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ORIGINAL ARTICLE

Prediction of Outcome in Acute Pancreatitis by the qSOFA and the New ERAP Score

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Abstract

Background Early identification of patients with acute severe pancreatitis is important for prompt and adequate treatment. Existing scores for pancreatitis are often laborious or require serial patient evaluation, whereas the qSOFA score, that was established to predict outcome in patients with suspected infection, is simple to perform.

Aims and Methods In this cohort study, we analyse the potential of the qSOFA score to predict outcome of patients with acute pancreatitis and refine the qSOFA score by rapid available laboratory parameters to the emergency room assessment of acute pancreatitis (ERAP) score. Validation was performed in a separate patient cohort.

Results In total 203 patients with acute pancreatitis were recruited. The qSOFA score has the potential to predict ICU admission (AUC = 0.730, $p = 0.002$) and organ failure (AUC = 0.799, $p = 0.013$) in acute pancreatitis. Respiratory rate, mental status, blood urea nitrogen and C-reactive protein are the rapid available parameters with the highest individual impact in binary logistic regression analyses. Their combination to the ERAP score can predict severity of acute pancreatitis according to the revised Atlanta classification (AUC = 0.689 ± 0.041, $p < 0.001$), ICU admission (AUC = 0.789 ± 0.067, $p < 0.001$), multi-organ dysfunction syndrome (AUC = 0.963 ± 0.024, $p < 0.001$) and mortality (AUC = 0.952 ± 0.028, $p = 0.001$). The performance and prognostic validity for organ failure and mortality were validated in an independent patient cohort.

Conclusion The qSOFA is a rapidly available prognostic score in acute pancreatitis with limited prognostic validity. A combination with the laboratory parameters BUN and CRP results in the new ERAP score with outstanding prognostic validity for multi-organ dysfunction syndrome and mortality.

Keywords Acute pancreatitis · Organ failure · Mortality · Prognostic score · Early assessment

Introduction

With an incidence of 30–45/100.000 person years and a mortality of up to 5%, acute pancreatitis is a frequent and potentially lethal disease [1–4]. While the majority of patients have a mild course of the disease and recover within a few days, some patients develop a severe pancreatitis with critical local and systemic complications [5]. Patients can suffer a fulminant systemic inflammatory response syndrome (SIRS) with multiple organ dysfunction syndrome (MODS) or an acute respiratory distress syndrome (ARDS) in the early phase of acute pancreatitis [6]. Therefore, early identification of patients at risk is crucial for adequate management.

Computer-based algorithms of a plethora of risk factors including novel biomarkers and genetic information might soon enable us to calculate each patient's individual risk to

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suffer complications of acute pancreatitis during the course of the disease. But without all this information, initial patient evaluation has to rely on a few quickly available parameters.

For risk stratification, several pancreatitis specific or general scores like the Ranson- and the BISAP score or the APACHE II score have been established [1, 7, 8]. However, all these scores are of limited use in clinical routine as several parameters and/or longitudinal clinical re-evaluation are required. To estimate the risk of patients to suffer multiple organ failure, the sequential organ failure assessment (SOFA) score has recently been developed and is by now the defining criterion of sepsis. In addition, the quick SOFA score (qSOFA) including respiratory rate, systolic blood pressure and altered mentation was validated for rapid preclinical patient evaluation or the emergency room setting and recommended in the sepsis-3 guideline [9–11]. In contrast to the SOFA score, the qSOFA score has not yet been demonstrated to be a reliable predictor of mortality in patients with acute pancreatitis [12, 13]. However, given its extraordinary simplicity, the qSOFA score would be an appropriate score particularly for the initial patient evaluation in the emergency. Since the qSOFA score is part of the sepsis guideline, it is routinely calculated for internal patients presenting to our emergency room.

Primary objective of this study is to analyse the potential of the qSOFA score to predict severity, need for intensive care treatment, development of MODS and mortality in patients with acute pancreatitis.

Secondary objective is to compare the prognostic potential of qSOFA to established scores including Ranson-, BISAP- and SOFA score as well as laboratory markers including C-reactive protein (CRP), blood urea nitrogen (BUN) and hematocrit.

Tertiary objective is to evaluate if the combination of the qSOFA score with established laboratory markers can improve the prognostic validity and, if applicable, to validate this new prognostic tool in a retrospective patient cohort.

