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## Performance of quick sequential organ failure assessment and modified age disease adjusted qadSOFA for the prediction of outcomes in emergency general surgery patients

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BACKGROUND: Sepsis is a highly prevalent condition and is associated with a reported in-hospital mortality rate up to 40% in patients with abdom-

inal sepsis requiring emergency general surgery (EGS). The quick sequential organ failure assessment score (qSOFA) has not been

studied for EGS patients.

METHODS: Retrospective cohort study in adult patients undergoing abdominal EGS at a university tertiary care center from 2016 to 2018. The

primary outcome was mortality. The effect of clinical variables on outcomes was assessed in univariable and multivariable logistic regression analyses. Based on these results, the qSOFA score was modified. The performance of scores was assessed using receiver

operating characteristics.

RESULTS: Five hundred seventy-eight patients undergoing abdominal EGS were included. In-hospital mortality was 4.8% (28/578). Indepen-

dent predictors for mortality were mesenteric ischemia (odds ratio [OR] 15.9; 95% confidence interval [CI] 5.2–48.6; p < 0.001), gastrointestinal tract perforation (OR 4.9; 95% CI 1.7–14.0; p = 0.003), 65 years or older (OR 4.1; 95% CI 1.5–11.4; p = 0.008), and increasing qSOFA (OR 1.8; 95% CI 1.2–2.8; p = 0.007). The modified qSOFA (qadSOFA) was developed. The area under the receiver operating characteristic curve of the qSOFA and qadSOFA for mortality was 0.715 and 0.859, respectively. Optimal cutoff

value was identified as qadSOFA  $\geq$  3 (Youden Index 64.1%).

**CONCLUSION:** This is the first study investigating the qSOFA as a predictor for clinical outcomes in EGS. Compared with the qSOFA, the new

qadSOFA revealed an excellent predictive power for clinical outcomes. Further validation of qadSOFA is warranted. (J Trauma

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LEVEL OF EVIDENCE: Diagnostic test/criteria; Level II.

**KEY WORDS:** Emergency general surgery; quick sequential organ failure assessment score (qSOFA); quick age disease sequential organ failure

assessment score (qadSOFA); sepsis; mortality.

**S** epsis is a highly prevalent condition and is associated with a 10% to 20% in-hospital mortality rate, exceeding up to 30% to 40% in patients with abdominal sepsis requiring surgery. <sup>1-6</sup> In this group of patients, adequate preoperative prediction of outcomes is crucial for the acute decision making. <sup>7</sup>

In 2016, the quick sequential (sepsis-related) organ failure assessment score (qSOFA) was introduced.8 The qSOFA includes three criteria with a maximum of three points: altered mentation (Glasgow Coma Scale [GCS] score, ≤14), hypotension (systolic blood pressure, ≤100 mm Hg), and tachypnea (respiratory rate, ≥22/min). The original SOFA grades the abnormality by organ system and takes into account the respiratory function (PaO<sub>2</sub>/FIO<sub>2</sub>), coagulation (platelets), liver function (bilirubin), cardiovascular function (vasopressor dosage), altered mentation (GCS score), and renal function (creatinine or urine output). The advantage of the qSOFA is given by its simplicity—particularly in situations and conditions where not all components of the SOFA are available, such as in an emergency department (ED) or on the surgical ward. Several studies have investigated the predictive value of the SOFA and qSOFA in various groups of patients with conflicting results regarding prognostic value e.g., area under the receiving operator curve for mortality in suspected infection (SOFA, 0.79; 95% CI 0.78–0.80 vs. qSOFA, 0.81; 95% CI 0.80–0.82). Currently, the 2021 surviving sepsis campaign advocated against the use of qSOFA as a single screening tool due to the poor sensitivity.

However, the usefulness of the qSOFA for patients requiring emergency general surgery (EGS) for acute abdominal diseases specifically has not been studied so far. Moreover, a recent international multisociety consensus guideline does not provide a clinically applicable pathway on how to early identify EGS patients at risk for sepsis.<sup>7</sup>

The aim of this study was (1) to assess the accuracy of the qSOFA to predict in-hospital mortality and the need for higher level of care (intensive care unit [ICU] admission and need for mechanical ventilation) and (2) to improve the score regarding the prognostic value in patients undergoing abdominal EGS. We hypothesized that the predictive power of the qSOFA is (1) of limited predictive value in an EGS population and (2) can be improved by modifying the score using the specific characteristics of the investigated patient population.

## **PATIENTS AND METHODS**

This retrospective cohort study included adult patients undergoing abdominal EGS at a tertiary hospital looking at the performance of the qSOFA in predicting clinical outcomes and aiming to improve the discriminatory power of the score. The study has been approved by the local ethics committee (Project BASEC-ID 2019–02338).

