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Predicting severe outcomes in acute pancreatitis

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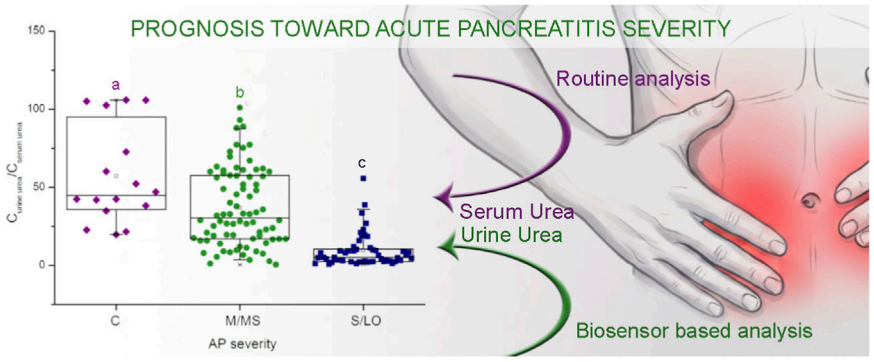
Acute pancreatitis (AP) is among the most complex inflammatory illnesses, with its incidence rising due to heightened stress, particularly from warfare. In fact, the severity prognosis, especially the severe (S) course in AP (SAP) in the early hours, is essential, as it considerably determines the patient's treatment options. Although there are various clinical, biochemical, and imaging criteria for determining the severity of AP, each scoring system has distinct limitations, as it is time-consuming because it requires evaluating approximately 10 parameters. This study presents a developed prognostic criterion (PC) that provides rapid prediction of the SAP, as it is based on the evaluation of just two parameters. The PC is calculated as the ratio of the urine urea concentration, measured by a proposed amperometric biosensor, to the serum urea concentration. The findings indicate that a PC value between 60 and 15 suggests a mild or moderate-severe course. Conversely, a PC value below 15 predicts a S course or potential lethal outcome (LO). The PC shows exceptional diagnostic accuracy in differentiating S/LO from healthy controls, yielding an area under the curve of 0.969 (95% CI: 0.924–0.998). At an optimal cutoff of ≤ 19.55, the PC yields 88.0% sensitivity and a perfect specificity of 100.0%. This PC offers a simple, personalized tool for physicians to identify high-risk patients and optimize treatment to reduce mortality. The proposed amperometric urea biosensor demonstrates reliable performance in raw urine, providing a practical solution for rapid clinical assessment. Overall, this represents a foundational step toward the development of non-invasive point-of-care diagnostics and prognostics, especially in resource-limited settings, such as Ukraine and neighboring countries currently providing care to refugees. A simple-to-operate amperometric biosensor with reliable performance in biological samples is proposed for PC determination.

KEYWORDS
acute pancreatitis, biosensor, severity prognosis, urea concentration, urine

1 Introduction

An infection, tissue damage, or surgery might trigger the inflammatory process. As a rule, the inflammatory response involves several steps, including tissue destruction, disrupted blood flow, and the proliferation of cellular elements, each aimed at repairing the damaged area (Rossaint and Margraf, 2021; Arumugam and Watanabe, 2017; Rossaint et al., 2019; Macovei et al., 2017). One of the most common inflammatory pancreatic diseases affecting all ages, with an annual growth, is acute pancreatitis (AP) (Manfredi et al., 2013; Sureka et al., 2016; Zerem et al., 2023; Sellers et al., 2021). Modern lifestyle-induced stress acts as a potent cofactor in the pathogenesis of AP. By triggering systemic oxidative stress and disrupting blood flow to the organ, it compromises pancreatic microcirculation and depletes essential cellular defenses (Binker and Cosen-Binker, 2014; Stefanaki et al., 2023).



GRAPHICAL ABSTRACT

AP not only causes a significant mental, physical, and economic burden, but it can also progress to a severe (S) course in AP (SAP), which is associated with a high risk of death (Olson et al., 2019). There are 3 degrees of AP severity classification based on the presence or absence of persistent organ failure and local and systemic complications: mild (M), moderately severe (MS), and S (Sarr et al., 2013). In fact, AP remains a significant cause of mortality, especially in its S form, where lethal outcomes (LO) may reach up to 50%. Unfortunately, currently available scoring systems have limited predictive accuracy and are often difficult to apply in clinical practice. This limitation is even more pronounced in pediatric patients, for whom many of these scoring systems are not validated or applicable. These gaps in risk stratification and clinical management highlight the need to identify novel, more reliable biomarkers for prognostic assessment (Mititelu et al., 2025; Banks et al., 2013; Suzuki et al., 2014; Sigounas et al., 2011).

The Atlanta clinical criteria, as well as various scoring systems, have been used in the initial management of AP to assess disease severity, including Ranson Acute Physiology and Chronic Health Evaluation (APACHE)-II, Bedside Index for Severity in Acute Pancreatitis (BISAP), and computed tomography severity index (CTSI) (Zerem et al., 2023). With exception of Ranson, the major advantage of these scoring systems is that all variables can be obtained within the first 24 h. Clinical scoring systems, including routine laboratory and inflammatory biomarkers, as well as imaging-based scores, usually are time-consuming since contain many variables should be evaluated. However, these methodologies are aimed at the diagnosis of AP itself. Still, they cannot promptly warn of the threat of SAP, as they are based on the criteria of the consequences of the disease that have already occurred. Moreover, the accuracy of these scoring systems in predicting SAP varies, with no statistically significant differences observed between them (Cho et al., 2015; Paul, 2020; Chooklin et al., 2023). Especially in the early stages of the disease, current prediction models lack specificity and reliability (Schütte and Malfertheiner, 2008). A critical determination was made regarding the risk of SAP following an analysis of 43 sources that examined 14,116 patients with AP, revealing that standard scoring techniques for predicting SAP, such as BISAP, APACHE-II, Ranson, and SIRS, are ineffective and do not support decision-making (Capurso et al., 2023).

As it was mentioned above, the diagnostic assessment of AP is based on clinical symptoms, laboratory assessments, and imaging results. At least two out of three of the following criteria must be present: clinical (upper abdominal pain), laboratory (serum lipase and/or amylase levels exceeding three times the upper limit of normal), and/or imaging (such as computed tomography (CT), magnetic resonance imaging, or ultrasonography) criteria (IAP/APA Acute Pancreatitis Guidelines Working Group, 2013). The AP onset involves rapid inflammation, which is accompanied by severe abdominal pain, nausea, and vomiting. At this stage, there are no treatments available that can alter the progression of the disease. The initial management focuses on providing supportive care, which includes proper risk assessment and monitoring, fluid administration, nutritional support, symptom control, and antibiotic therapy (De-Mad et al., 2023; Walkowska et al., 2022). Unfortunately, a SAP is not directly indicated by any of the specific signs and symptoms (Lee and Cho, 2022). Usually, AP diagnosis is performed 3–7 days after symptoms start because it is made not only by blood tests and clinical findings but also by radiological characterization, and the progress is also confirmed by computed tomography. However, the late stage of AP has already entered into force during this period, which causes not only complex complications but also LO. Meanwhile, such an approach is used in clinical practice since there are no simple, rapid tests available to predict the SAP. The rapid and early prognosis of the SAP would allow the choice of appropriate planning therapy and avoid serious complications of the disease or even death (Popov et al., 2016; Werner et al., 2003).