Methods

For this cohort study, patients presenting with acute pancreatitis to the emergency department at the tertiary referral center Klinikum rechts der Isar der Technischen Universität München from June 2018 to February 2020 were enrolled. Exclusion criteria were as follows: symptom onset > 72 h before admission, analgosedation, intubation or vasopressor therapy at admission or referral, age < 18 years and pregnancy. For the diagnosis of acute pancreatitis, two of the following criteria were required: Elevated serum lipase activity above 3 times of the upper limit of the reference range, typical clinical presentation including acute onset of epigastric pain and abdominal tenderness, typical imaging findings in ultrasound or computed tomography. Acute pancreatitis was classified according to the revised Atlanta classification [6]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of HELSINKI as reflected in a prior approval by the institution's human research committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, project number 216/18 S) on June 12, 2018. Due to the strictly observational design of the study written, informed consent was waived. The study was registered at the German Clinical Trial Registry (No. DRKS00023141). All relevant data are included in the article or provided as supplementary tables.

Four endpoints were analyzed as outcome parameters: severity of acute pancreatitis according to the revised Atlanta classification, admission to intensive care unit (ICU), MODS and in-hospital mortality. Admission to ICU was a clinical decision depending on the condition of the patient. The qSOFA score was compared to the established prognostic tools Ranson score, BISAP score, the sepsis defining SOFA score and the rapidly and routinely available laboratory prognostic parameters C-reactive protein (CRP), blood urea nitrogen (BUN) and hematocrit. Cut-offs for CRP (15 mg/dl), BUN (8.9 mmol/l) and hematocrit (44%) were used as previously defined by Pongprasobchai et al., the BISAP score and Brown et al. [9–11, 14–17] The scores were obtained at admission and—if necessary—completed within 48 h.

A binary logistic regression model was used to evaluate the independent effect of the individual qSOFA parameters and univariate significant laboratory prognostic parameters on the course and outcome of acute pancreatitis. Factors with a high independent prognostic impact were combined and make up the new emergency room assessment of acute pancreatitis (ERAP) score. The prognostic accuracy of the combined parameters was tested retrospectively in a previous patient cohort. This patient cohort consists of 223 patients who presented to our emergency department with acute pancreatitis between November 2009 and January 2016.

Statistical analysis was performed using IBM SPSS Statistics 25 (SPSS Inc, Chicago, Illinois, USA). Samples were checked for normal distribution using the Shapiro–Wilk test. Descriptive data of normally distributed parameters are presented as mean ± standard deviation and as median and range for non-parametric parameters. The Mann–Whitney-U and Kruskas–Wallis tests were used to analyse non-parametric variables and the t-test and a one-way analysis of variances (ANOVA) to analyse variables with normal distribution. To compare qualitative parameters, chi-square test and in small samples (expected frequency of test variable less than 5) Fisher's exact test was used. All statistical tests were two-sided with a level of significance (p-value) of 5%. Receiver operating characteristics (ROC) curve analysis was used to compare

different prognostic scores and laboratory parameters. The scores and parameters were classified according to their area under the curve (AUC) value in acceptable (AUC 0.7–0.79), excellent (AUC 0.8–0.89) and outstanding (AUC 0.9–1) prognostic tools [18]. To control the false discovery rate due to multiple testing, p was adjusted (adj. *p*) by the Benjamini Hochberg procedure if necessary. To improve the predictive validity of the qSOFA score established, laboratory markers to predict severity of acute pancreatitis were evaluated in our patient cohort. The qSOFA parameters and laboratory markers with $p < 0.05$ in univariate analysis were analyzed in a binary logistic regression model with 'enter' as variable selection method.

Table 1 Patients characteristics

Age	56.1 ± 17.3
Gender (♂: ♀)	1.3: 1
Etiology	*n* (%)
Alcoholic	97/203 (47.8%)
Biliary	62/203 (30.5%)
Idiopathic	24/203 (11.8%)
Hypertriglyceridemia	11/203 (5.4%)
Drug induced	7/203 (3.4%)
Autoimmune	2/203 (1%)
History of chronic pancreatitis	66/203 (32.5%)
Atlanta classification	
Mild	130/203 (64%)
Moderately severe	59/203 (29%)
Severe	14/203 (6.9%)
Admission to ICU	14/203 (6.9%)
Median days on ICU (range)	8.5 (1–76)
multi-organ dysfunction syndrome > 48 h	5/203 (2.5%)
Necrotizing pancreatitis	17/203 (8.4%)
Mortality	5/203 (2.5%)

Results

In total, 203 patients with acute pancreatitis were included in the study. Patient characteristics are reported in Table 1.