## **Data Collection**

Adult patients (age ≥18 years) undergoing EGS for mesenteric ischemia (MI), gastrointestinal (GIT) perforation, bowel obstruction, cholecystitis, appendicitis, or incarcerated hernia at a tertiary university hospital, between January 1, 2016, and December 31, 2018, were retrospectively included. Patients with documented objection to general consent, other surgical interventions (e.g., nontraumatic bleeding, pancreatic necrosectomy,

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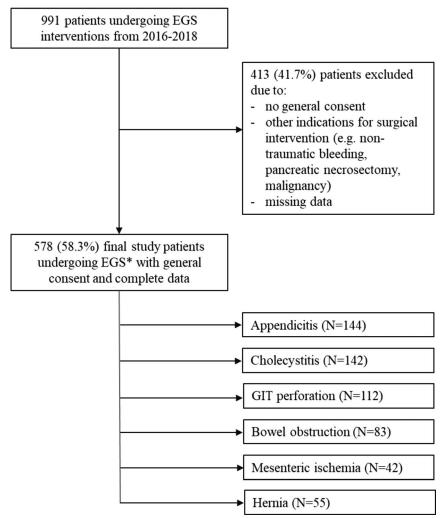


Figure 1. Study Outline. \*Undergoing surgery for either of the following diseases: appendicitis, cholecystitis, GIT perforation, bowel obstruction, MI or hernia.

malignancy) or incomplete data were excluded. Patient demographics, disease, treatment and outcome variables were extracted from electronic medical records. The qSOFA on admission to the ED was calculated according to the Sepsis-3 guideline<sup>8</sup> including the following criteria: systolic blood pressure of 100 mmHg or lower (1 point), respiration rate of 22 breaths per minute or greater (1 point), and altered mentation defined as decreased neurology as GCS score of 14 or less (1 point).

## **Definitions**

Gastrointestinal perforation was defined as gastric or duodenal perforation, small/large bowel perforation, or anastomotic leakage. Bowel obstruction included small or large bowel obstruction. The diagnosis of MI was based on intraoperative confirmation of findings. In case of bowel perforation due to an incarcerated hernia, the patient was categorized to the GIT perforation subgroup. Significant morbidity was defined as a complication requiring at least a surgical, endoscopic or radiological intervention, corresponding to a Dindo-Clavien classification of ≥3a.<sup>22,23</sup>

#### **Outcomes**

The primary goal of this study was to assess the predictive power of the qSOFA score for the primary outcome (in-hospital mortality) and secondary outcomes (ICU admission, and mechanical ventilation). The secondary goal was to improve the discriminatory power qSOFA score based on the specific characteristics of this patient population.

## **Statistical Analysis**

Categorical variables were reported as numbers and percentages, continuous variables as medians and interquartile ranges (IQR). Normality of data distribution of continuous variables was assessed using normal distribution plots, inspection of histograms, skewness, and the Shapiro-Wilk test. Categorical and continuous variables were compared using Pearson  $\chi^2$  test and Mann-Whitney U test, respectively.

Multivariable forward logistic regression analysis was applied to identify potential independent predictors for mortality, ICU admission and the need for mechanical ventilation. Variables with *p* values less than 0.20 in univariable analysis were entered into the equation of the forward logistic regression

TABLE 1. Effect of Patient and Disease Characteristics on Mortality

	Total	Survivors	Non-survivors	OR (95% CI)	<i>p</i> **
n=	578	550	28		
Age ≥65 years	260 (45%)	237 (91.2%)	23 (8.8%)	6.08 (2.28–16.21)	< 0.001
Age*	60 (44–75)	59 (43–74)	78 (69–84)	1.06 (1.03-1.09)	< 0.001
Male	314 (54.3%)	298 (94.9%)	16 (5.1%)	1.13 (0.52-2.43)	0.759
BMI $[kg/m^2]$ *	26.0 (22.8-29.1)	26.0 (22.8-29.1)	26.6 (22.4-31.0)	1.00 (0.98-1.03)	0.906
MI	42 (7.3%)	31 (73.8%)	11 (26.2%)	10.83 (4.67–25.11)	< 0.001
GIT perforation	112 (19.4%)	101 (90.2%)	11 (9.8%)	2.88 (1.31-6.33)	0.006
Gastric duodenal perforation	28 (4.8%)	27 (96.4%)	1 (3.6%)	0.72 (0.09-5.48)	0.748
Small bowel perforation	18 (3.1%)	16 (88.9%)	2 (11.1%)	2.57 (0.56-11.76)	0.209
Colon perforation	44 (7.6%)	36 (81.8%)	8 (18.2%)	5.71 (2.35-13.86)	< 0.001
Anastomotic leakage	22 (3.8%)	22 (100%)	0 (0%)	-	0.281
Bowel obstruction	83 (14.4%)	79 (95.2%)	4 (4.8%)	0.99 (0.34-2.94)	0.991
Small bowel obstruction	54 (9.3%)	52 (96.3%)	2 (3.7%)	0.74 (0.17-3.19)	0.682
Large bowel obstruction	29 (5%)	27 (93.1%)	2 (6.9%)	1.49 (0.34-6.61)	0.598
Cholecystitis	142 (24.6%)	140 (98.6%)	2 (1.4%)	0.23 (0.05-0.96)	0.028
Appendicitis	144 (24.9%)	144 (100%)	0 (0%)	-	0.002
Hernia	55 (9.5%)	55 (100%)	0 (0%)	-	0.079
GCS score ