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

PhD thesis

Doctoral School of Clinical Medicine
Head: Lajos Kemény, MD, PhD, DSc
Programme leader: Péter Hegyi, MD, PhD, DSc

Szabolcs Kiss, MD
Centre for Translational Medicine, Department of Medicine,
University of Szeged, Szeged, Hungary

Supervisors:
Andrea Szentesi, PhD
Hussain Alizadeh MD, PhD

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Szeged, Hungary

1. 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: 3.402)**

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: 4.379)**

2. 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.).

Sum of scientific papers: 52 (D1:17, Q1:28, Q2:7, Q3:0, Q4:0)

Cumulative impact factor based on Clarivate Journal Citation Reports: 252.571

First and last author impact factor based on Clarivate Journal Citation Reports: 7.781

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

Hirsch index based on MTMT2 system: 8

3. 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; AUC - area under the receiver operator curve; BMI - body mass index; CECT - contrast-enhanced computer tomography; CI – confidence interval; 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; ICU - intensive care unit;

IL-6 - interleukin-6; IQR - interquartile range; 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; WBC - white blood cells; WMD - weighted mean difference

4. 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. 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, multicenter cohort study regarding acute necrotizing pancreatitis (ANP). This study is the first to combine prediction of necrosis development and artificial intelligence in AP.

5. INTRODUCTION

Biomarkers are biological observations that could serve as a surrogate for or predict clinical endpoints or intermediate outcomes that are more challenging to measure. Due to their limitations, biomarkers are often integrated into clinical scoring systems to enhance their supportive potential.

Clinical scoring systems are algorithms, which were created to standardize clinical practice and aid clinical decision-making. 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. Despite the many constraints, we use a lot of efficient clinical scoring systems in our daily practice. Furthermore, successful clinical scores are increasingly integrated into clinical trial designs at multiple levels, e.g., assessment for eligibility or comparing patients.

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. In the past two decades, there has been meaningful progress in the development of AI. 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.

6. RATIONALE, OBJECTIVES AND HYPOTHESES

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.

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.

7. 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. The study protocol was registered on PROSPERO (CRD42020176836).

Search strategy, selection, data extraction, and risk of bias assessment

The systematic literature search was conducted in five bibliographic databases 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"). 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. Four review authors independently extracted data into a standardized data collection form. Data extraction was validated by a fifth review author. 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. Any disagreement was resolved based on consensus.

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. Statistical heterogeneity was analyzed using the I^2 the χ^2 tests to obtain probability values: $p<0.10$ was defined as indicating significant heterogeneity. 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. Statistical analyses were performed with Stata 15 SE (Stata Corp).

METHODS OF THE ACUTE PANCREATITIS STUDY

Ethical approval, data source, and eligibility criteria

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.

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. All patients fulfilled the AP diagnostic criteria of the revised Atlanta classification. In all cases deemed eligible a contrast-enhanced computer tomography (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 confirmed by CECT during hospitalization; and (2) absence of necrosis development. ANP was defined as a lack of parenchymal enhancement or findings of peripancreatic necrosis, such as an acute necrotic collection on CECT. The assessed predictors of ANP were

gender, age, body mass index (BMI), and laboratory parameters measured in the first 24 hours after clinical admission.

Predictive modelling

The process of predictive modelling with thirty-one variables is depicted in Figure 1. Missing data were handled with a k-nearest-neighbor-based data imputer algorithm. The SMOTE algorithm 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. 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. 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. Finally, the model was deployed as an online application using the Streamlit Python-based framework. 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).

