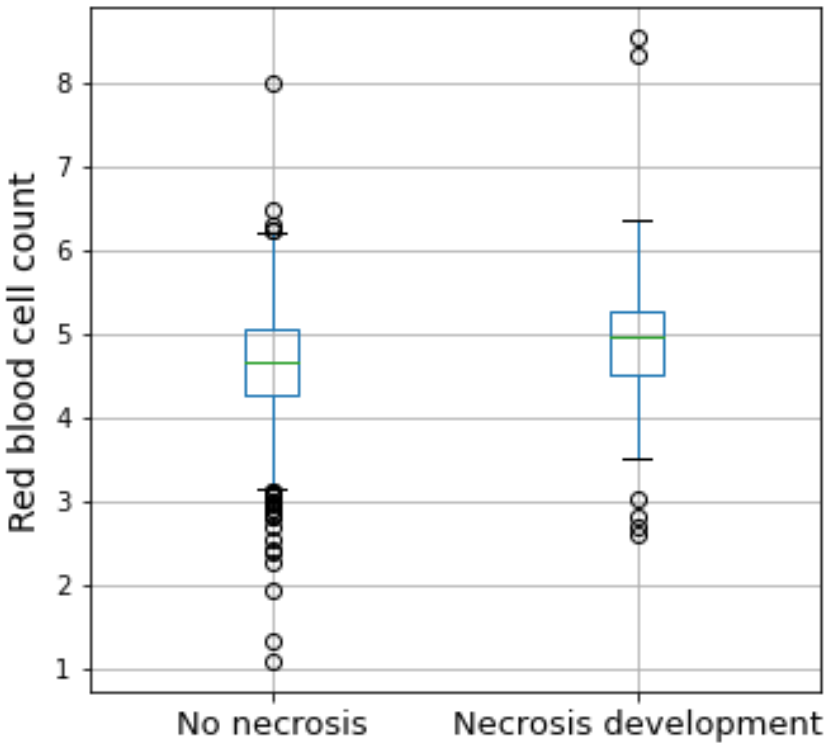
Supplementary Figure 21: The comparison in terms of total white blood cell count showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



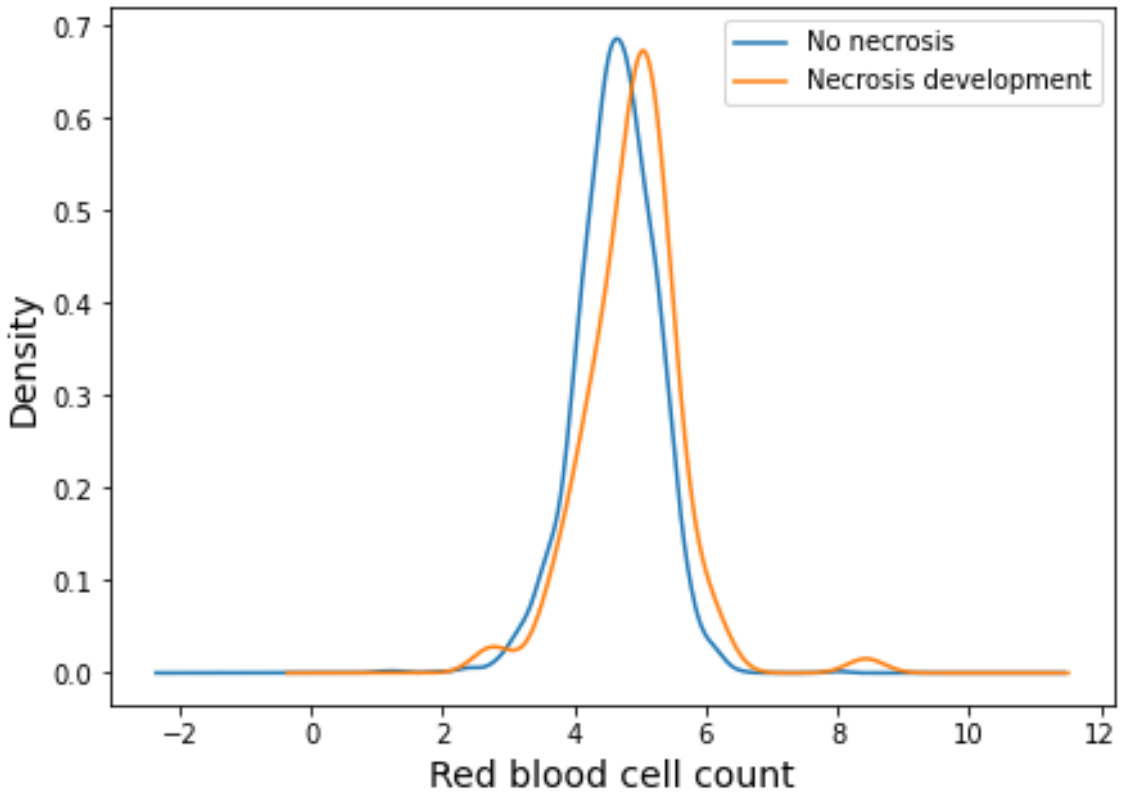
n=2095 **n=226**



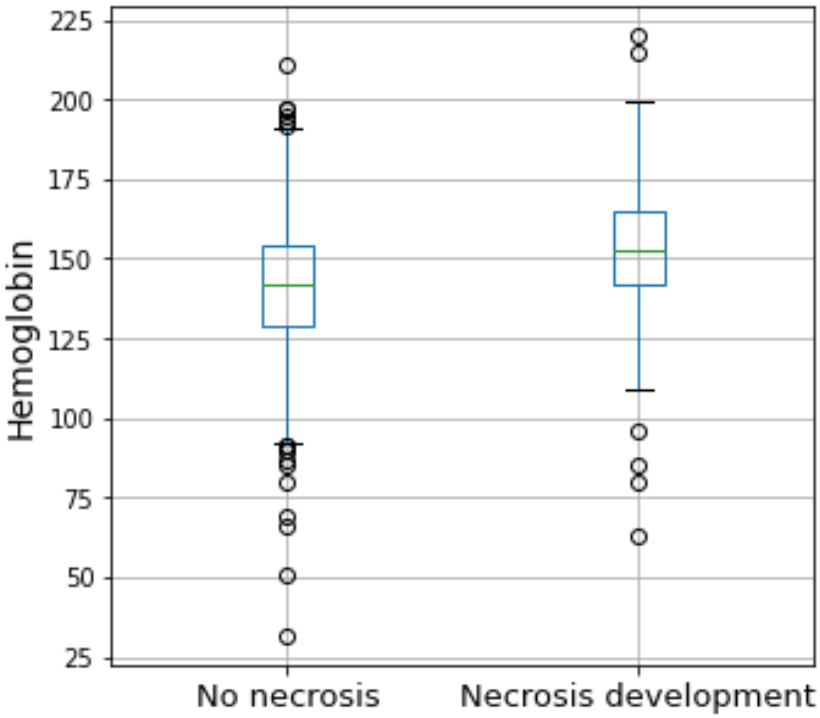
Supplementary Figure 22: The comparison in terms of red blood cell count showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



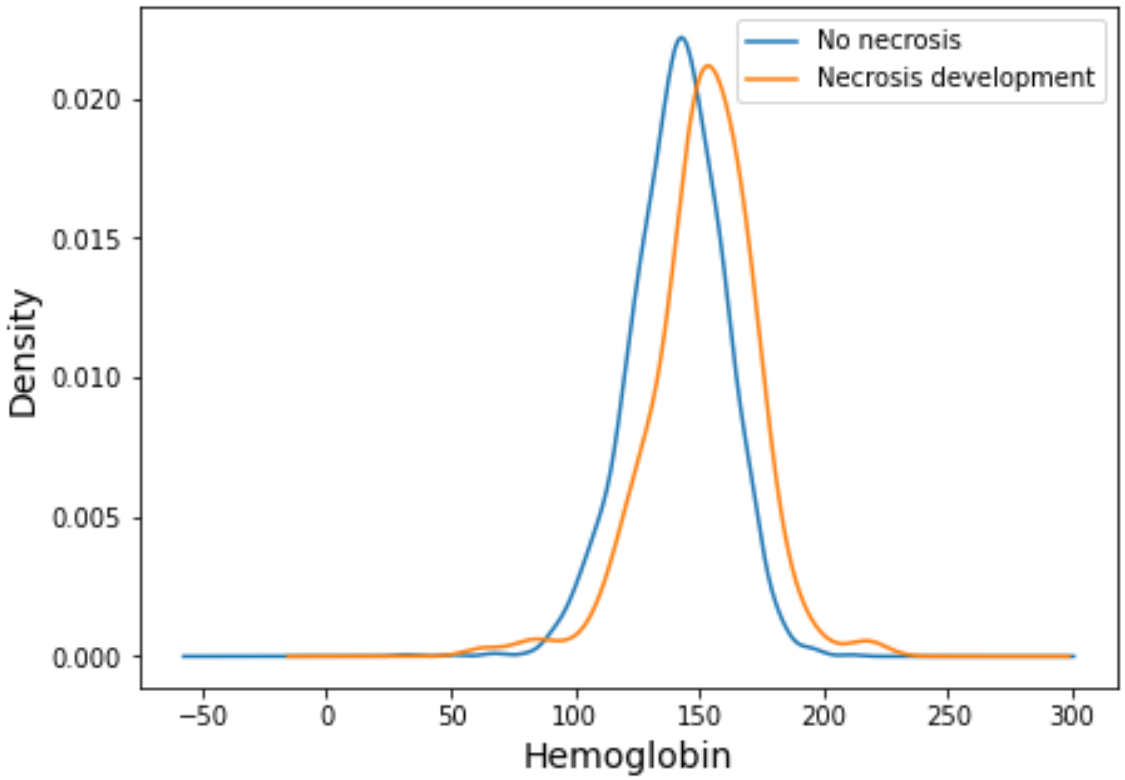
n=1716 **n=185**



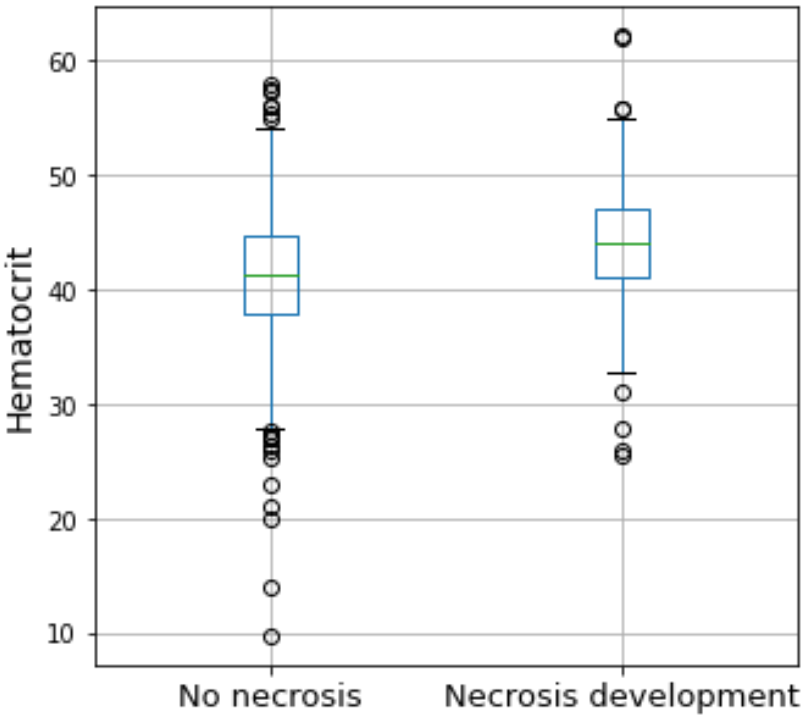
Supplementary Figure 23: The comparison in terms of hemoglobin showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