A wide range of laboratory parameters has been examined to manage and predict the severity of AP, including glucose, albumin, C-reactive protein (CRP), hematocrit (HTC), triglycerides (TG), procalcitonin, creatinine, blood urea nitrogen (BUN), glomerular filtration rate (eGFR), and cortisol. However, the optimal specific biomarker for accurately assessing and forecasting the severity of AP remains unidentified (Walkowska et al., 2022; Lee and Cho, 2022; Popov et al., 2016; Werner et al., 2003; Baillie and AGA Institute Governing Board, 2007; Nebiker et al., 2018). As mentioned above the BUN is one of the routine laboratory tests that is used to characterize patients of pancreatitis rapidly. In previous research it was shown that serial BUN measurement is valuable for predicting mortality in AP (Wu et al., 2009). Nevertheless, BUN mainly reflects

intravascular volume status, and it is an indicator of kidney dysfunction (Wang et al., 2014).

In AP not only the pancreas is affected; the disease can rapidly progress to a severe form, with simultaneous liver and kidney dysfunction. The latest study based on meta-analysis demonstrated an association between BUN to albumin ratio and mortality in AP (Xia et al., 2025). It is well known that albumin is exclusively synthesized in the liver, thus it reflects a hepatic function (Carvalho and Machado, 2018). Consequently, a combination of biomarkers reflecting both liver and kidney dysfunction can effectively indicate the severity of AP. Both organs are essential for maintaining urea concentrations in the blood and urine; urea is synthesized in the liver from ammonia-derived waste products of protein metabolism, while the kidneys facilitate its filtration, reabsorption, and ultimate excretion into the urine. The functional status of these organs can be reflected by urea concentrations in both blood and urine (Banks et al., 2013; Walkowska et al., 2022; Liu et al., 2021). Thus, the range of urea concentration in different body fluids can indicate renal and liver function and may serve as a viable indicator associated with AP severity.

In the present study, utilizing the urinary-to-serum urea ratio (PC) demonstrated a distinctly superior prognostic and diagnostic performance compared to evaluating individual urea concentrations in serum or urine alone. According to our data, no studies describing urinary urea as a diagnostic factor for assessing the severity of AP have been found in the literature. The fact that this factor influences the course of AP is a novelty. The results of this investigation revealed that urine urea content below the norm is even more critical during the AP progress than BUN. Specifically, while serum urea levels showed acceptable early discrimination and urine urea excelled in late-stage differentiation, the combined ratio synergized these individual trends into a singular robust index, yielding an outstanding AUC of 0.969 for severe status identification. Overall, our goal was not only to present the fact that the severity of AP can be predicted by monitoring the urea and BUN ratio, but also to propose a particularly simple determination of this parameter by using electrochemical biosensor. The suggested combination of PC and a biosensor has primary advantage and innovation over existing approaches, which are time-consuming and necessitate specialized preparation for execution. The study demonstrates that the amperometric biosensor-based technique provides a viable alternative for predicting the SAP diagnosis. In this investigation, it was discovered that a lower-than-normal urea content in urine is critical in the course of AP. We introduce a prognostic criterion (PC) based on urea concentrations in distinct body fluids, establishing specific numerical thresholds to forecast AP progression. Our proposed PC-based score, which consists of only two parameters, is simple, rapid, and potentially highly useful in resource-limited settings, such as Ukraine and neighboring countries.

2 Materials and methods

2.1 Materials

Urease from *Canavalia ensiformis* EC. 3.5.1.5 (specific activity 1378.0 U mg^{-1}) was purchased from Sigma, bovine serum albumin was purchased from Merck KGaA, the graphite rod (diameter 3 mm, length 150 mm) was purchased from Sigma–Aldrich, second fraction of thermaly reduced graphene oxide (TRGO) was synthesized according to (Razumiene et al., 2020) semi-permeable terylene membrane (thickness 12 μm, pore diameter 0.4 μm) were obtained from Sterlitech, USA., graphite (extra pure grade) was purchased from Sigma Merck, 1,6-Hexamethylene diisocyanate and polyvinyl alcohol 100,000 (degree of hydrolyzation 86–89 mol%) was purchased from Fluka. Other chemical reagents obtained from Sigma–Aldrich were of analytical grade and used without further purification. A 0.02 M phosphate buffer solution (PBS) pH = 7.2 was prepared by mixing stock solutions of KH_2PO_4 and Na_2HPO_4. All aqueous solutions were prepared with distilled water.

2.2 Preparation of the biosensor and electrochemical measurements

The initial stage of the process involved the formation of a layer of TRGO on the inner surface of the ring-fixed semipermeable terylene film (working area Ø 2.4 mm). This was achieved by applying TRGO paste, which had been prepared by mixing TRGO powder with a pasting liquid comprising 10% polyvinyl dichloride in acetone. Subsequently, 5 μL of a mixture comprising urease, bovine serum albumin in PBS, and glutaraldehyde was deposited on the TRGO-layered surface and held at 4 °C overnight. Following the immobilization of the enzyme in this manner, the resulting enzymatic membrane was mechanically attached to the surface of the graphite electrode, thereby forming a biosensor designed for the detection of urea in urine or blood serum samples. The principal scheme of the biosensor, membranes containing TRGO with enzyme, graphite electrode, and signal registration system for urea measurements are presented in Figure 1.

The provided figure illustrates that the urea biosensor comprises an enzymatic membrane and a rod-shaped graphite electrode. This sensor was integrated into an electrochemical signal registration device - analyzer.

Chronoamperometric measurements were conducted with a custom-made analyzer (Vilnius University, Life Sciences Centre, Institute of Biochemistry), utilizing a conventional three-electrode electrochemical cell comprising a platinum auxiliary electrode, a saturated Ag/AgCl reference electrode, and the biosensor as the working electrode. These measurements were conducted in the thermostatic electrochemical cell of the analyzer (1.65 mL) at 20 °C. The current-time responses of the biosensor to multiple concentrations of urea in PBS were monitored at 0 V working potentials versus Ag/AgCl in a stirred PBS buffer solution (pH 7.2). In the case of urine assessments, 50 μL of samples that had been diluted 10 times with PBS were added to the cell. Aiming to evaluate blood serum, 50 μL of undiluted samples were added to the cell.

The performance of the biosensor was evaluated by comparing the current-time responses in relation to substrate concentration (C). The response current was measured on three occasions in the solution containing C, and the mean value was calculated.

2.3 Determination of the biosensor accuracy

The concentration of urine urea ($C_{urine\ urea}$) and blood serum ($C_{serum\ urea}$) was obtained at Bioanalysis department, Institute of

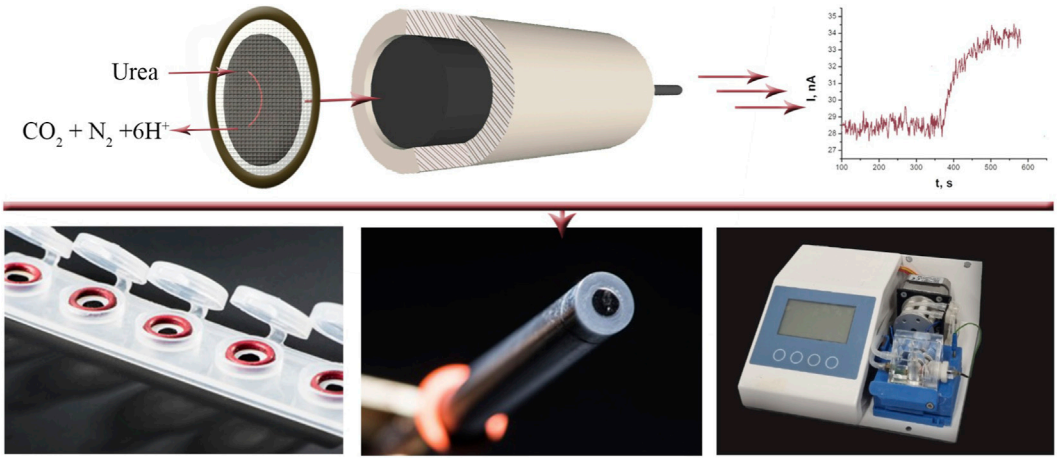


FIGURE 1
The urea detection system: biosensor scheme, membranes containing TRGO and the enzyme, graphite electrode and signal registration device.