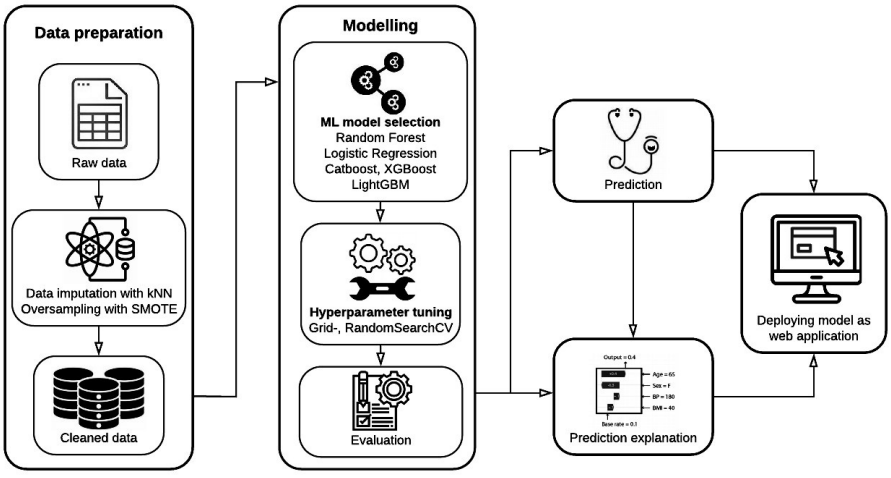

Figure 1. Flowchart representing the process of developing the model

8. RESULTS

RESULTS OF THE COVID-19 STUDY

Systematic search and selection

Out of the 103,461 records identified, our systematic search yielded 93 eligible studies from 16 countries.

Weighted mean differences

Pooled analyses showed that among all COVID-19 patients mortality was associated with increased baseline WBC, absolute neutrophil count (ANC), CRP, LDH, procalcitonin (PCT), fibrinogen, D-dimer, ferritin, CK, and interleukin-6 (IL-6) ($p<0.05$ in all cases). In the same population, decreased baseline ALC, CD3+, CD4+ and CD8+ lymphocyte count, absolute eosinophil count (AEC), absolute monocyte count (AMC), and platelet count was associated with increased mortality ($p<0.05$ in all cases).

Pooled analyses found that among all critically ill COVID-19 patients, mortality was associated with increased baseline LDH, increased CRP, and decreased platelet levels ($p<0.05$ in all cases). 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 who did not: WBC, ANC, CRP, LDH, PCT, CK, fibrinogen, D-dimer, ferritin, and IL-6 ($p<0.05$ in all cases).

Intensive care requirement was also associated with decreased baseline ALC, CD3+ lymphocyte count, CD4+ and CD8+ lymphocyte count, and haemoglobin ($p<0.05$ in all cases).

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. 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%). 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 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%).

Risk of bias assessment

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 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. In 9.76% of the cases, ANP was confirmed. ANP was associated with a significantly higher risk for mortality, severe disease course, and all the investigated local and systemic complications (Figure 2). ANP was also associated with longer hospitalization (9.13±6.21 days vs 20.78±19.70 days, p<0.001).