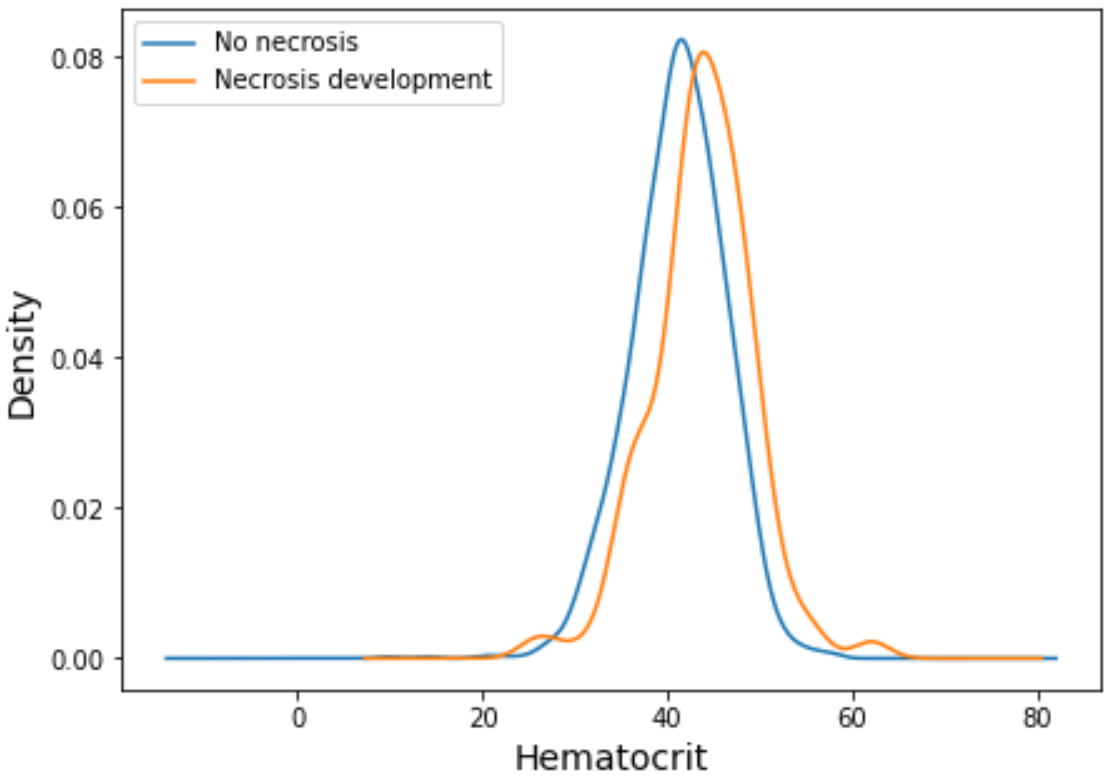
n=1697 **n=187**



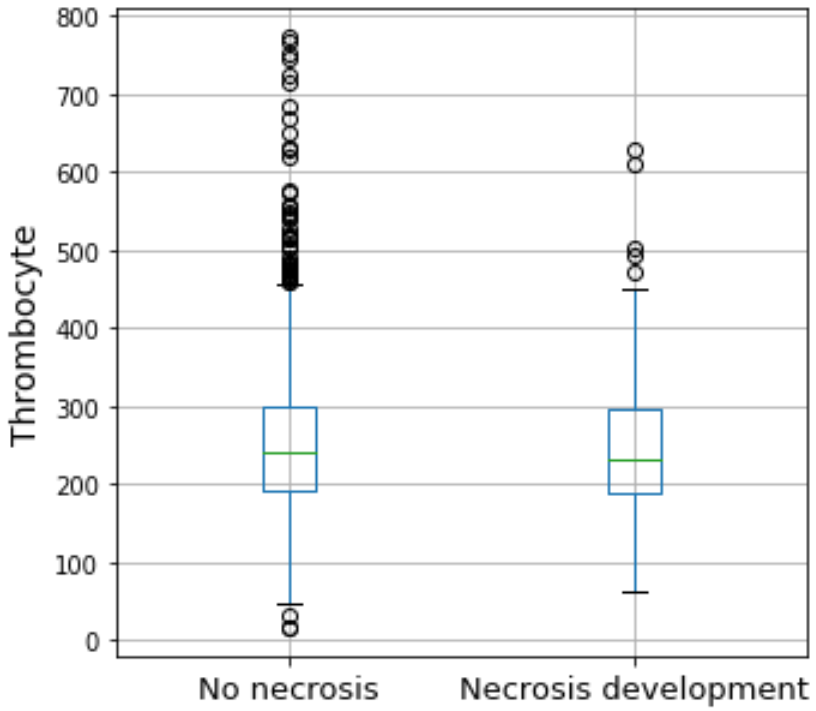
Supplementary Figure 24: The comparison in terms of hematocrit showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



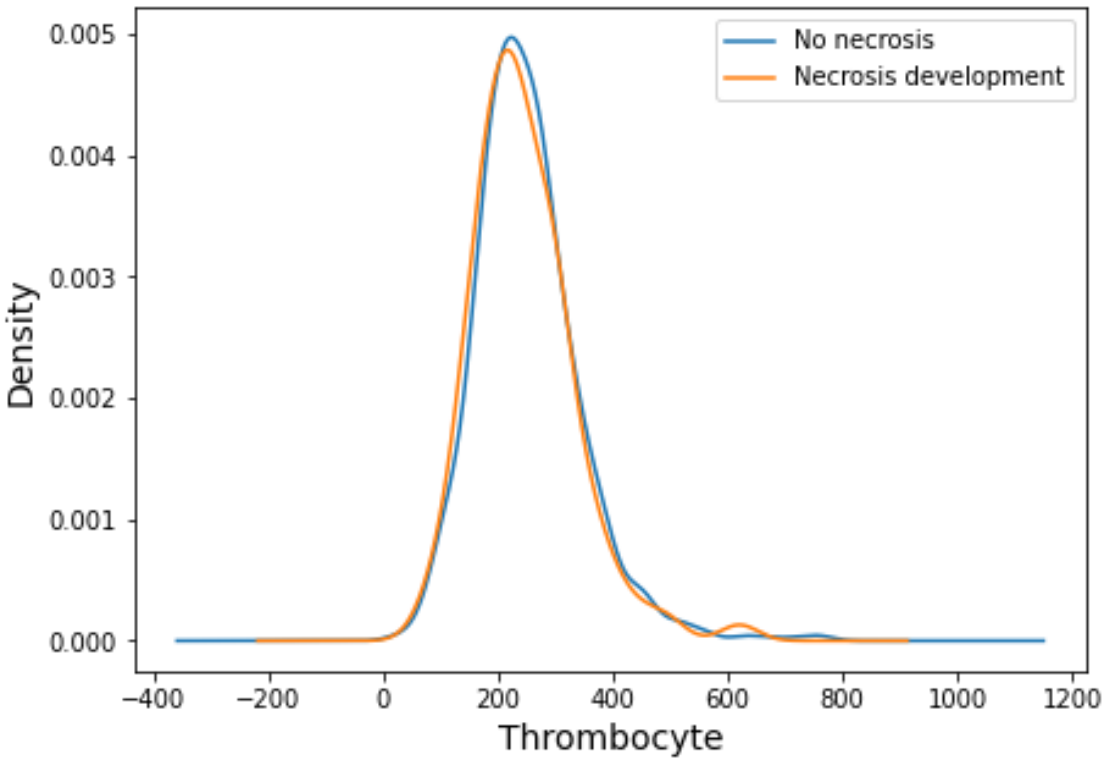
n=1721 **n=187**



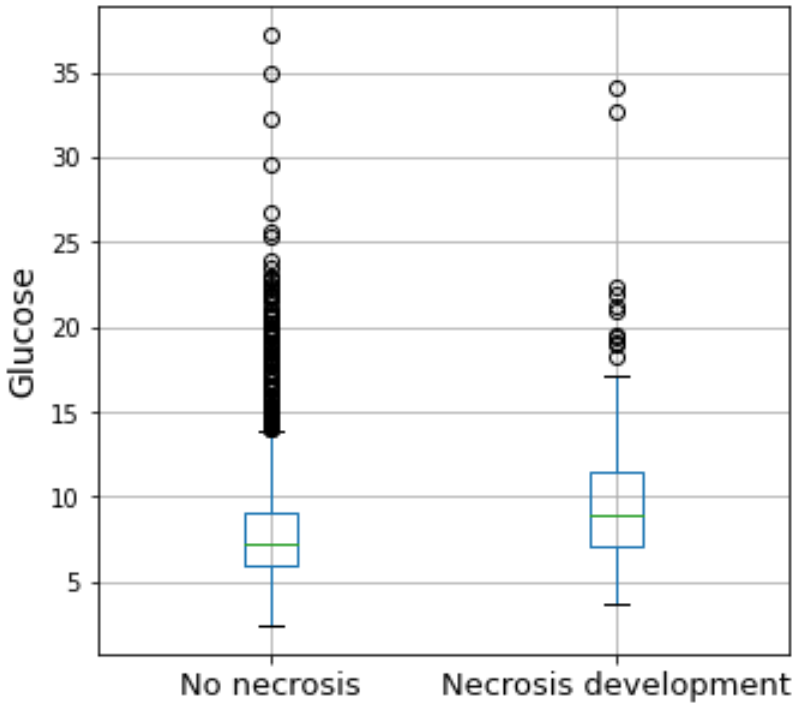
Supplementary Figure 25: The comparison in terms of thrombocyte count did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.524).



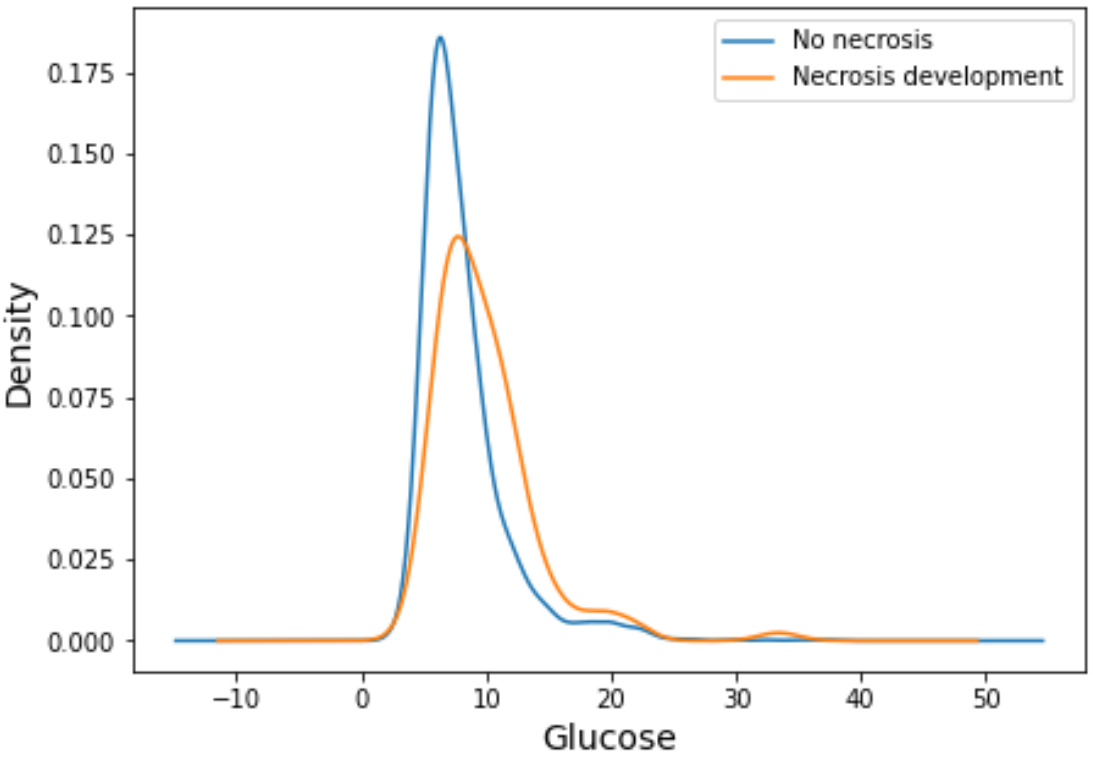
n=1715 **n=187**



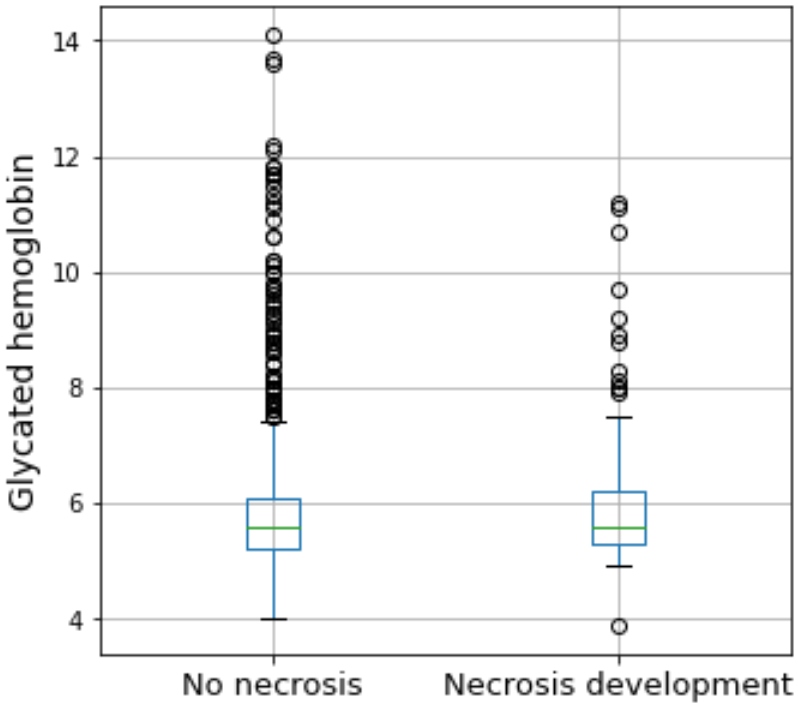
Supplementary Figure 26: The comparison in terms of glucose showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