Biochemistry, Life Science Center of Vilnius University by self-developed urea biosensor as was described in Section 2.2. Aiming to verify the accuracy of the biosensor action in real samples, the concentration of urea in blood serum was compared with data obtained at VUH Santaros Clinics Laboratory of Biochemistry using ARCHITECT plus ic8200 (Abbott, Abbott Park, Illinois, USA) analyzer.

2.4 Statistical analysis

Comparison among groups was performed by one-way analysis of variance (ANOVA). Prior to conducting ANOVA, the assumption of variance homogeneity was formally evaluated using Levene's test (absolute deviations). Consequently, standard one-way ANOVA was appropriately applied. To control for family-wise error rates across multiple group comparisons, a *post hoc* correction (Tukey's test) was implemented, and p-values less than 0.01 were regarded as statistically significant. Missing data were managed via complete-case analysis, excluding incomplete records to ensure unbiased prognostic performance metrics.

To evaluate the diagnostic accuracy and prognostic performance of the PC in differentiating between clinical severity groups, receiver operating characteristic (ROC) curve analysis was performed. Five distinct clinical classification scenarios were evaluated: all patients versus healthy controls (M/MS + S/LO vs. C), severe patients versus healthy controls (S/LO vs. C), mild/moderate patients versus healthy controls (M/MS vs. C), severe versus non-severe cohort (S/LO vs. C + M/MS), and severe versus mild/moderate patients (S/LO vs. M/MS). The overall discriminative power was quantified using the Area Under the Curve (AUC). To robustly estimate the precision of the AUC values, 95% confidence intervals (95% CI) were calculated using a non-parametric bootstrapping approach with 1,000 resamples. The optimal diagnostic cutoff thresholds were determined using Youden's J statistic (Youden's J = Sensitivity + Specificity - 1) to maximize overall diagnostic accuracy, while also incorporating clinical relevance considerations—specifically balancing sensitivity and high specificity to ensure reliable risk stratification and prevent false-positive classifications in clinical practice. Because The PC and $C_{urine\ urea}$ values naturally decrease with increasing disease severity, the classification model utilized a lower-than-or-equal-to (≤) decision rule to identify target clinical conditions. Conversely, because $C_{serum\ urea}$ increase with disease severity, a greater-than-or-equal-to (≥) direction rule was utilized for the serum models. Sensitivity and specificity metrics were calculated at each optimal threshold.

2.5 Patients

We conducted a prospective observational study and, all of the patients admitted to Vilnius University hospital "Santaros klinikos" with a diagnosis of AP and an onset of the diseases within the last 72 h were included in the study. A total of 136 AP patients' (37females, 99 males) samples of the same race and ethnicity and 16 age/sex-matched healthy control samples were studied in accordance with the Institutional IRB approval (No. 158200-17-941-455). The patient's ages ranged from 23 to 91 years old (average age of 59). The AP etiology was alcoholic in 64 (47.5%), biliary in 44 (32.5%) and idiopathic in 28 (20%). The diagnosis was established on the basis of acute abdominal pain, with at least three-fold elevated levels of serum amylase and typical radiological findings. The contrast-enhanced computed tomographic scan was performed on days 5–7 after the onset of the disease. The patients were followed up with during their stay at the hospital until either the time for discharge or lethal outcome. All AP patients with no history of previous episode of the disease were admitted to the emergency room less than 24 h after the symptoms started. The diagnosis was confirmed by biochemical changes, clinical examination, and ultrasound examination. Disease severity (M, MS, S) was evaluated using the Modified Atlanta Classification. If patients' condition became unstable, they were treated at the intensive care unit (ICU).

2.6 Urine and blood sampling

Urine and blood samples were taken daily, upon admission and for the 3-day study period. Urine samples were collected

from a AP patients and then were subjected to a process of aliquoting, which involved the division of the samples into smaller volumes, and subsequently stored within a −80 °C freezer. The collection of serum samples was conducted using BD Vacutainer 3.5 mL SST(TM) II PET tubes, which contain a clot activator (silica) and a separating gel, specifically designed for blood sampling. Following clotting, blood samples were subjected to centrifugation at 2,500× *g* for 10 min at room temperature. Serum aliquots were cryogenically stored post-centrifugation at temperatures of at least −70 °C. Prior to the assay, the frozen samples were allowed to reach room temperature gradually and were then gently agitated. All collection and processing of the samples was performed in accordance with the ethical approval and clinical sample handling guidelines of Vilnius University.

3 Results

3.1 Characterization of urea biosensor

The publications (Razumiene et al., 2020; Razumienė et al., 2022) described the urea biosensor's functioning, accuracy in presence of added potential interfering compounds, and applicability for hemodialysis fluids. The biosensor's development technology enabled excellent operational and storage stability (up to 7 months) and appropriate reproducibility (relative standard deviation (RSD) of about 2%). The analytical recovery of the TRGO-based biosensor in urine of 101 ÷ 104% with RSD of 1.2 ÷ 1.7% and in blood of 92.7 ÷ 96.4%, RSD of 1.0 ÷ 2.5%, confirmed that the biosensor is acceptable and reliable (Razumiene et al., 2020). In this study, the biosensor was adopted for urine and blood serum assessments. Upon the introduction of the urea sample to the electrochemical cell, the biosensor produced a substrate-dependent anodic response. The signal from the urea analyzer is derived from the difference between the steady-state current and the background current measured at a working potential of 0 V relative to Ag/AgCl. The linear part of the calibration curve expressed in current vs. urea concentration is presented in Figure 2. The calibration curve was obtained experimentally by adding 0.125, 0.25, 0.5, 1.0, 1.5, and 2.5 mM of urea in PBS to the electrochemical cell of the analyzer.

The sensitivity of the biosensor was determined by calculating the slope of the urea calibration curve's linear range (0.1–2.5 mM). As shown in Figure 2, the developed biosensor exhibits a sensitivity of 80 nA to 1 mM of urea and LOD of 0.02 mM at an electrode potential of 0 V.

Aiming to verify the accuracy of the biosensor action in real samples, the concentration of urea in blood serum was compared with data determined by an approved method. The values of urea obtained in blood serum by the biosensor were compared with the amounts determined in the biochemistry laboratory of VUH Santaros Clinics by the ARCHITECT plus ic8200 analyzer (Abbott, Abbott Park, Illinois, USA). Data obtained by both methods are presented in Figure 3.