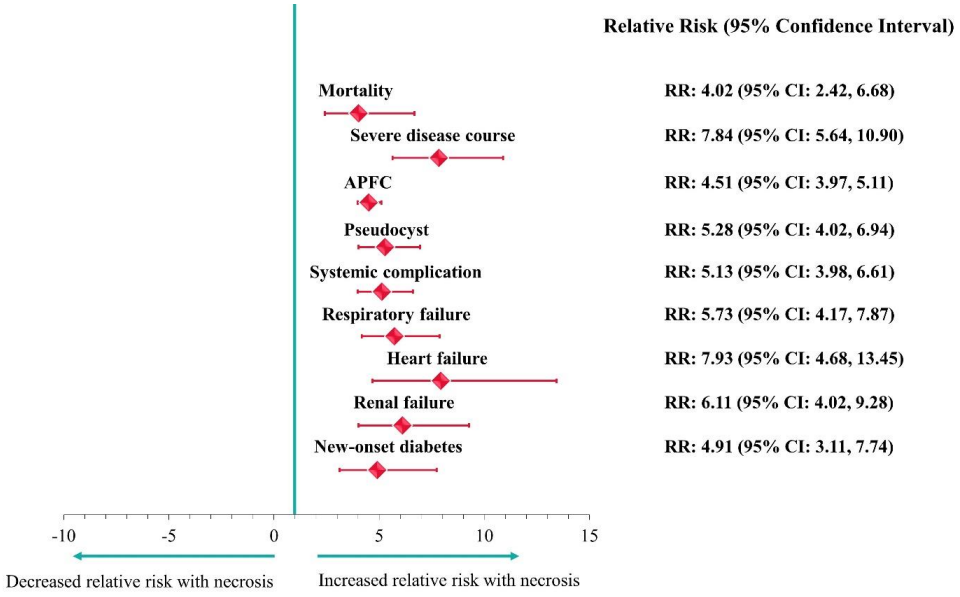

Figure 2. Association between necrosis development and other complications in acute pancreatitis

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. The relationship between the size of the data set and the model performance was assessed. The steady increase of AUC values parallel with the amount of data 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 3).

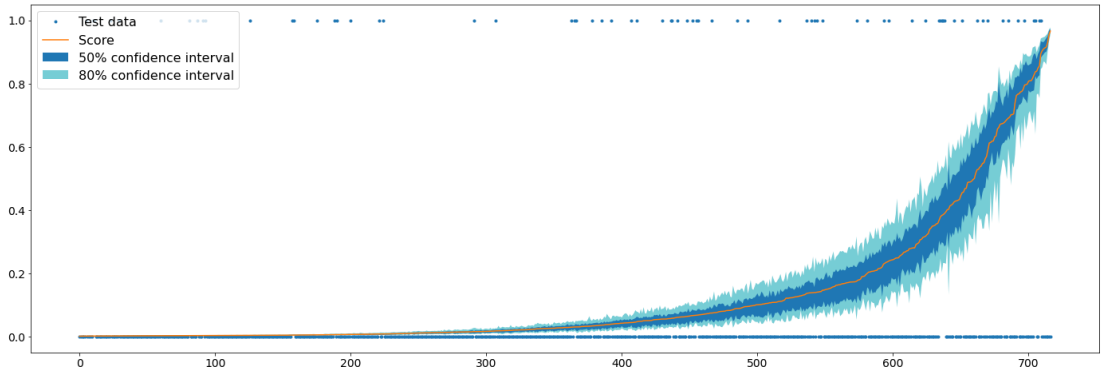

Figure 3. The predicted necrosis probabilities with the corresponding 50% (between the 25th and 50th percentiles) and 80% confidence (between the 10th and 90th percentiles). The assessment of the impact on the model output showed that glucose, CRP, ALP, gender, and WBC have the five highest SHAP values. The most influential predictors are shown in Figure 4 Panel A.

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. 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 4 Panel B).