CRP and BUN are distributed differently between mild versus moderately severe and severe pancreatitis according to the revised Atlanta classification. Also, Ranson, BISAP, SOFA and qSOFA score significantly differ between these two groups. Although the median qSOFA score is the same, the distribution is significantly different and moderately severe, and severe cases of acute pancreatitis are associated with higher qSOFA values. Details about prognostic markers and scores concerning the revised Atlanta classification are reported in Table 2.

qSOFA

Of the 203 patients with acute pancreatitis, 179 have a qSOFA score of 0, 21 have a qSOFA score of 1 and 3 a score of 2. No patient has a qSOFA score of 3. The qSOFA score is statistically significant in predicting ICU admission and MODS. The best sensitivity and specificity is achieved with a cut-off of ≥ 1 (sensitivity 53%, specificity 92% for ICU admission, 67% and 90% for MODS, respectively). The qSOFA score has an AUC of 0.73 (ICU admission) and 0.79 (MODS) in patients with acute pancreatitis.

Regarding sensitivity and specificity, most parameters and scores are only acceptable predictors of a moderately severe or severe pancreatitis. Figure 1 displays ROC curve analysis comparing those scores and parameters as predictors of the primary endpoints and Table 3 shows the corresponding AUC values.

The best score/parameters to predict severity of acute pancreatitis according to the revised Atlanta classification are the Ranson score, SOFA score and BUN. Yet, they have only acceptable AUC values. The best prognostic score for ICU admission in patients with pancreatitis is the Ranson

Table 2 Prognostic parameters /scores (range) and severity of acute pancreatitis

Risk parameter/score	All patients	Revised Atlanta classification		*p*
		Mild	Moderately severe and severe	
Hematocrit (%)	40.8 (19.7–63.5)	40.8 (23.1–47.0)	40.8 (19.7–63.5)	0.692
CRP (mg/dL)	1.5 (0.1–34.6)	1.4 (0.1–30.3)	3.0 (0.1–34.6)	**0.001**
BUN (mg/dL)	15 (4–58)	12 (7–24)	16 (4–68)	**< 0.001**
Ranson	2 (0–7)	1 (0–5)	3 (0–7)	**< 0.001**
BISAP	1 (0–4)	0 (0–4)	1 (0–4)	**< 0.001**
SOFA	0 (0–16)	0 (0–6)	2 (0–16)	**< 0.001**
qSOFA	0 (0–2)	0 (0–2)	0 (0–2)	**0.004**