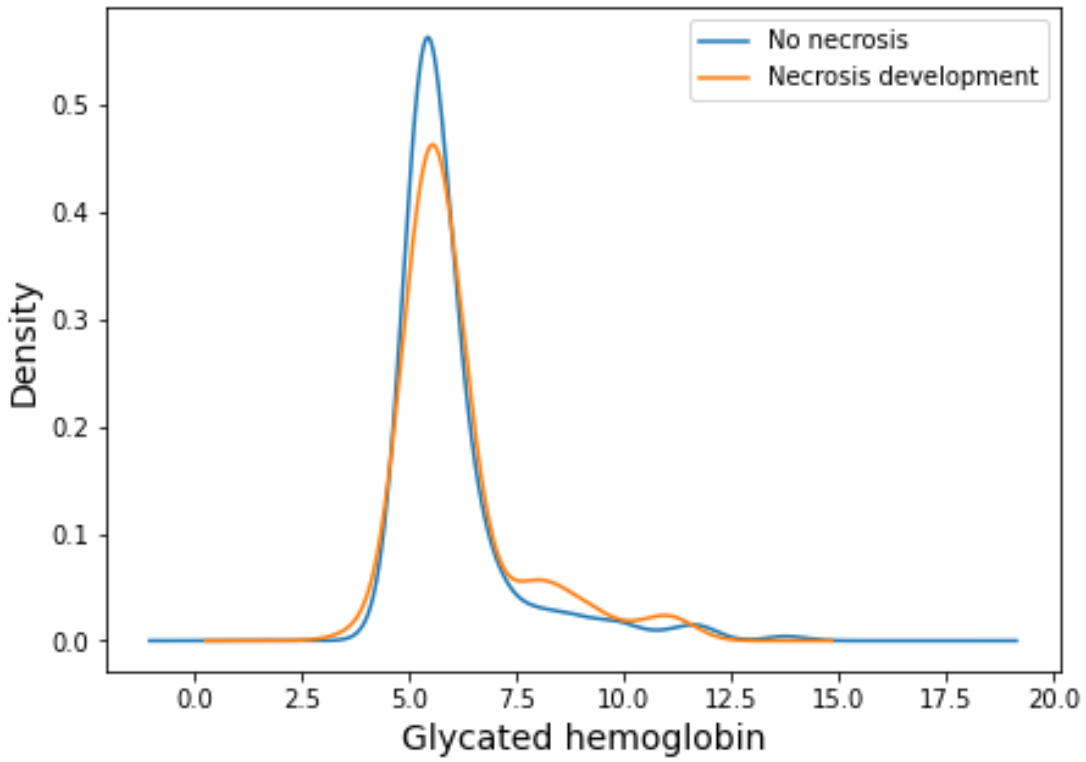
n=1954 **n=201**



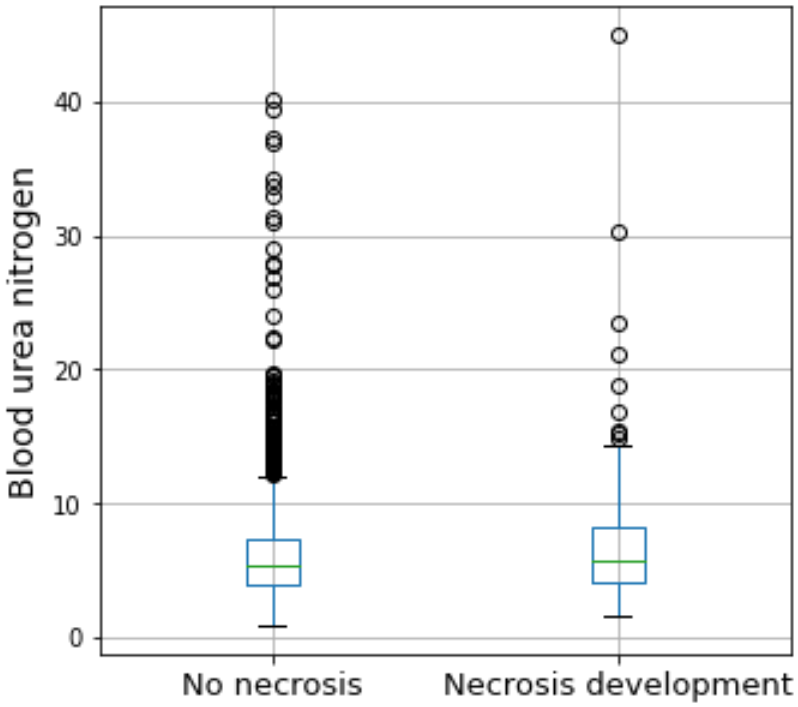
Supplementary Figure 27: The comparison in terms of glycated hemoglobin did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.567).



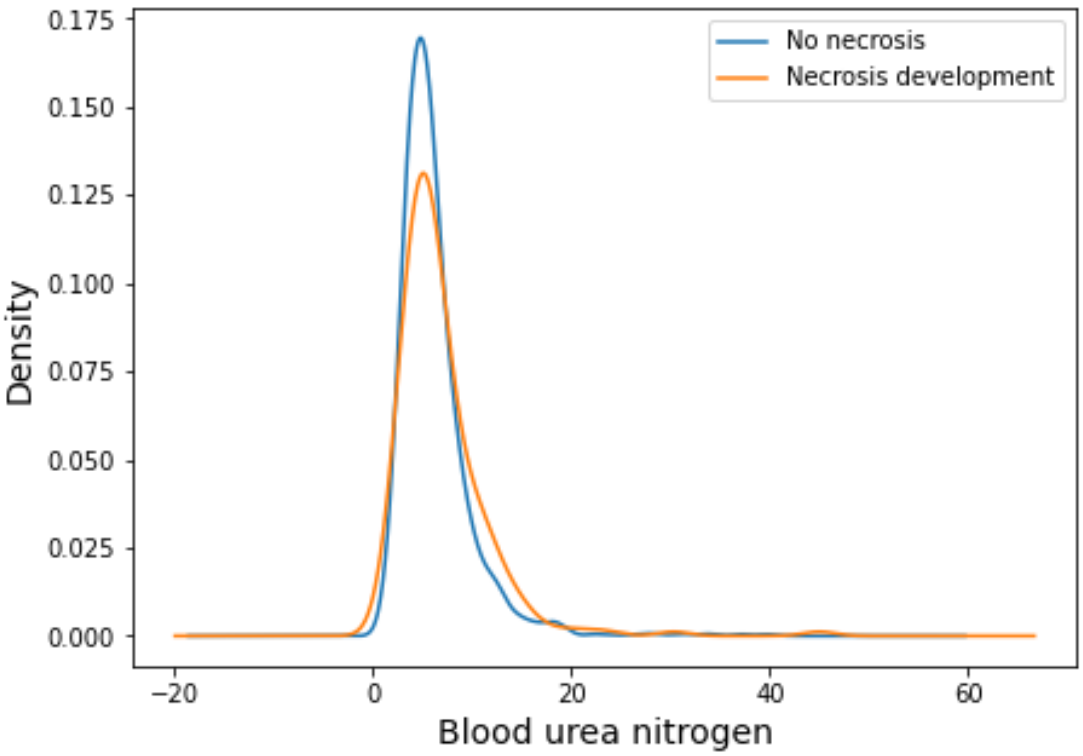
n=645 **n=84**



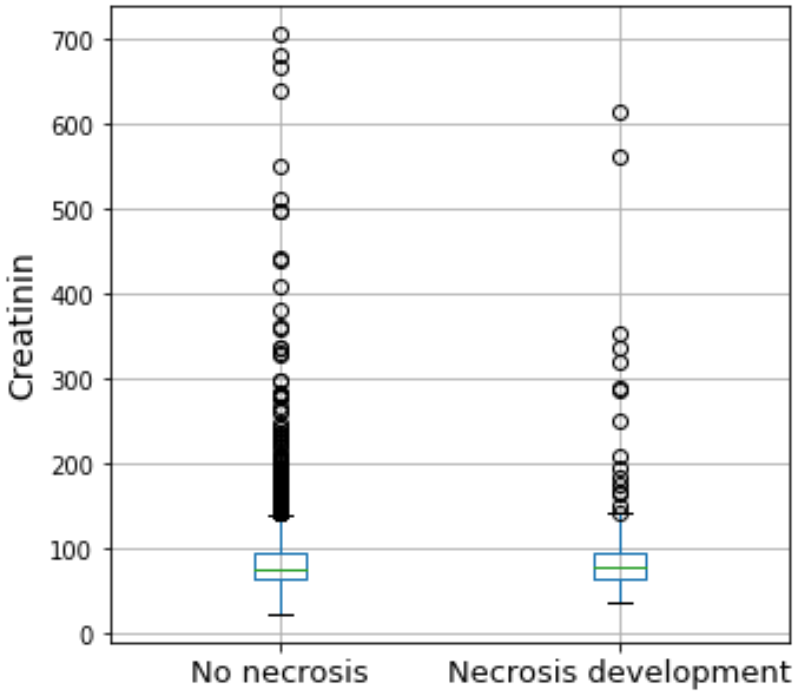
Supplementary Figure 28: The comparison in terms of blood urea nitrogen did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.168).



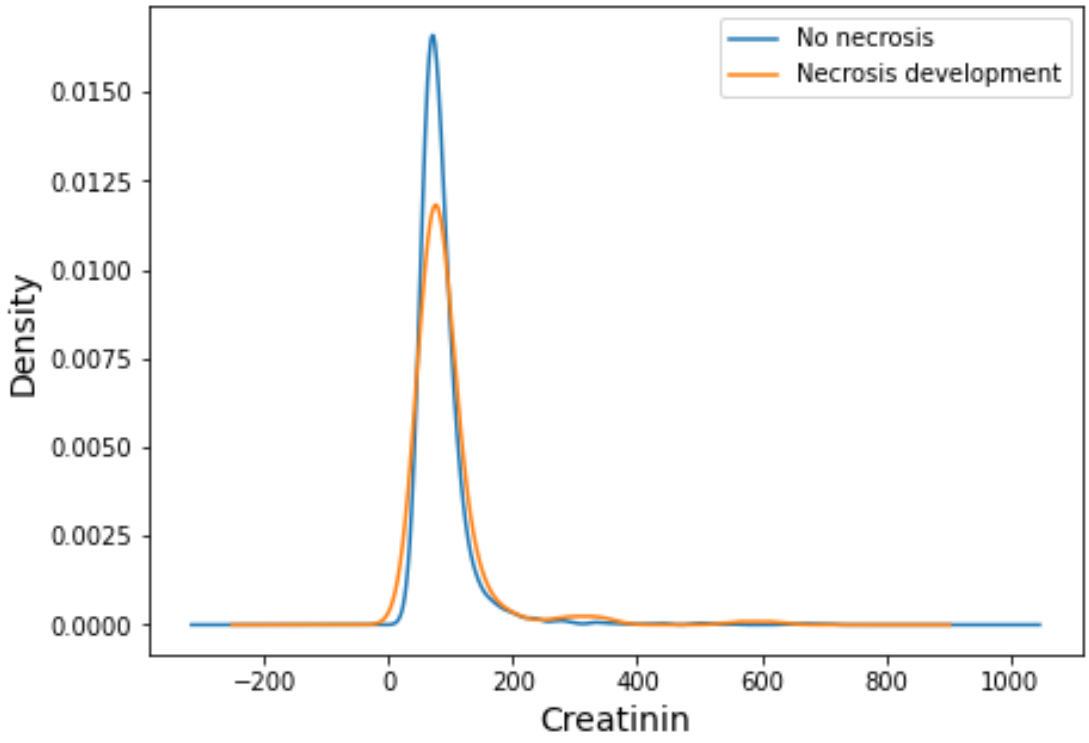
n=1972 **n=209**



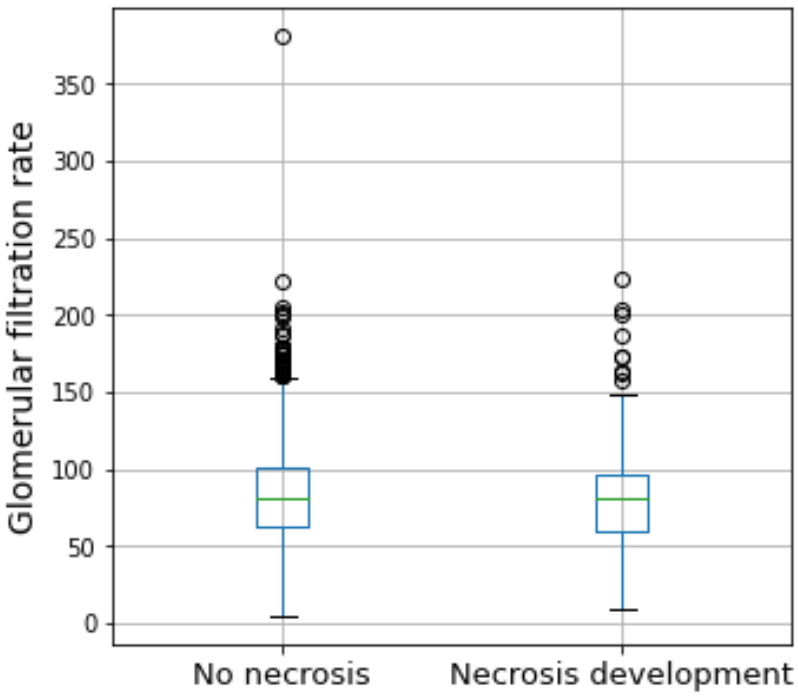
Supplementary Figure 29: The comparison in terms of creatinin did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.292).