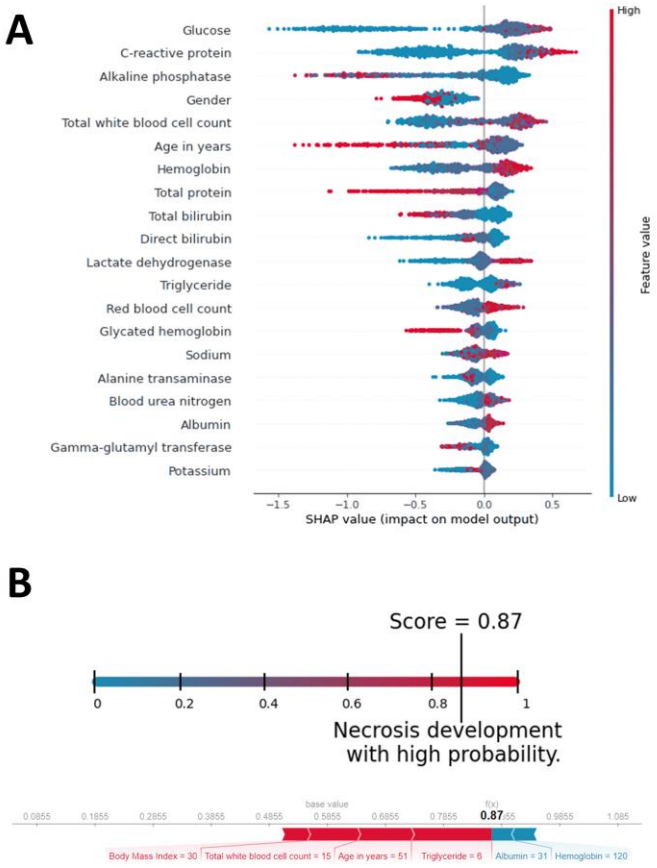

Figure 4. Panel A: the features with the highest impact on model output based on the SHAP values. The higher the predictor is on the list, the bigger the impact on model output. Each patient is represented by a dot. The x-axis represents the extent of the impact on prediction. The color of the dot shows 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.

9. DISCUSSION

ELABORATION AND EXPLANATION

COVID-19 study

Our study provided further evidence for the 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. Lymphocyte depletion might be explained by direct viral damage or by the imbalance of inflammatory mediators. We

also found that CD3 +, CD4 +, and CD8 + cells were greatly decreased in non-survivors. Importantly, these lymphocyte subsets play a role in viral clearance, reducing overreaction of the immune system, and developing long-term immunity. 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. In support of this idea, higher neutrophil counts also "predisposed" patients to unfavorable disease outcomes. 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. 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, possibly because of a bacterial superinfection, which could contribute to a rapid deterioration in the clinical course of the disease. Our pooled analyses did not indicate a clear prognostic role for platelet counts. However, studies found that decreasing levels of platelet are associated with adverse outcomes during the hospital stay. 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. 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. 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. 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. With the occurrence of ANP in around one-

tenth of patients, our results are comparable with previously reported data. In our cohort, necrosis was associated with a four to eight-fold increased risk of local and systematic complications, severe disease course, and mortality. We also observed prolonged hospitalization indicating the impact of ANP on short-term outcomes. 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. Despite the fact that our study covered only 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. 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. 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. AI-assisted tools have to overcome many challenges. 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. 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, our work contained the widest coverage of laboratory parameters in this topic with the largest sample size. 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. 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.

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. 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. 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. 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

Acute pancreatitis (AP) is the most frequent gastrointestinal disease requiring acute hospitalization. As the underlying pathophysiology of AP becomes more and more familiar by the accumulation of scientific data, several potential therapeutic targets have been identified. Since some of these specific therapies may be available soon, prompt initiation of treatment after early identification of ANP could be even more important. Development of ANP is associated with several short- and long-term complications, e.g., endocrine insufficiency, but CECT is not performed 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. Further research is needed on other potential predictive factors, which could be incorporated into the current model to further improve predictions.

10. 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, most of these associations can also be observed with the new

variants. 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.

11. THESIS ACKNOWLEDGEMENT

Foremost, I would like to express my gratitude to my advisors, **Andrea Szentesi** and **Hussain Alizadeh** for the continuous support of my PhD study and research, for their patience, motivation, enthusiasm, and immense knowledge. I could not have imagined having better advisors and mentors for my PhD study. Besides my advisors, I would like to express my deepest appreciation to **Péter Hegyi** for giving me the opportunity to research and providing me invaluable guidance throughout my research. I thank my **fellow labmates** for the stimulating discussions, for the sleepless nights we were working together before deadlines, and for all the fun we have had in the last years. My sincere thank also goes to the **Heim Pál National Pediatric Institute** for providing me the friendly environment, support and time to complete my thesis beside my clinical work. It is impossible to extend enough thanks to **my family**, who gave me encouragement and a keen interest in my academic achievements. Last but not least, I would also like to give a special thanks to **my loving wife** for her continuous support and unending inspiration. Without her, I could not conquer all the problems I had met.