The relationship between the data obtained by the two methods in Figure 3 is linear, and the correlation coefficient (r_{xy} = 0.9945) showed a good agreement between the urea concentrations determined by the biosensor and the VUH Santaros Clinics biochemistry laboratory. The slope of the correlation was 0.99, which indicates, that results, determined using the amperometric biosensor, are slightly lower than those of analysis of VUH Santaros Clinics Laboratory of Biochemistry analysis. These findings suggest that, in general, the urea biosensor generates a correct and accurate response to urea in serum.

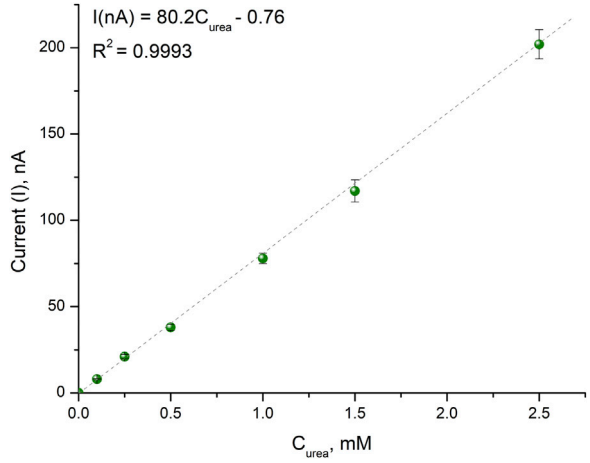


FIGURE 2
Steady-state current (I) as a response of the biosensor on urea concentration (C_{urea}). The linear regression equation is I(nA) = 80.2C_{urea} - 0.76 with a coefficient of determination of R^2 = 0.9993. E = 0 V vs. Ag/AgCl; PBS (20 mM; pH 7.2).

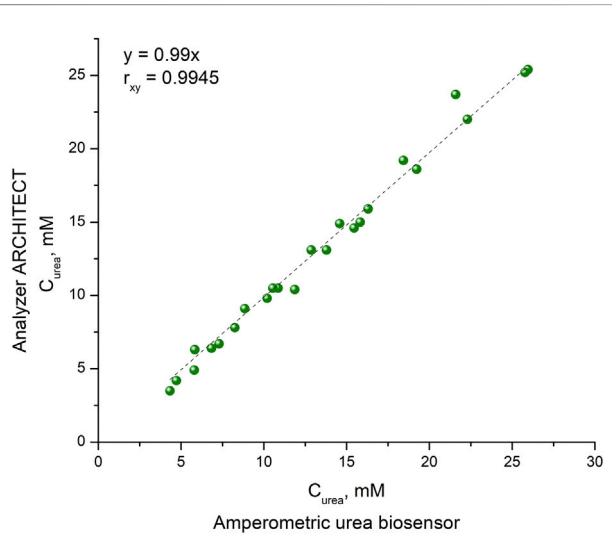


FIGURE 3
Correlation between urea concentrations obtained in serum using the amperometric urea biosensor and by the analyzer ARCHITECT plus ic8200 in Biochemistry Laboratory of VUH Santaros Clinics. The linear regression equation is y = 0.99x with a coefficient of correlation of r_{xy} = 0.9945. E = 0 V vs. Ag/AgCl; PBS (20 mM; pH 7.2).

3.2 Numerical values of the PC

To determine the ranges of reliable PC numerical values, a cohort consisting of C, M, MS, and S patients has been assessed in terms of both serum and urine urea. Among S patients, seven of them later had LO. From the pooled data from the control group and the patients admitted to the hospital with a diagnosis of AP taken during the first 78 h, PC expressed as ratio of $C_{urine\ urea}/C_{serum\ urea}$ was studied as a function of the severity of AP. OriginPro 8.5 was used to calculate an overall ANOVA Tukey test statistics to evaluate $C_{urine\ urea}/C_{serum\ urea}$ level found in urine and serum vs. AP severity. The obtained dependence of $C_{urine\ urea}/C_{serum\ urea}$ vs. severity of AP is presented in Figure 4.

Based on the results of these programs, it was concluded that if the $C_{urine\ urea}/C_{serum\ urea}$ numerical value is between 60 and 16, this patient has a M or MS of AP. In contrast, if the PC value is less than 15, this patient has a S course in AP.

Figure 4 illustrates that the mean of the $C_{urine\ urea}/C_{serum\ urea}$ is distinctly correlated with the progression of AP, exhibiting a linear decline as the severity of AP escalates. Overall ANOVA p-value was reported on $6.42 \cdot 10^{-14}$. A p-value smaller than 0.01 means that a significantly different group was found. Additionally, the multiple comparisons of groups were conducted using the Tukey test. Patients with S/LO in AP had significantly lower values of $C_{urine\ urea}/C_{serum\ urea}$ compared to the C and M/MS groups in AP. Patients with the M/MS course in AP also had significantly different values of $C_{urine\ urea}/C_{serum\ urea}$ compared to the C group. The data clearly showed if the $C_{urine\ urea}/C_{serum\ urea}$ is between 60 and 15, the M/MS course in AP severity is proposed. If the PC value is less than 15, an S course in AP or even LO is predicted for such a patient.

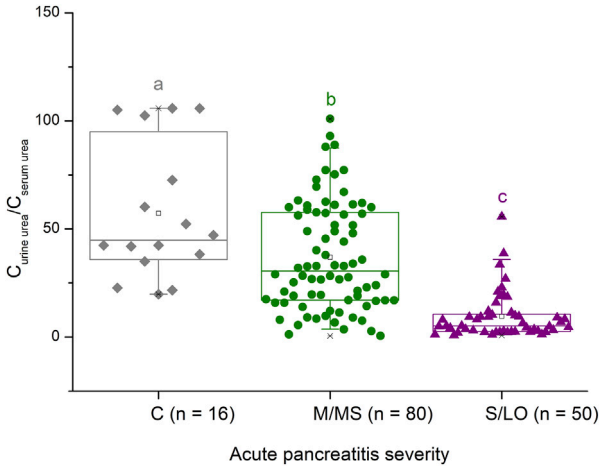


FIGURE 4
$C_{urine\ urea}/C_{serum\ urea}$ vs. severity in AP. Control (C), mild (M), moderately severe (MS), severe (S) groups, and lethal outcomes (LO). Data was obtained using a urea biosensor (E = 0 V, 20 mM PBS, pH = 7.2). Data are presented as box plots representing medians and interquartile ranges, with individual data points overlaid. Exact sample sizes are indicated on the x-axis. Different lowercase letters (a, b, c) indicate statistically significant differences between groups ($p < 0.01$).

3.3 Establishment of prognostic criterion (PC)

The possibility to find the numerical values of the PC were based on hypothesis that the excretion of urea into urine and blood depends on the severity course of AP. For PC determination the samples of urine and blood serum were taken from 16 controls (C) and 136 AP patients at Vilnius University Hospital (VUH) Santaros Clinics Abdominal Surgery Department. Disease severity (M, MS and S) was evaluated using the Modified Atlanta Classification. To test the hypothesis that the excretion of urea into urine and blood depends on the progression severity of AP an analysis of variance (ANOVA) with the Tukey criterion was employed. The dependence of urea levels on the progression of AP in urine and blood serum is presented in quartile plots in Figures 5A,B .

The data indicate that as AP severity increases, urine urea levels decrease (Figure 5A), whereas serum urea concentrations concurrently increase (Figure 5B).

The results of the ANOVA analysis indicated that the obtained p-values were $2.62 \cdot 10^{-11}$ (in urine) and $1.35 \cdot 10^{-7}$ (in serum), which were significantly lower than the chosen significance level of 0.01. This provides a basis to assert that the excretion of urea into urine and blood depends on the severity of AP. To identify which group means differed significantly, the Tukey criterion was employed. A statistical analysis of urea levels in both urine and serum revealed that the group means differed significantly between the severe/lethal outcome (S/LO) AP severity group and the C patient group. This was also observed between the S/LO and M/MS AP severity groups, which were found to be statistically different. However, no significant difference was observed between the M/MS severity group and the C patient group, indicating that they were statistically similar. As illustrated in Figures 5A,B, the severity of AP is accompanied by increased urea levels in blood serum. In contrast, a decrease in urea levels is observed in urine. In fact, it can be stated that the urea concentration in the urine can be a criterion for predicting the S course of AP.

3.4 Prognostic performance: ROC analysis

Receiver operating characteristic (ROC) curves were generated to evaluate the predictive performance of $C_{urine\ urea}$, $C_{serum\ urea}$, and their ratio (PC) in determining clinical severity. Five distinct clinical scenarios were evaluated. The corresponding ROC curves of PC are presented in Figure 6. The complete predictive metrics across all clinical scenarios of PC, $C_{urine\ urea}$ and $C_{serum\ urea}$ are summarized in Table 1.

ROC analysis of $C_{urine\ urea}$ displayed exceptional efficacy in identifying advanced states of AP. S/LO vs. C yielded an outstanding AUC of 0.921 (95% CI: 0.849–0.971). At the optimal cutoff of ≤ 106.50, the $C_{urine\ urea}$ biomarker achieved a sensitivity of 75.0% and a perfect specificity of 100.0%. However, its accuracy in early-stage disease was negligible M/MS vs. C, AUC = 0.502 (95% CI: 0.369–0.625). In contrast, $C_{serum\ urea}$ demonstrated superior capability in detecting early pathological changes. In M/MS vs. C, $C_{serum\ urea}$ generated a strong and highly significant AUC of 0.805 (95% CI: 0.690–0.903). At a cutoff of ≥ 6.00, it provided a sensitivity of 60.0% and a specificity of 93.8%. For the differentiation of S/LO vs. C, $C_{serum\ urea}$ biomarker exhibited an AUC of 0.834 (95% CI: 0.718–0.925).

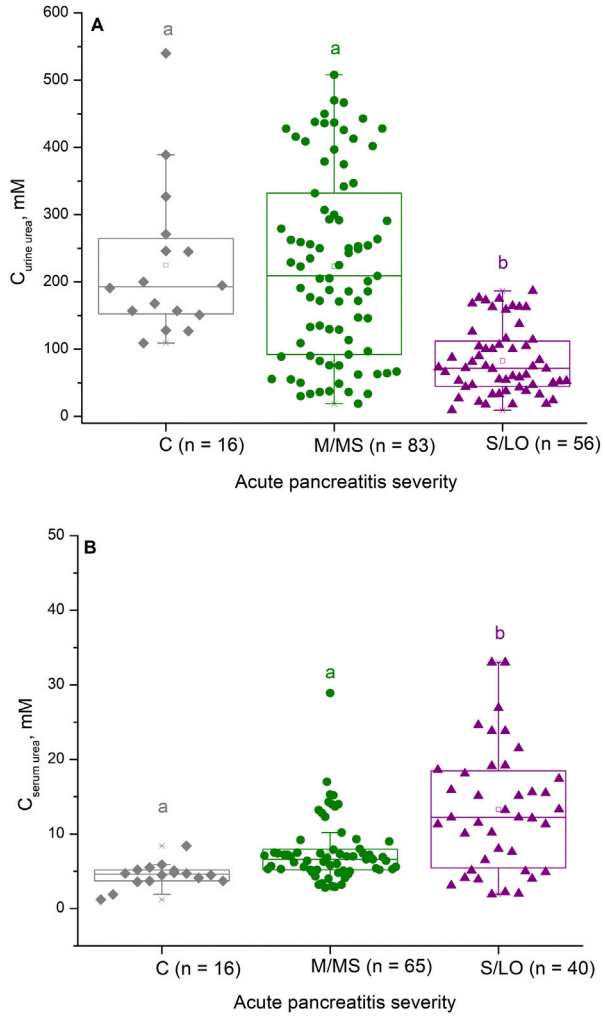


FIGURE 5
The dependence of urea concentration in urine **(A)** and blood serum **(B)** on the severity of AP. Control (C), mild (M), moderately severe (MS), severe (S) groups and lethal outcomes (LO). Data was obtained using the urea biosensor (E = 0 V, 20 mM PBS, pH = 7.2). Data are presented as box plots representing medians and interquartile ranges, with individual data points overlaid. Exact sample sizes are indicated on the x-axis. Different lowercase letters (a, b) indicate statistically significant differences between groups ($p < 0.01$).

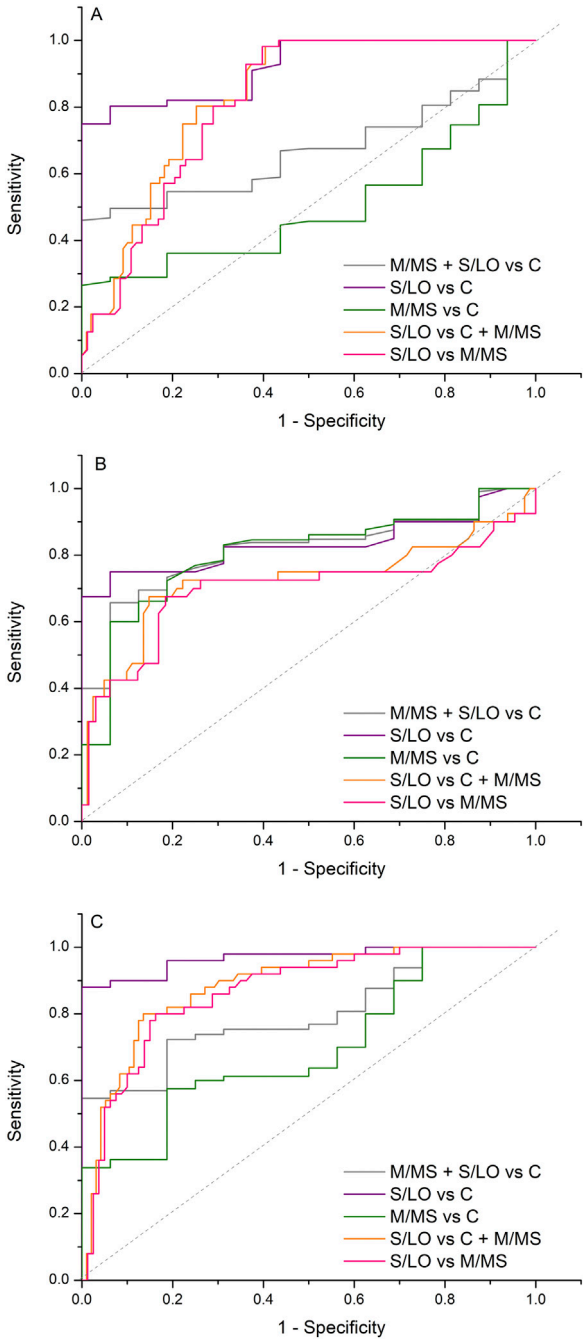


FIGURE 6
Receiver operating characteristic (ROC) curves for predicting $C_{urine\ urea}$ **(A)**, $C_{serum\ urea}$ **(B)** and PC **(C)** across different clinical severity cohorts and classification scenarios. The plot illustrates the trade-off between sensitivity and specificity across five clinical comparison: all patients vs. healthy controls (M/MS + S/LO vs. C), severe patients versus healthy controls (S/LO vs. C), mild/moderate patients vs. healthy controls (M/MS vs. C), severe vs. non-severe cohort (S/LO vs. C + M/MS), and severe vs. mild/moderate patients (S/LO vs. M/MS).