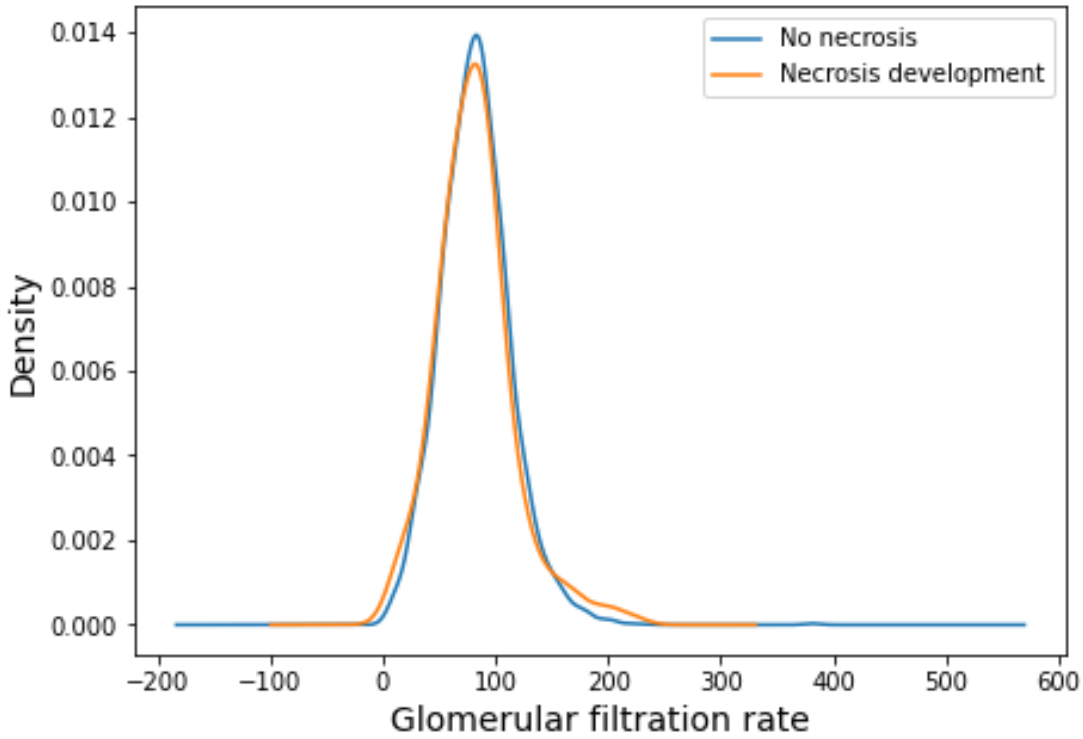
n=2019 **n=215**



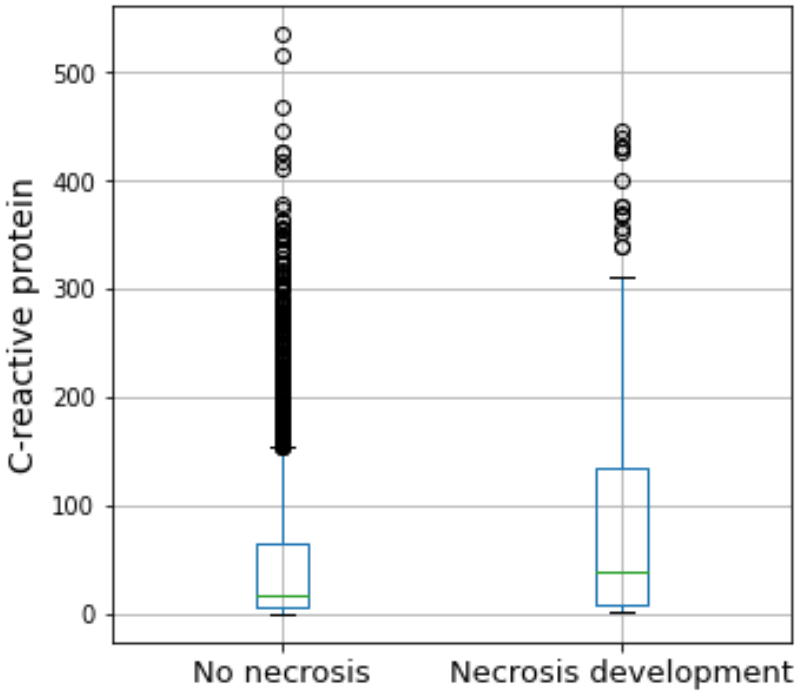
Supplementary Figure 30: The comparison in terms of glomerular filtration rate did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.598).



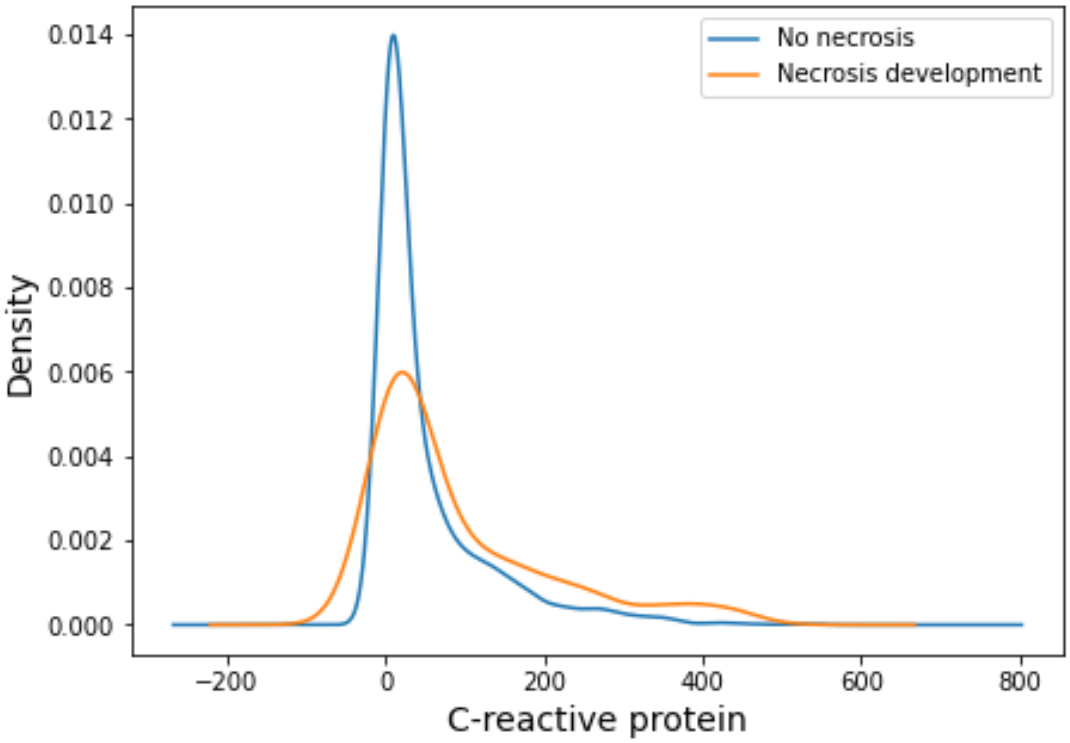
n=1982 **n=208**



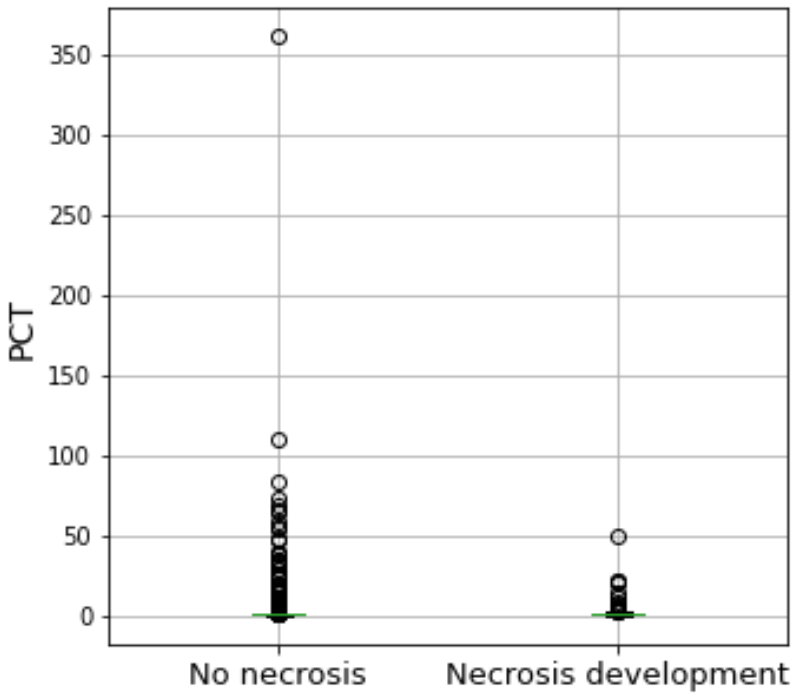
Supplementary Figure 31: The comparison in terms of C-reactive protein showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



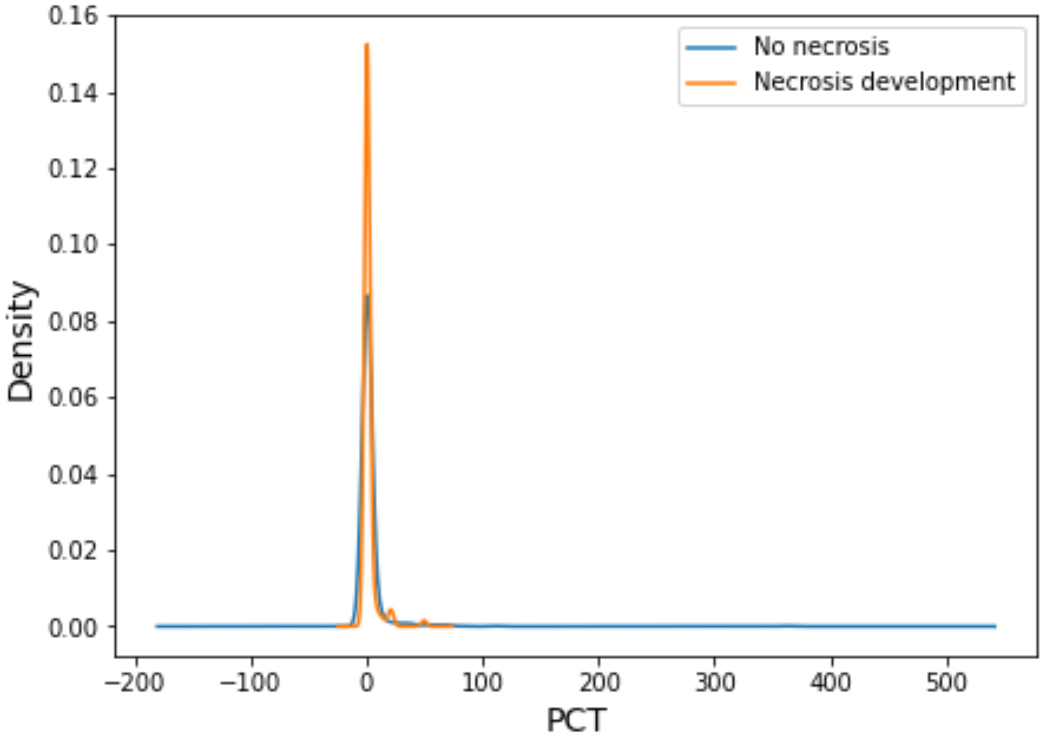
n=2014 **n=209**



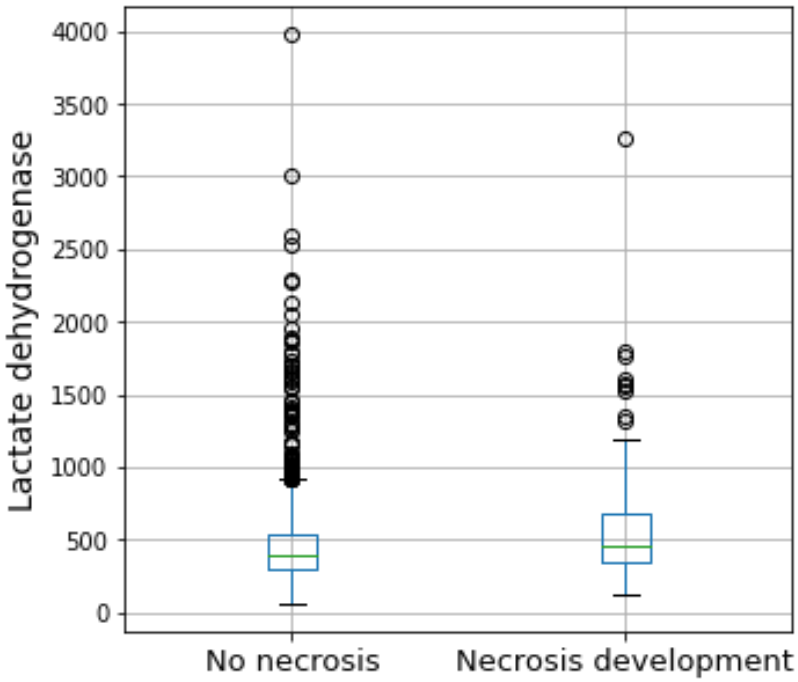
Supplementary Figure 32: The comparison in terms of procalcitonin showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.047).



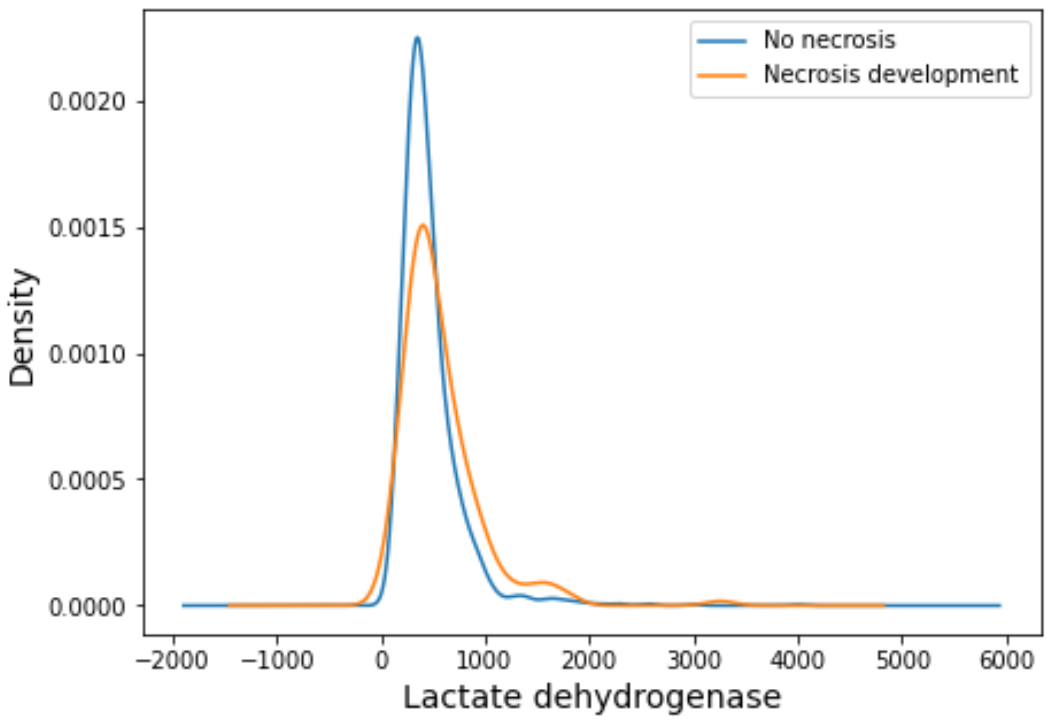
n=776 **n=113**



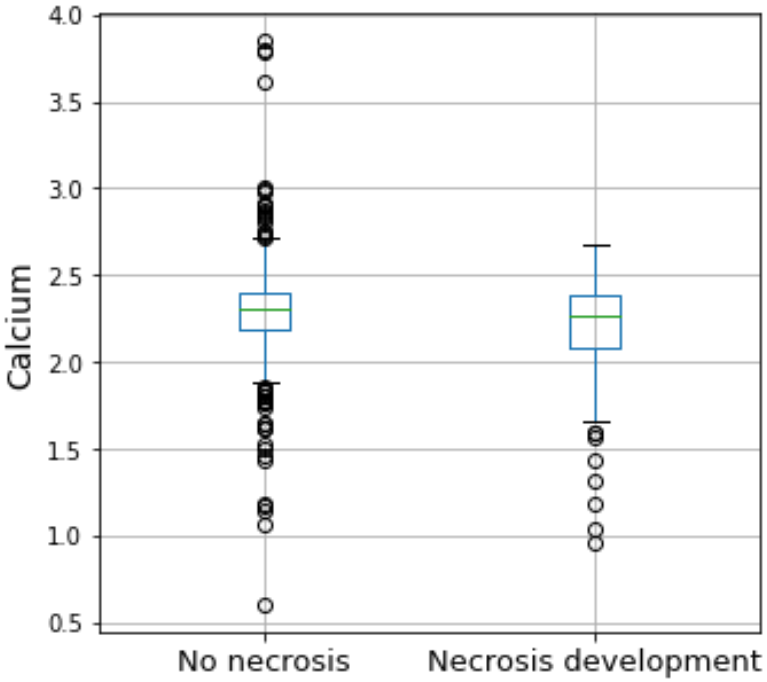
Supplementary Figure 33: The comparison in terms of lactate dehydrogenase showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.002).



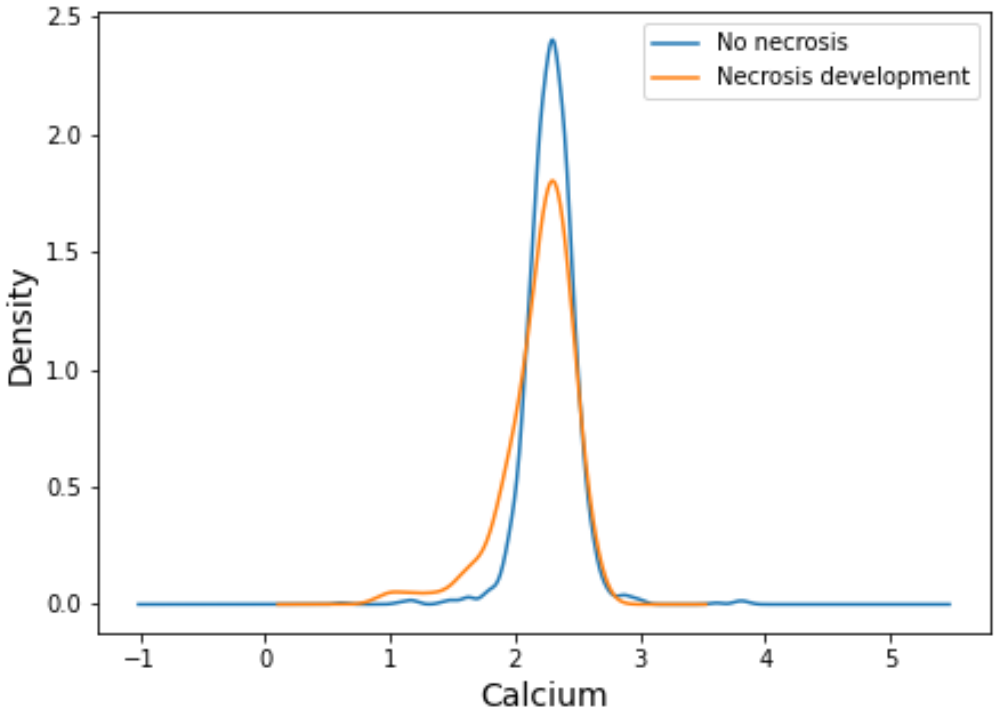
n=1490 **n=160**



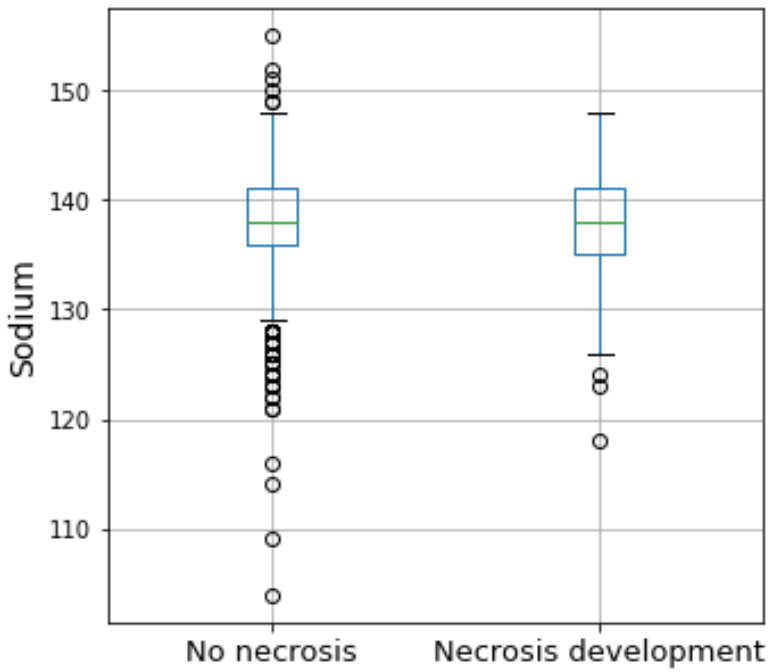
Supplementary Figure 34: The comparison in terms of calcium showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



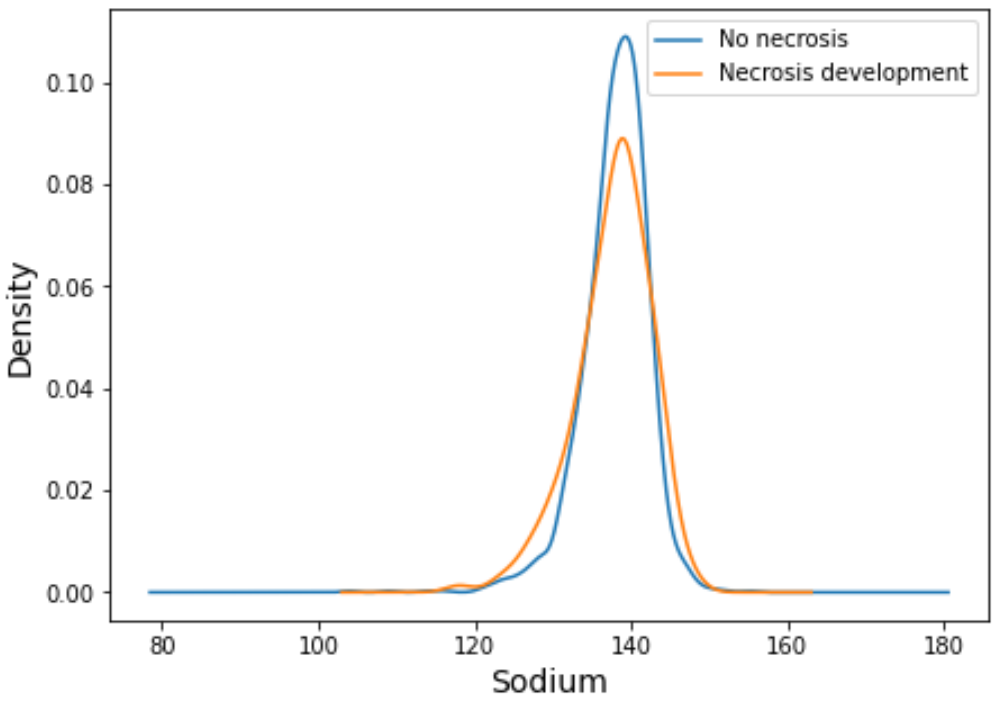
n=1392 **n=160**



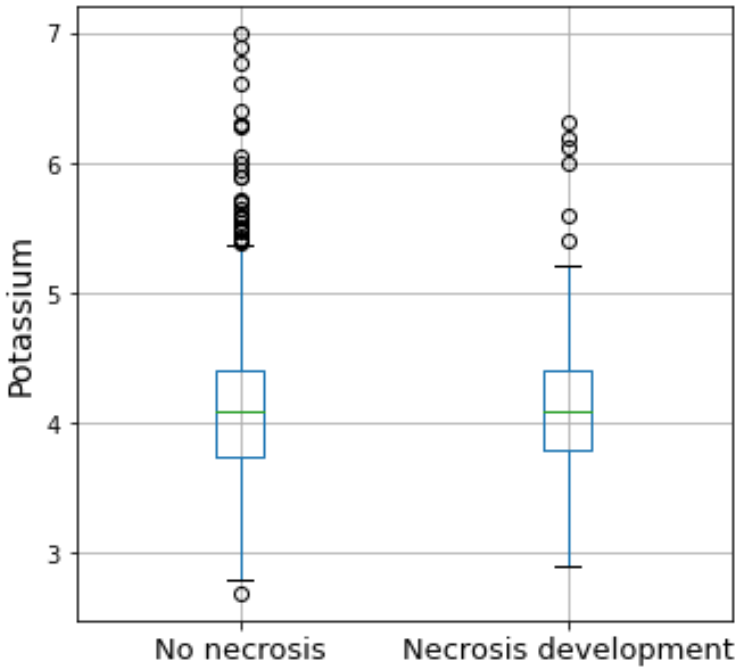
Supplementary Figure 35: The comparison in terms of sodium did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.567).