Results in bold are significant with $p < 0.05$

CRP C-reactive protein; *BUN* blood urea nitrogen

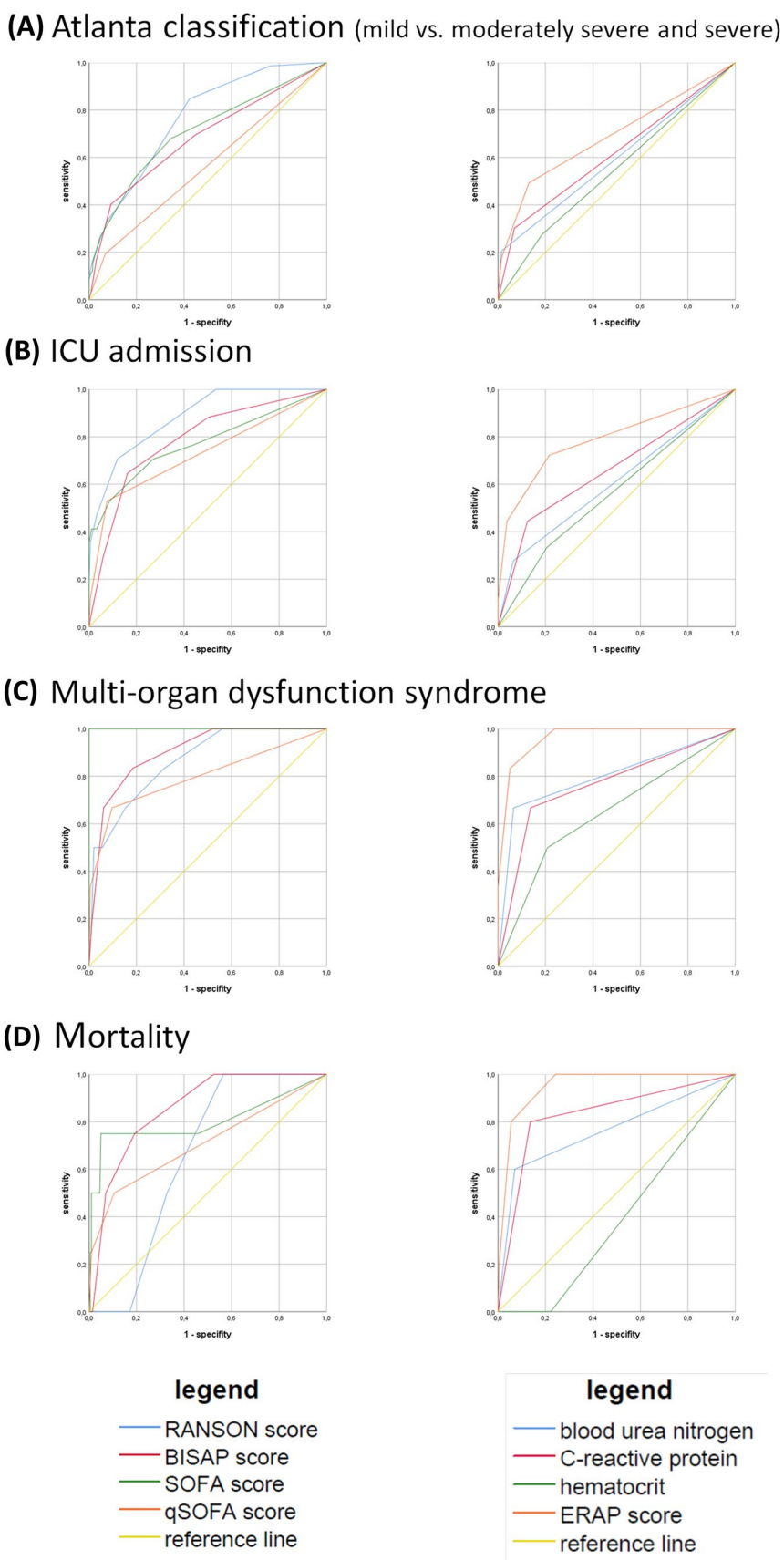

Fig. 1 Receiver operating characteristic (ROC) curve analysis of Ranson, BISAP, SOFA, qSOFA and ERAP score as well as C-reactive protein (CRP), blood urea nitrogen (BUN) and hematocrit

Table 3 AUC values of prognostic scores and parameters (AUC: area under the curve)

Score	AUC	Standard deviation	95% confidence interval		p (adj.$p = 0.032$)
Atlanta classification					
Ranson	0.765	0.033	0.699	0.831	**< 0.000**
BISAP	0.683	0.041	0.603	0.763	**0.000**
SOFA	0.706	0.040	0.628	0.784	**0.000**
qSOFA	0.563	0.043	0.478	0.648	0.139
BUN	0.595	0.043	0.510	0.680	**0.025**
CRP	0.616	0.043	0.532	0.700	**0.006**
Hematocrit	0.545	0.043	0.461	0.628	0.291
ICU admission					
Ranson	**0.883**	0.039	0.806	0.960	**0.000**
BISAP	0.786	0.060	0.668	0.903	**0.000**
SOFA	0.771	0.074	0.627	0.915	**0.000**
qSOFA	0.730	0.077	0.579	0.881	**0.002**
BUN	0.606	0.078	0.454	0.759	0.136
CRP	0.660	0.076	0.512	0.808	**0.025**
Hematocrit	0.564	0.074	0.418	0.710	0.371
Multi-organ dysfunction syndrom					
Ranson	**0.864**	0.068	0.732	0.997	**0.002**
BISAP	**0.902**	0.054	0.797	1.000	**0.001**
SOFA	**1.000**	0.000	1.000	1.000	**0.000**
qSOFA	0.799	0.119	0.566	1.000	**0.013**
BUN	**0.800**	0.116	0.572	1.000	**0.012**
CRP	0.765	0.115	0.540	0.990	**0.027**
Hematocrit	0.646	0.124	0.402	0.890	0.224
Mortality					
Ranson	0.652	0.064	0.525	0.778	0.300
BISAP	**0.856**	0.072	0.715	0.997	**0.015**
SOFA	**0.802**	0.159	0.490	1.000	0.039
qSOFA	0.708	0.160	0.393	1.000	0.155
BUN	0.765	0.134	0.502	1.000	0.043
CRP	**0.832**	0.105	0.626	1.000	**0.011**
Hematocrit	**0.389**	0.103	0.186	0.592	0.396