The data presented in the Table 1 show that, utilizing the PC ($C_{urine\ urea}$ and $C_{serum\ urea}$ ratio) demonstrated a distinctly better prognostic and diagnostic performance compared to evaluating individual urea concentrations in serum or urine alone. When distinguishing the entire patient cohort from healthy controls, the PC achieved a good discriminative capacity with an AUC of 0.800 (95% CI: 0.702–0.885). At the optimal cutoff threshold of ≤ 19.69, it demonstrated a balanced performance with 54.6% sensitivity and a perfect specificity of 100.0%. Notably, the highest classification accuracy was observed when identifying S/LO against C, yielding an outstanding AUC of 0.969 (95% CI: 0.924–0.998). At a cutoff threshold of ≤ 19.55, the PC achieved 88.0% sensitivity and 100.0% specificity, indicating near-perfect differentiation.

Furthermore, the PC demonstrated robust capability as a risk-stratification tool to isolate severe outcomes from the remaining combined cohort (S/LO vs. C + M/MS), generating an AUC of 0.883 (95% CI: 0.821–0.934). For this classification, the optimal threshold was established at ≤ 12.00, providing 80.0% sensitivity and 86.5% specificity. Similarly, when directly

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TABLE 1 ROC performance metrics of the PC, $C_{urine\ urea}$ and $C_{serum\ urea}$ across clinical severity cohorts.

Comparison scenario	Value under analysis	AUC (95% CI)	Optimal cutoff	Sensitivity	Specificity
M/MS + S/LO vs. C	PC	0.800 (0.702–0.885)	≤19.69	54.6%	100.0%
	$C_{urine\ urea}$	0.671 (0.574–0.765)	≤106.50	46.0%	100.0%
	$C_{serum\ urea}$	0.816 (0.721–0.896)	≥6.00	65.7%	93.8%
S/LO vs. C	PC	**0.969** (0.924–0.998)	≤19.55	88.0%	100.0%
	$C_{urine\ urea}$	0.921 (0.849–0.971)	≤106.50	75.0%	100.0%
	$C_{serum\ urea}$	0.834 (0.718–0.925)	≥6.50	75.0%	93.8%
M/MS vs. C	PC	0.695 (0.568–0.822)	≤34.00	57.5%	81.2%
	$C_{urine\ urea}$	0.502 (0.369–0.625)	≤97.00	26.5%	100.0%
	$C_{serum\ urea}$	0.805 (0.690–0.903)	≥6.00	60.0%	93.8%
S/LO vs. C + M/MS	PC	**0.883** (0.821–0.934)	≤12.00	80.0%	86.5%
	$C_{urine\ urea}$	0.832 (0.771–0.889)	≤176.40	98.2%	59.6%
	$C_{serum\ urea}$	0.725 (0.598–0.831)	≥10.06	67.5%	85.2%
S/LO vs. M/MS	PC	**0.866** (0.797–0.927)	≤12.00	80.0%	83.8%
	$C_{urine\ urea}$	0.815 (0.743–0.883)	≤176.40	98.2%	60.2%
	$C_{serum\ urea}$	0.698 (0.579–0.821)	≥10.06	67.5%	81.5%

PC, developed prognostic criterion, $C_{urine\ urea}$, concentration of urine urea, $C_{serum\ urea}$, concentration of blood serum, CI-confidence interval, AUC, area under the curve, directional criteria (≤ or ≥) maximize Youden's J statistic. Clinical comparison: all patients versus healthy controls (M/MS + S/LO vs. C), severe patients versus healthy controls (S/LO vs. C), mild/moderate patients versus healthy controls (M/MS vs. C), severe versus non-severe cohort (S/LO vs. C + M/MS), and severe versus mild/moderate patients (S/LO vs. M/MS). Values in bold indicate peak AUC metrics.

comparing severe to S/LO vs. M/MS, the PC maintained high discriminatory power (AUC = 0.866, 95% CI: 0.797–0.927) at the same threshold of ≤ 12.00 (80.0% sensitivity, 83.8% specificity). Conversely, differentiating M/MS vs. C yielded the lowest, yet statistically significant, accuracy with an AUC of 0.695 (95% CI: 0.568–0.822).

3.5 Investigation over-time of the PC

In order to verify how long after collecting samples for PC value determination this prediction is appropriate, 3-day samples from patients were tested. Figure 7 shows how the mean urea concentrations in the S/LO group changed on the 1st, 2nd, and 3rd days of urine sample collection.

A one-way ANOVA was conducted to compare the effects of sample collection days on urine urea levels between C and three S/LO groups (Figure 7). The analysis revealed a significant difference among all groups; the p-value was reported as $1.68 \cdot 10^{-6}$. Tukey's test indicated that all S/LO groups showed significant differences from the C group. The means of $C_{urine\ urea}$ for the S/LO groups were as follows: the first day had a mean of 89.5 ± 13.4 mM, the second day had a mean of 84.8 ± 9.2 mM, and the third day had a mean of 80.3 ± 16.2 mM. In contrast, the C group had a mean of $C_{urine\ urea}$ of 218.2 ± 29.4 mM. This could indicate worsening kidney and liver functions during the 72-h period. Pairwise comparisons indicated the value of $C_{urine\ urea}$ is dependent upon the time of sample collection. It is observed that as the duration of hospital admission increases, the value of $C_{urine\ urea}$ slightly decreases until it reaches its lowest point on the third day.

ROC analysis demonstrated the key diagnostic insights (AUC in Figure 7). Absolute Specificity in the early phase (1st and 2nd days). On both days, the $C_{urine\ urea}$ exhibits a perfect specificity of 100.0% at its respective optimal cutoff thresholds (≤100.00 and ≤106.50). From a clinical standpoint, this is a critical asset: any patient presenting with a marker value below these thresholds can be classified as a severe case with virtual certainty, completely eliminating the risk of false-positive diagnoses among healthy individuals during the initial days. On the 3rd day, the optimal cutoff increases to ≤ 127.00, shifting the performance profile to favor high sensitivity (90.0%). This implies that by the third day, the $C_{urine\ urea}$ is capable of successfully capturing 90% of all true severe cases, minimizing the risk of missing critically ill patients (false negatives) as the clinical condition stabilizes. Temporal Cutoff Dynamics: The steady upward shifts in the optimal decision threshold over time—moving from ≤ 100.00 (1st day) to ≤ 106.50 (2nd day) and finally to ≤ 127.00 (3rd day)—reflects the underlying kinetic stabilization of the $C_{urine\ urea}$. It suggests that while S patients maintain significantly suppressed values relative to C, their levels undergo a gradual, predictable progression that requires adjusting the clinical decision threshold depending on the day of evaluation.