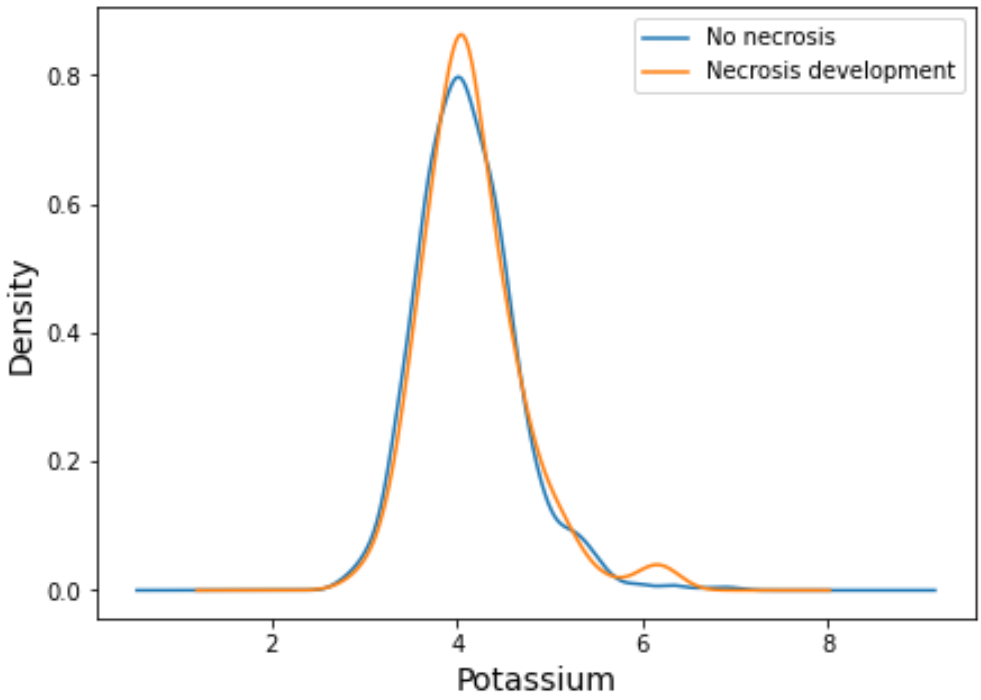
n=1643 **n=174**



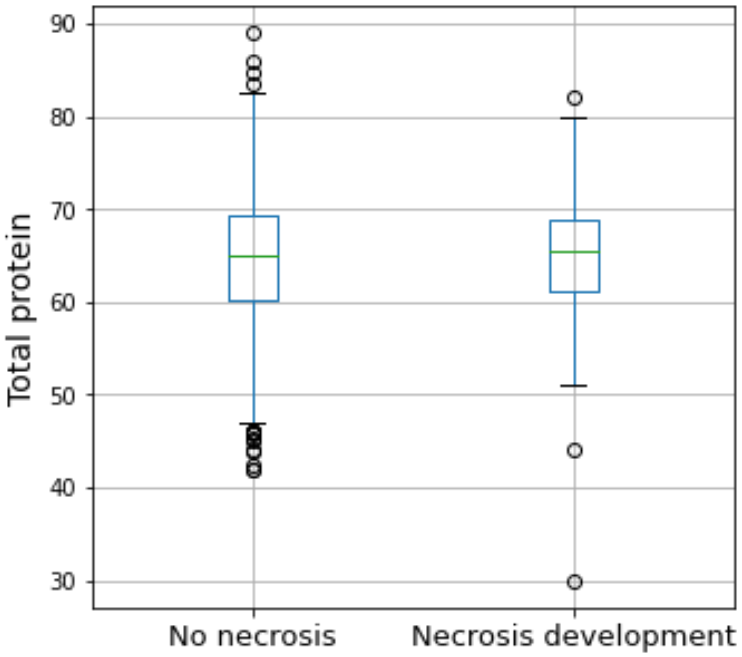
Supplementary Figure 36: The comparison in terms of potassium did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.576).



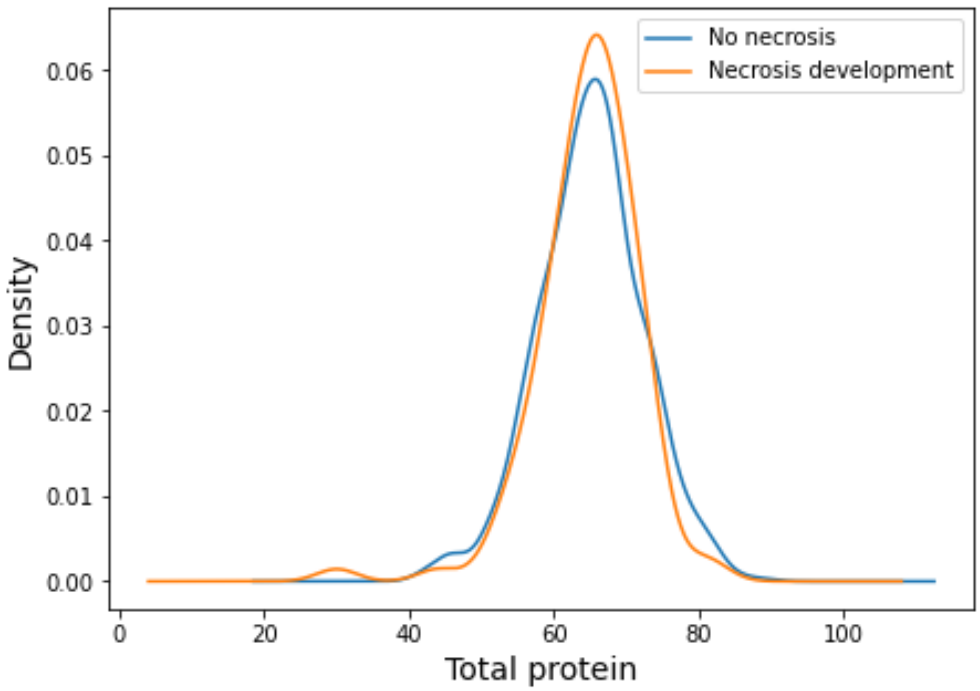
n=1649 **n=176**



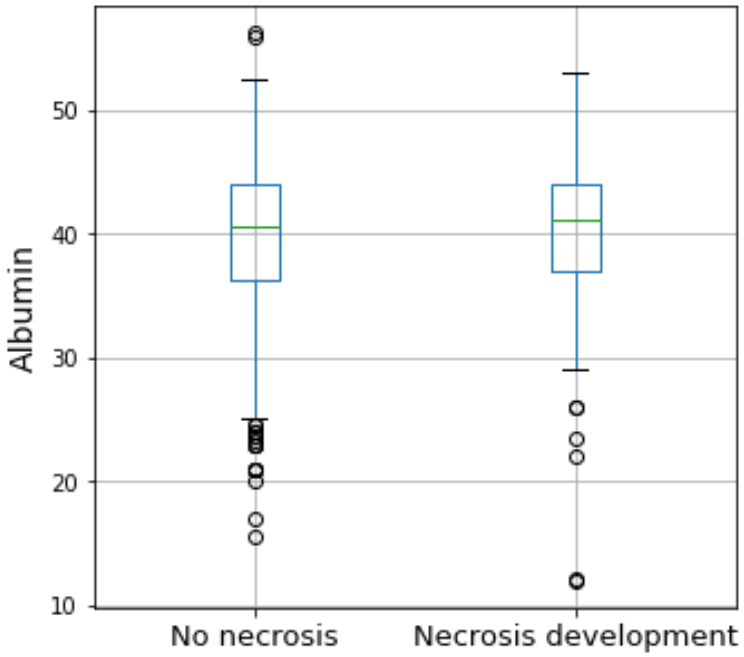
Supplementary Figure 37: The comparison in terms of total protein did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.598).



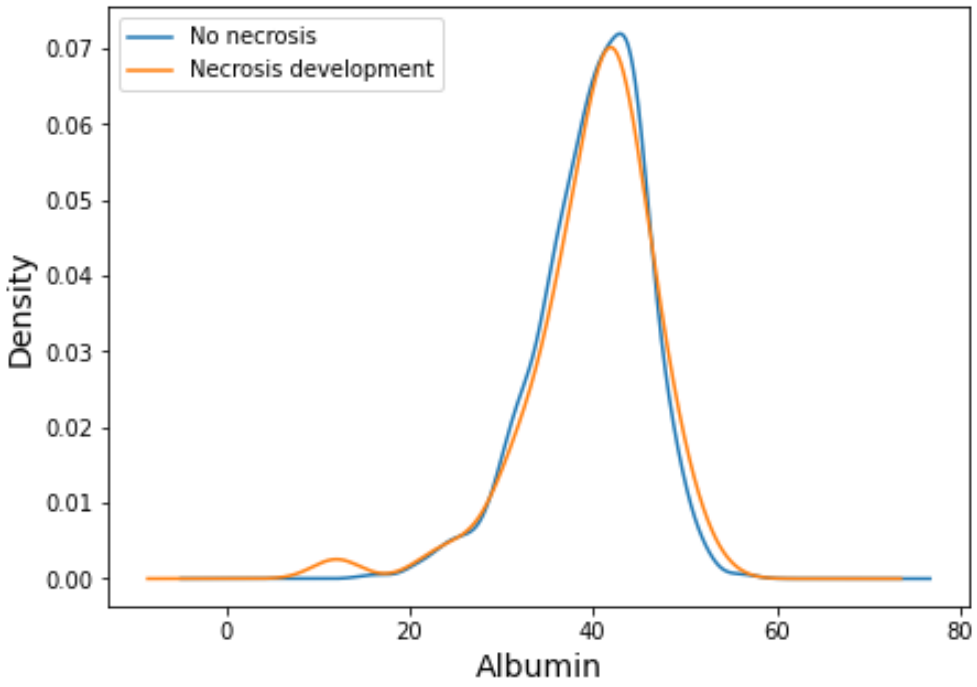
n=800 **n=100**



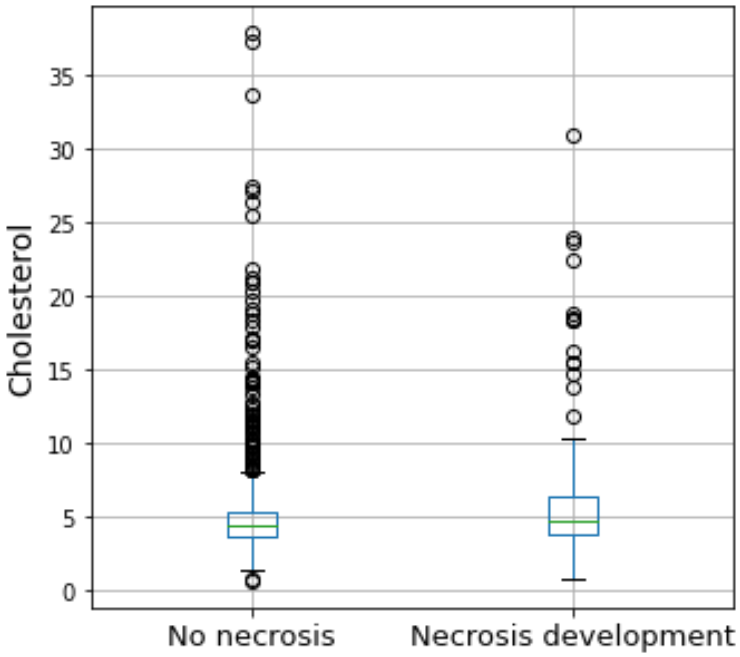
Supplementary Figure 38: The comparison in terms of albumin did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.822).