Results in bold are significant with $p < 0.05$

score with an excellent AUC. Due to similar definitions, the SOFA score very accurately predicts patients who are at risk to develop a MODS. According to the AUC, the BISAP score is an outstanding tool and the Ranson score as well as BUN are excellent predictors of MODS.

The BISAP- and SOFA scores as well as CRP are excellent predictors of mortality in acute pancreatitis.

Emergency Room Assessment of Acute Pancreatitis (ERAP) Score

To analyse the individual qSOFA parameters for their independent prognostic power, the endpoint MODS is used as the qSOFA score has its best AUC for the prediction of MODS in acute pancreatitis. In univariate analysis, BUN above 8.9 mmol/l (66.7% vs. 6.6%, $p < 0.001$) and CRP above 15 mg/dl (66.7% vs. 13.7%, $p = 0.005$) are significantly associated with MODS as opposed to hematocrit above 44% (50% vs. 20.8%, $p = 0.117$). In a binary logistic regression model with MODS as dependent variable and respiratory rate > 21/min, systolic blood pressure < 101 mmHg, GCS < 15, BUN > 8.9 mmol/l and CRP > 15 mg/dl as independent variables, all prognostic variables but systolic blood pressure are statistically significant independent prognostic parameters. Details on the regression model are reported in Table 4.

The ERAP score consisting of two clinical parameters (respiratory rate > 21/min and GCS < 15) and two laboratory parameters (BUN > 8.9 mmol/l and CRP > 15 mg/dl) can statistically significantly predict severity of acute pancreatitis (AUC 0.689 ± 0.041, $p < 0.001$), ICU admission (AUC 0.789 ± 0.067, $p < 0.001$), MODS (AUC 0.963 ± 0.024, $p < 0.001$) and mortality (AUC 0.952 ± 0.028, $p = 0.001$). Corresponding ROC-curves are displayed in Fig. 1. An ERAP > 1 predicts MODS with a sensitivity of 83.3% and a specificity of 94.9% and mortality with 80% and 94.4%, respectively.

Table 4 Binary logistic regression model with MODS as dependent variable

Variable	Regression coefficient B	Standard error	Adjusted odds ratio (expB)	95% CI of adjusted odds ratio		p
BUN > 8.9 mmol/l	2.98	1.26	19.74	1.68	231.69	**0.018**
AF > 21/min	3.81	1.38	45.14	3.01	676.94	**0.006**
GCS < 15	3.36	1.55	28.81	1.38	603.44	**0.030**
Syst. blood pressure < 101 mmHg	0.77	2.95	2.16	0.01	695.05	0.794
CRP < 15 mg/dl	2.79	1.34	16.33	1.19	223.97	**0.037**

Results in bold are significant with $p < 0.05$

R^2 (Nagelkerke) = 0.598; $p < 0.001$

ERAP Validation

To validate the accuracy of the ERAP score in predicting outcome in acute pancreatitis, the score was retrospectively applied on a previous patient cohort of 223. Mean age (54 ± 18 years) and gender distribution (♂: ♀ 1.4:1) are comparable to our study cohort. Patient characteristics of the validation cohort are displayed in supplementary Table 1 and AUC values for the prediction of ICU admission, MODS, and mortality in Table 5.