4 Discussion

Indeed, in the etiology of AP, stressors of contemporary living are a significant cofactor. Inducing systemic oxidative stress and impairing blood flow to the organ affects pancreatic microcirculation and diminishes vital cellular defenses. Complex

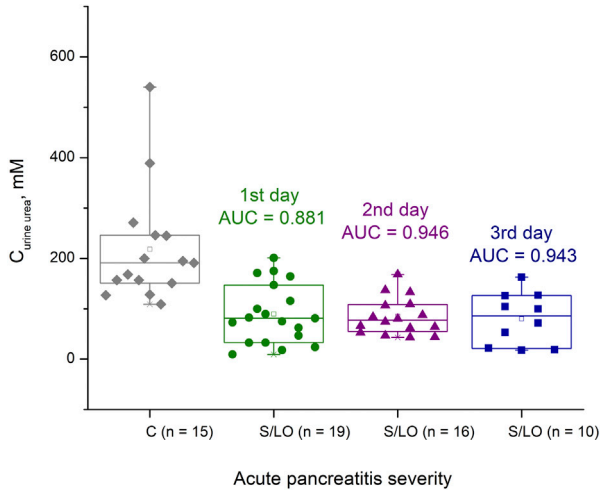

FIGURE 7
$C_{urine\ urea}$ vs. severity in AP and control group on 1st, 2nd, and 3rd day. Control (C), mild (M), moderately severe (MS), severe (S) groups, and lethal outcomes (LO), area under the curve (AUC). Data are presented as box plots representing medians and interquartile ranges, with individual data points overlaid. Exact sample sizes are indicated on the x-axis. Different lowercase letters (a, b) indicate statistically significant differences between groups ($p < 0.01$).

metabolic disorders, such as osteosarcopenic obesity, prediabetes, metabolic syndrome, diabetes type 1 and 2, polycystic ovaries syndrome, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, as well as nonalcoholic fatty pancreas disease, are all products of the damaging actions of chronic stress and associated para-inflammation.

Moreover, the clinical translation of advanced pharmaceuticals is increasingly challenged by drug-induced AP. Recent studies have highlighted AP and cholangitis secondary to sodium-glucose cotransporter-2 inhibitors and immune checkpoint inhibitors. While offering vital pharmacovigilance insights, these studies depend on centralized, multi-step laboratory testing that cannot deliver rapid risk stratification (Li et al., 2025; Pan et al., 2025; Xiao et al., 2026; Cheng et al., 2025; He et al., 2024).

Indeed, diagnosing AP is not a problem; nevertheless, forecasting that AP will move to a S course, aided by a variety of stressful factors, is undoubtedly remains problematic. Therefore, all prognostic tools that can provide early warning about the S course in AP are highly desirable (Binker and Cosen-Binker, 2014; Stefanaki et al., 2023).

Although BISAP, APACHE II, and SIRS are widely used for early risk stratification in AP, each has important limitations. BISAP provides a simple bedside assessment but has only moderate sensitivity and may fail to identify patients who subsequently develop severe disease. APACHE II is comprehensive and can be applied dynamically, but its complexity, dependence on numerous physiological variables, and lack of pancreatitis-specific parameters limit routine clinical use. SIRS is readily available and sensitive to systemic inflammation, but its low specificity and susceptibility to non-pancreatic factors result in a substantial false-positive rate. Consequently, none of these systems alone provides sufficiently accurate early prediction of severe acute pancreatitis. In fact, these conventional scores have limitations in early, accurate, and individualized prediction, which provides the rationale for developing/validating novel biomarkers.

Laboratory parameters used for the diagnosis of AP, such as glucose, albumin, CRP, HTC, T, procalcitonin, creatinine, eGFR, and cortisol, provide a general picture of the body's condition but do not predict the course of AP. As mentioned above, the BUN is also a routine laboratory test used to characterize patients with pancreatitis. It has been shown that serial BUN measurements are valuable for predicting mortality in AP (Wu et al., 2009). Namely, BUN in this study was taken as a parameter that could improve the accuracy of PC for prediction of the SAP. Primarily, our prognostic criterion is based on urinary urea determination. In fact, this investigation revealed that urine urea content below the norm is even more critical during the AP progress than BUN. Both hepatic and renal functions are essential for maintaining urea concentrations in the blood and urine; urea is synthesized in the liver from ammonia-derived waste products of protein metabolism, while the kidneys facilitate its filtration, reabsorption, and ultimate excretion into the urine (Banks et al., 2013; Walkowska et al., 2022; Liu et al., 2021). Urea concentration with normal organ function should be within the range of 200–600 mM (Vanholder et al., 2018; Colombo et al., 2023). Thus, the lower-than-normal urea content in urine reflects the poor functioning of the waste process of ammonia formation after breaking down proteins and indicates hepatic and renal dysfunction.

Furthermore, this work established a biosensor-based technique for the determination of urea. The data depicted in Figure 3 indicate that the proposed biosensor provides a robust and precise response to urea, thereby establishing its utility as a convenient and reliable analytical instrument. Data obtained from the analysis of urea in urine and serum using the biosensor (Figure 5) indicate that as AP severity increases, urine urea levels decrease, whereas serum urea concentrations concurrently increase. It is known that then liver function is impaired, urea synthesis capacity is reduced, manifesting as pathologically reduced urea levels in both serum and urine (Adeva et al., 2012). In contrast, in the case of renal insufficiency, blood urea levels typically increase, while urinary urea levels decrease, as the kidneys are unable to adequately filter or properly reabsorb urea (Gowda et al., 2010). It can be concluded that reduced urinary urea levels in severe S/LO cases indicate hepatic dysfunction. Meanwhile, the diverging trends between urine and serum urea concentrations reflect impaired renal function that significantly affects the course of AP.

This investigation discovered that a lower-than-normal concentration of urea in urine is associated with AP, and decreased urea amount is crucial for the occurrence of S or LO courses. The ANOVA analysis revealed that group C is statistically reliably separated from the S/LO groups. Also, the S/LO separated from M/MS in urine and serum. Meanwhile, no statistically reliable difference was observed between the M/MS and control groups. Using the ratio of both parameters, i.e., urine and serum urea concentrations ($C_{urine\ urea}/C_{serum\ urea}$), allowed us to distinguish

all groups with statistical reliability (Figure 4). We called this ratio a 'prognostic criterion' and determined the PC numerical values for all AP severity cases. This method simply predicts an M/MS course in AP severity if the PC value is between 60 and 15. If the PC value is less than 15, an S course in AP or even LO is predicted for such a patient.

Prognostic performance of PC was characterized by ROC curves. Five distinct clinical scenarios presented in Figure 6 and Table 1 revealed that the PC shows exceptional diagnostic accuracy in differentiating S/LO from healthy C, yielding an AUC of 0.969 (95% CI: 0.924–0.998). At an optimal cutoff of ≤ 19.55, the marker yields 88.0% sensitivity and a perfect specificity of 100.0%. It is important to mention that our designated PC cutoff value of 15 enhances the accuracy of the prediction. Proposed PC also efficiently differentiates between S/LO and M/MS status (AUC = 0.883), establishing a clear clinical threshold at ≤ 12.00 with 80.0% sensitivity and 86.5% specificity. In general, the ROC curve analysis verified that the PC has a strong diagnostic and prognostic utility, particularly for the identification of advanced AP stages. For comparison, the main characteristics of conventional scoring systems can be presented. A large meta-analysis found that BISAP, APACHE-II, Ranson and SIRS all have only modest ability as early laboratory markers to change the probability of SAP, because APACHE II ≥ 8 at admission had approximately 72% sensitivity and 76% specificity for M/S AP. BISAP possess the sensitivity 74.4% and specificity 81.5%. SIRS: sensitivity 74.4%, specificity 62.7%. It is also worth noting the drawback that the Ranson score requires 48 h, whereas APACHE II requires the assessment of 14 parameters.