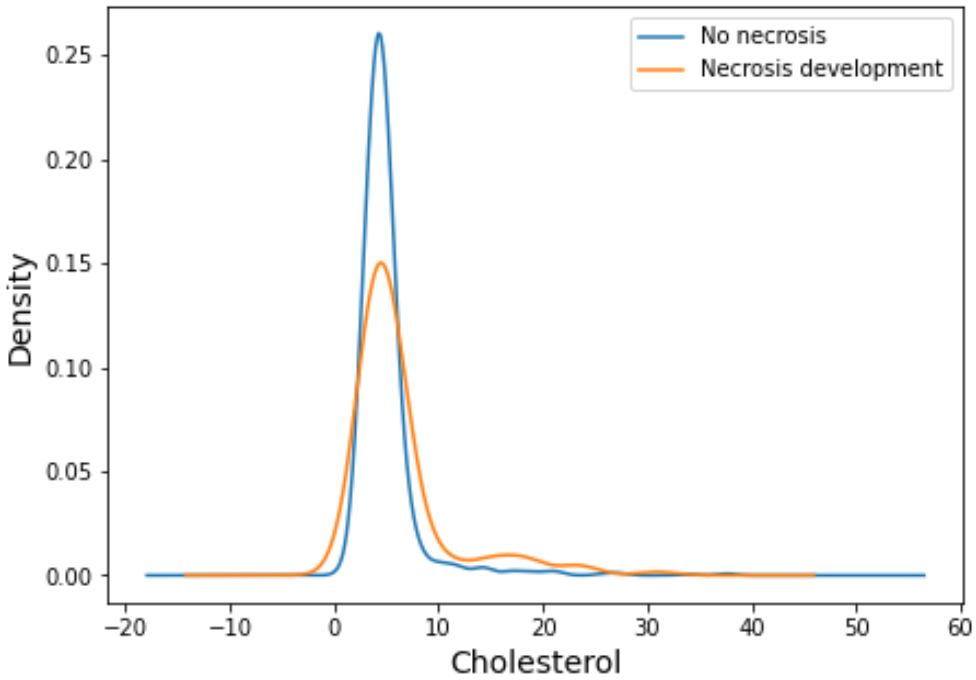
n=940 **n=119**



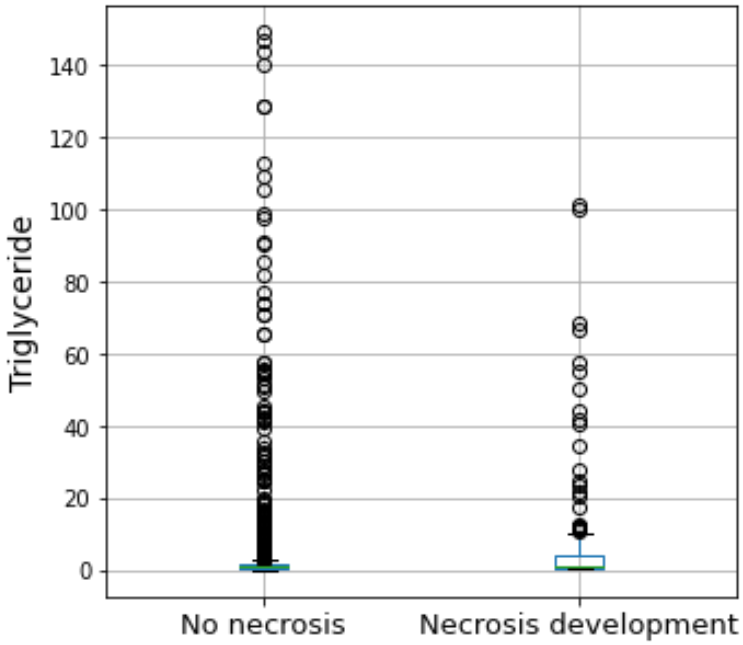
Supplementary Figure 39: The comparison in terms of cholesterol showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.002).



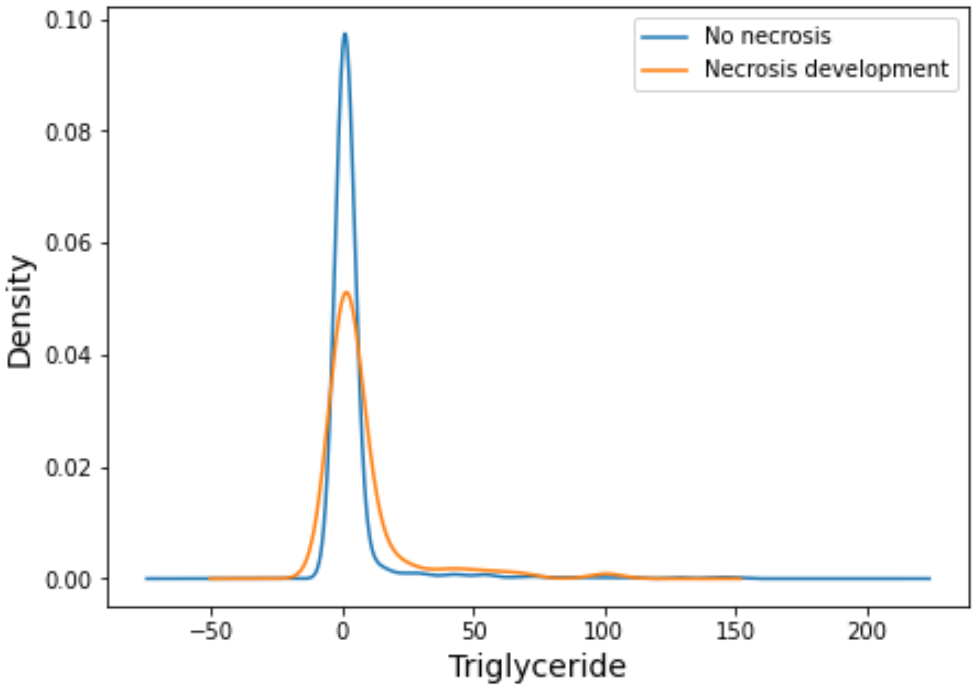
n=1124 **n=133**



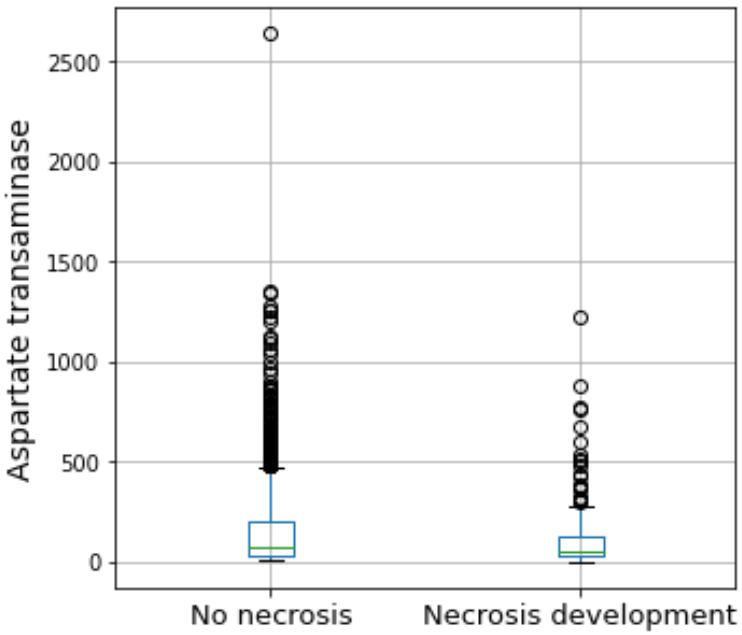
Supplementary Figure 40: The comparison in terms of triglyceride showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.003).



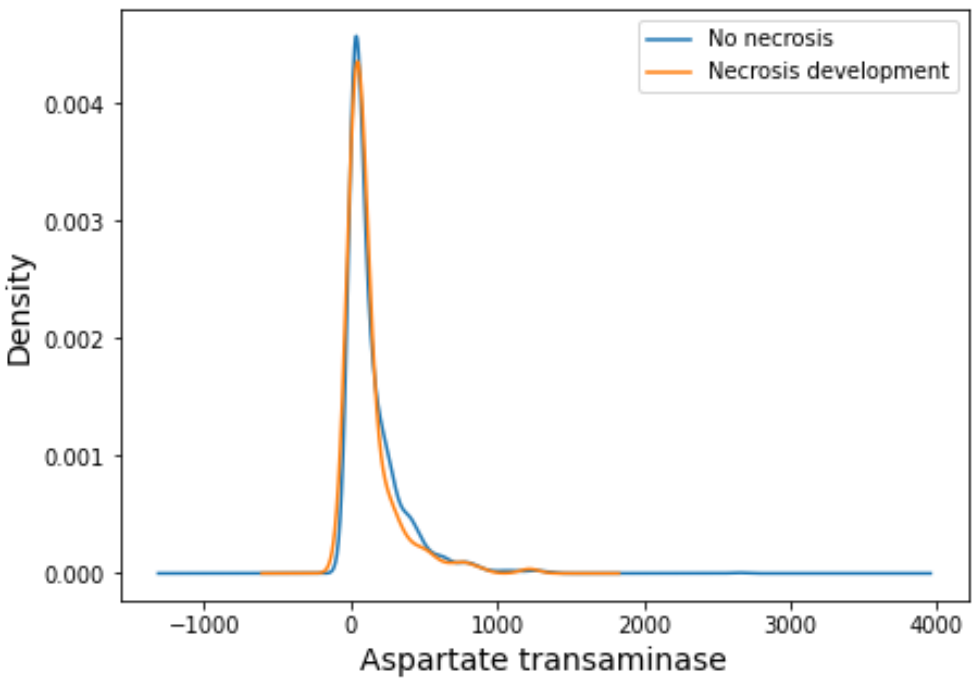
n=1233 **n=144**



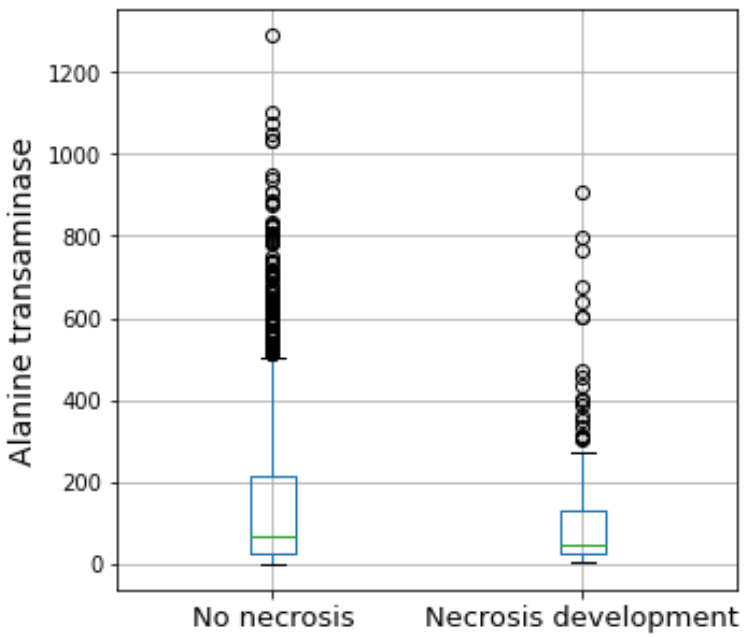
Supplementary Figure 41: The comparison in terms of aspartate transaminase showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.008).



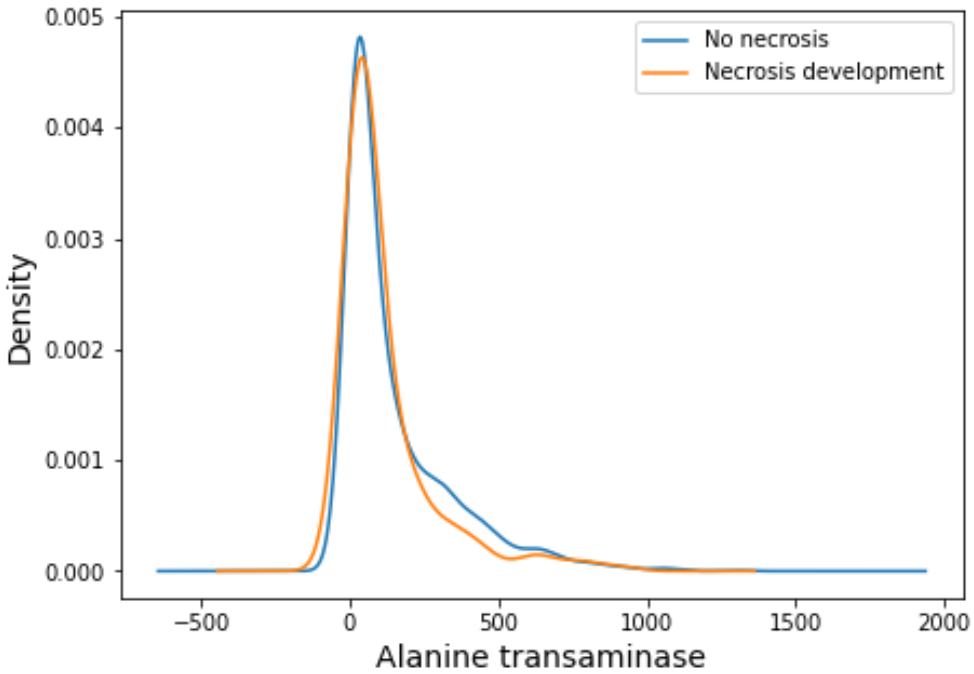
n=1562 **n=168**



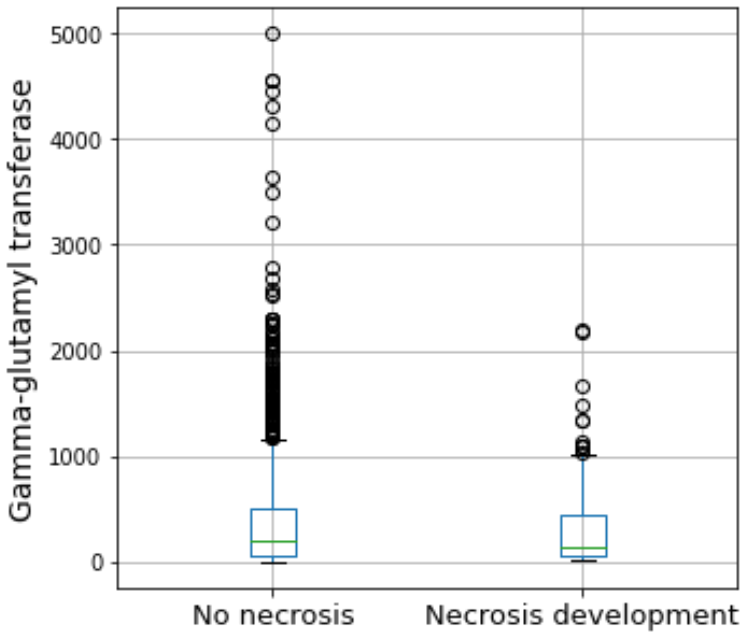
Supplementary Figure 42: The comparison in terms of alanine transaminase showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.018).