Discussion

Acute pancreatitis is the third most common diagnosis at discharge of hospitalized patients in gastroenterology and hepatology in the United States [19]. As only few of those patients develop a severe pancreatitis but patients with severe pancreatitis have a mortality of up to 30% it is important to early identify patients at risk of a severe pancreatitis [20, 21]. For this reason, prognostic scores and markers were evaluated and established in recent decades. An ideal prognostic marker is quick and easy to obtain and widely available at hospital admission of the patient. Established laboratory markers like CRP are well validated and can accurately predict outcome in acute pancreatitis. However, previous studies evaluating CRP as predictor in acute pancreatitis showed the best results for CRP 24 h after admission in contrast to markedly lower negative and positive predictive values at the time of admission [1]. Sepsis with hyper-inflammation resulting in hypovolemic shock shares similar pathogenic features with acute pancreatitis. Also, early recognition and adequate treatment is essential for the outcome in both diseases [22]. The qSOFA score is quick and easy to obtain and has an excellent predictive validity for mortality in sepsis, particularly outside of an ICU, i.e., out-of-hospital, in the emergency department, or on a general hospital ward [9]. So far, the qSOFA score has not been associated with a complicated course of acute pancreatitis [23]. According to our data, the qSOFA score can predict ICU admission and MODS in acute pancreatitis. There is also an association of the qSOFA score to the severity of pancreatitis although the predictive validity is not significant in ROC curve analysis. However, the prognostic validity of the qSOFA score according to its AUC values is limited and particularly the Ranson- and BISAP scores, that were developed and validated for acute pancreatitis, have better AUC values. However, the BISAP score consists of 8 different parameters and especially the Ranson score requires repeated assessment of clinical and laboratory parameters. Thus, to get a quick but reliable prognostic tool, we modified the qSOFA score and identified two clinical and two laboratory parameters with high prognostic impact. Altered mentation and respiratory rate as clinical parameters of the qSOFA score and CRP and BUN as quickly and routinely available laboratory parameters were selected. We named the combination of these parameters '**E**mergency **R**oom **A**ssessment of acute **P**ancreatitis'—ERAP score. Similar to the BISAP score, the ERAP score can be calculated with routinely available clinical and laboratory parameters at initial patient presentation. However, by reducing the required parameters from 8 to only 4, the ERAP score provides an extraordinarily feasible screening tool.

The ERAP score has outstanding AUC values for predicting MODS and mortality and an acceptable AUC for ICU admission. Only the Ranson score, which is laborious to calculate, is superior in predicting ICU admission. In general, AUC values of all prognostic parameters are lowest for the prediction of severity. This can be explained by the fact, that some of the scores were established before publication of the revised Atlanta classification in 2012. In addition, the revised Atlanta classification defines the severity of pancreatitis by local as well as systemic complications that can occur early and late in the course of the disease like walled off necrosis. Such heterogeneous complications in pathogenetically different states of the disease are by nature hard to predict by selected parameters.

The ERAP score was validated in an existing patient cohort that is comparable to the study cohort and sensitivity, and specificity rates did not differ between the validation cohort and the study cohort. This confirms the potential of the ERAP score as quick and easy score to assess the risk of

Table 5 Validation of the ERAP score in predicting the outcome of acute pancreatitis

	n	AUC	SD	*p*	95% CI		PPV (%)	NPV (%)
ICU admission	47/223	**0.787**	0.042	0.000	0.703	0.870	**73.1**	**85.8**
Multiorgan dysfunction syndrome	14/223	**0.922**	0.025	0.000	0.872	0.971	**34.6**	**97.5**
Mortality	11/223	**0.887**	0.059	0.000	0.772	1.000	**30.8**	**98.5**

Results in bold are significant with $p < 0.05$

AUC area under the curve, *SD* standard deviation, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

organ failure and mortality in patients with acute pancreatitis within the first hour at the emergency department.

Limitations of the Study

Although the prognostic potential of the qSOFA score and the new ERAP score were analyzed and established with prospective patient data, validation of the ERAP score was performed on an existing patient cohort. Also both cohorts were recruited at a single center which inherits the risk of a referral bias. AUC values of established scores and markers in our patient cohort are comparable to reported data [7, 8]. With an AUC above 0.8, sensitivity and specificity of the SOFA score are further in line with recent publications [13]. Contrary to previous reports, the SOFA score is statistically just not significant in predicting mortality after multiple testing adjustment, which might be due to a comparably low mortality rate. However, the statistical power of the data should be interpreted with caution due to the low number of patients at risk for rare end points, like mortality, and its validation in a retrospective patient cohort. Prospective confirmation of the results in a larger multicenter cohort would be desirable.

Conclusion

The qSOFA is a rapidly available prognostic score with limited prognostic value in acute pancreatitis. Combining the two qSOFA criteria respiratory rate and mental status with the laboratory parameters BUN and CRP results in the emergency room assessment of acute pancreatitis (ERAP) score, which is a sensitive prognostic score for the prediction of MODS and mortality in acute pancreatitis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-021-06945-z.

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Declaration

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of HELSINKI and its later amendments or comparable ethical standards.

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