In fact, the present study, utilizing the urinary-to-serum urea ratio (PC) demonstrated a distinctly superior prognostic and diagnostic performance compared to evaluating individual urea concentrations in serum or urine alone (Table 1). Specifically, while serum urea levels showed acceptable early discrimination (AUC = 0.805 for M/MS vs. C) and urine urea excelled in late-stage differentiation (AUC = 0.921 for S/LO vs. C), the combined ratio synergized these individual trends into a singular robust index, yielding an outstanding AUC of 0.969 for severe status identification. From a physiological standpoint, individual concentrations are highly susceptible to confounding systemic factors such as dietary protein intake, metabolic catabolism, and acute dehydration. Calculating the ratio effectively normalizes these individual fluctuations, serving as a surrogate marker for renal clearance dynamics. Consequently, when disease severity escalates—characterized by concurrent serum accumulation and impaired urinary excretion—the ratio amplifies the statistical distance between clinical cohorts, minimizing individual data overlap and providing clinicians with a significantly more reliable diagnostic threshold. We conclude that, in SAP, multifactorial influences are not more significant than the influence of the specific factor determining lower-than-normal urinary urea excretion. This conclusion was based on the following fact: urine samples were collected as random spot samples. Because some critically ill patients were unable to void urine spontaneously. The control group was selected from the general hospital admission population based on a single criterion—the absence of an acute pancreatitis diagnosis. Given that these patients were admitted for various reasons, their biochemical parameters likely showed wide variability; nevertheless, the control group remained statistically distinct from the SAP. The fact that statistically distinct AP severity groups were identified despite the random nature of the urine sampling underscores the significance of the urinary urea factor in the course of SAP.

The significance of predicting the progression of SAP in the initial hours of a patient's illness is well established; however, patients frequently present to the hospital too late for admission. Consequently, an investigation was conducted to assess the validity of PC beyond the first day after AP diagnosis. Therefore, a study was carried out to ascertain the reliability of PC over three consecutive days. Figure 7 shows that the mean urea concentration ranged from 89.5 ± 13.4 mM to 80.3 ± 16.2 mM, indicating that PC predictions can be accurate on the third day as well. This hypothesis was confirmed by ROC analysis data. ROC revealed that the classification power of the marker intensifies as time progresses. The lowest accuracy is observed on 1st day (AUC = 0.881), which then peaks on 2nd day (AUC = 0.946) and remains exceptionally high on 3rd day (AUC = 0.943). This indicates that the biological shift separating severe cases from healthy conditions becomes more pronounced and statistically robust over a 48-to-72-h window. The observation that the PC is increasingly evident on the third day substantiates the theory of hepatic and renal impairment and suggests a gradual reduction in organ function. Thus, PC value may serve as a caution for healthcare practitioners to implement additional measures for the management of liver and kidney function.

This study provides a practical engineering and clinical solution: a non-invasive biosensing tool that eliminates the protracted 48-h observation window and complex multi-parameter scoring, enabling accurate severity triage within the crucial hours of hospital admission.

Nevertheless, the study offered a straightforward biosensor approach for quantifying concentrations; the data in Figure 3 indicate that alternative methods, such as standard laboratory BUN tests, can also ascertain PC values.

Despite the promising performance of the developed PC and $C_{urine\ urea}$, $C_{serum\ urea}$ in predicting SAP, several limitations of this study should be acknowledged. First, this was a single-center prospective observational study conducted at a single institution (Vilnius University Hospital Santaros Klinikos), which may introduce potential selection biases and limit the generalizability of the results to broader populations. Second, although the overall cohort size is adequate, the sample sizes within certain groups were relatively small, warranting cautious interpretation and larger-scale validation. Third, the study lacks external validation using an independent cohort from another clinical center. Future research should focus on multicenter prospective studies involving diverse patient demographics and pediatric populations to confirm the broader clinical utility of PC. Moreover, to examine the relevance of the PC specifically with partners from Ukraine in the context of emergency situations and investigate the application of PC in other areas of medical care, e.g., during peritoneal dialysis.

5 Conclusion

This investigation revealed that reduced urea excretion in urine is crucial for severe (S) or lethal outcomes (LO) in acute pancreatitis (AP). Furthermore, the ratio of urine to blood urea concentration ($C_{urine\ urea}/C_{serum\ urea}$) can statistically differentiate the severity of AP into M/MS and S/LO courses. On the basis of the ratio $C_{urine\ urea}/C_{serum\ urea}$, a prognostic criterion (PC) was developed to predict the severity of AP. It has been scientifically demonstrated that if the PC value is less than 15, the patient is at danger of a S course in AP or even LO. The use of the PC-based score is also appropriate on the second day of hospital admission. This is important if the patient did not seek medical attention in a timely manner and the AP process has already progressed, but organ damage is not yet visible.

ROC analysis convinced that the PC shows exceptional diagnostic accuracy in differentiating S/LO from healthy C, yielding an AUC of 0.969 (95% CI: 0.924–0.998). At an optimal cutoff of ≤ 19.55, the marker yields 88.0% sensitivity and a perfect specificity of 100.0%. The PC also efficiently differentiates between S/LO and M/MS status (AUC = 0.883), establishing a clear clinical threshold at ≤ 12.00 with 80.0% sensitivity and 86.5% specificity. The results of this investigation revealed that urine urea content below the norm is even more critical during the AP progress than BUN. Specifically, while serum urea levels showed acceptable early discrimination (AUC = 0.805 for M/MS vs. C) and urine urea excelled in late-stage differentiation (AUC = 0.921 for S/LO vs. C), the combined ratio synergized these individual trends into a singular robust index, yielding an outstanding AUC of 0.969 for severe status identification.

ROC analysis revealed that the classification power of the marker intensifies as time progresses that indicates that the biological shift separating severe cases from healthy conditions becomes more pronounced and statistically robust over a 48-to-72-h window.

For rapid and simple measuring urea concentration in biological samples, such as urine or blood serum the amperometric biosensor has been proposed. Given that researchers can measure PC using a compact biosensor response registration device and untreated urine or serum samples, this method could be invaluable in resource-constrained environments, such as Ukraine and other nations currently assisting refugees. Moreover, the method can be attributed to methods that possess reduced pain levels.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the authors declare that the work described has been carried out in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of VILNIUS UNIVERSITY (protocol code Nr.158200-17-941-455, date of approval 3 October 2017). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JR: Investigation, Conceptualization, Writing – original draft, Validation, Supervision. VG: Writing – original draft, Investigation, Methodology. IS-U: Writing – original draft, Validation, Data curation, Writing – review and editing.

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Conflict of interest

Authors JR, VG, and IS-U are named inventors of Lithuanian Patent No. LT7049B, entitled "Method for estimating the severity of acute pancreatitis", which is related to the subject matter of this manuscript. The patent is owned by Vilnius University and has not been licensed. The authors receive no direct financial benefit or royalties from the patent.

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