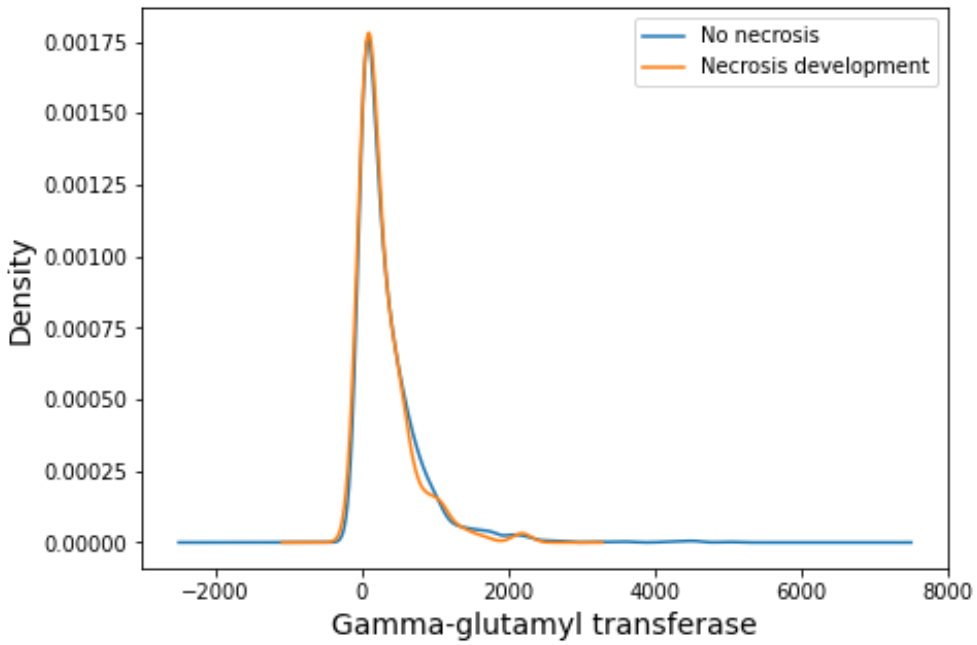
n=1525 **n=167**



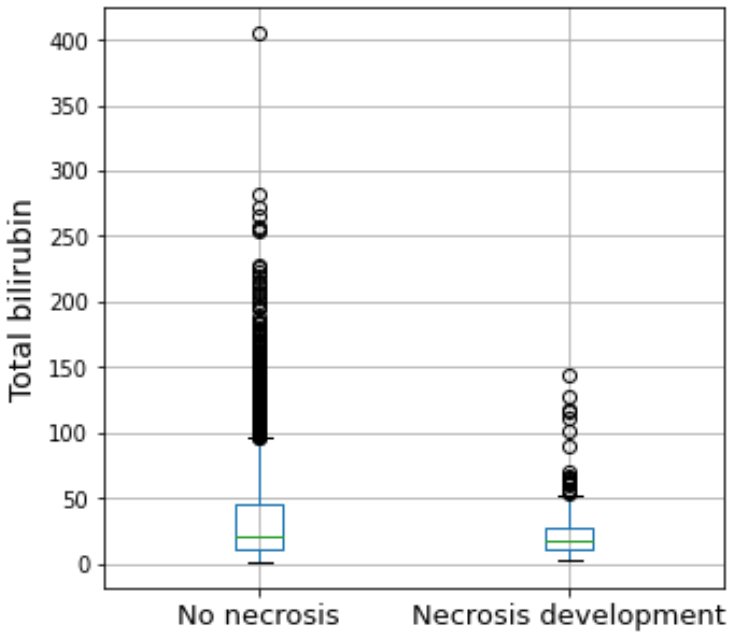
Supplementary Figure 42: The comparison in terms of gamma-glutamyl transferase did not show statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.060).



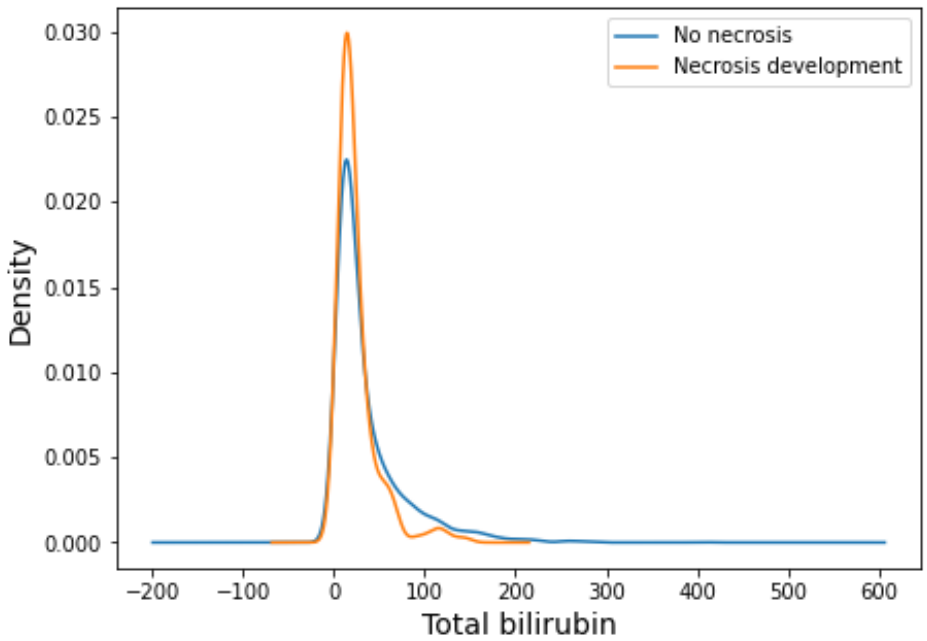
n=1914 **n=192**



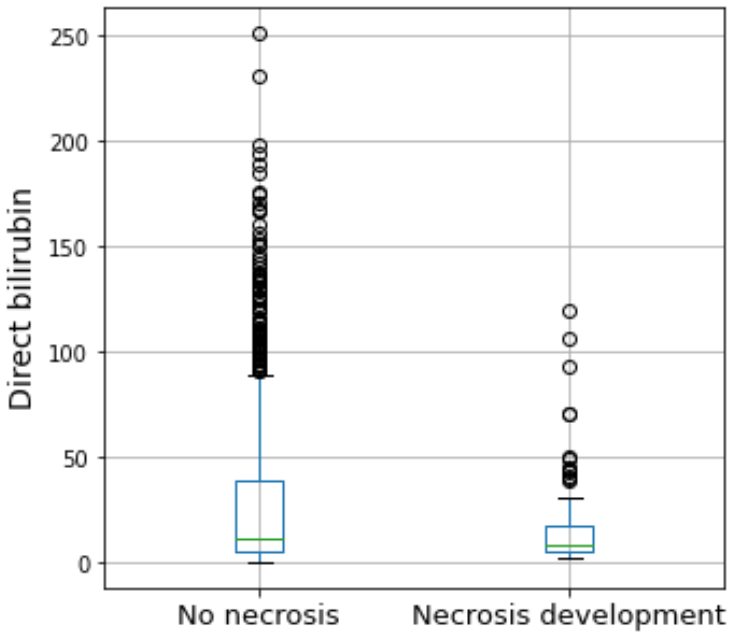
Supplementary Figure 43: The comparison in terms of total bilirubin showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



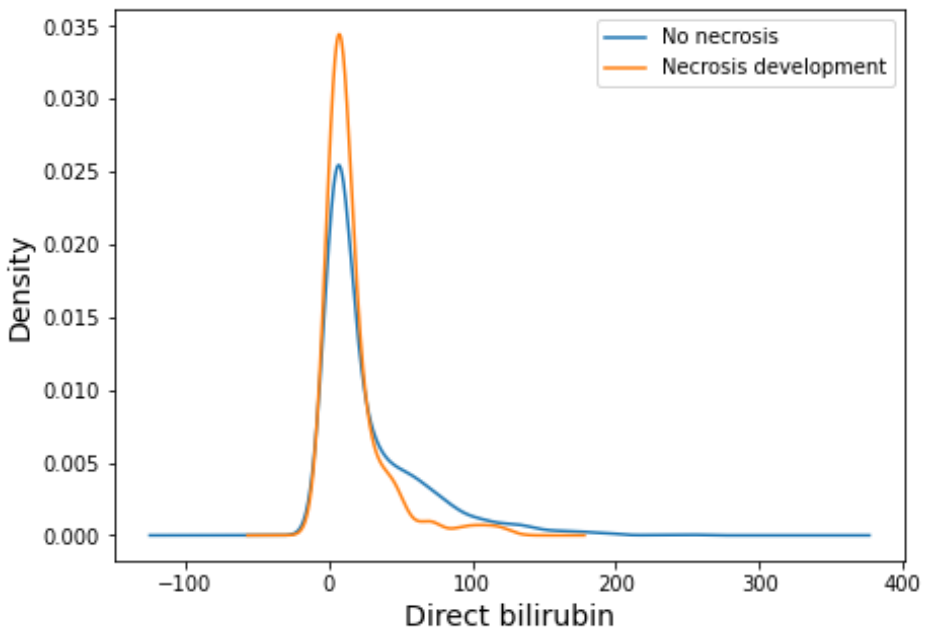
n=1959 **n=200**



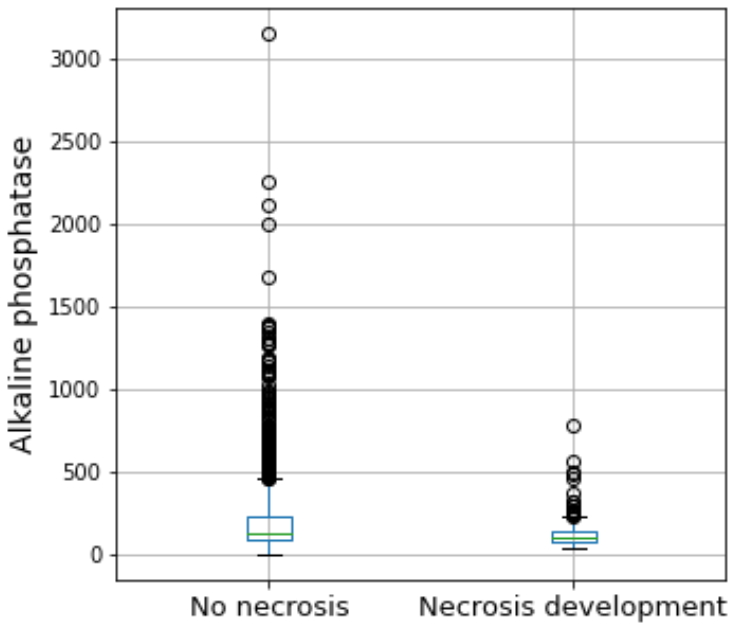
Supplementary Figure 44: The comparison in terms of direct bilirubin showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p=0.004).



n=1098 **n=107**



Supplementary Figure 45: The comparison in terms of alkaline phosphatase showed statistically significant difference between acute pancreatitis patients with and without necrosis development (Kolmogorov–Smirnov test, p<0.001).



n=1915 **n=194**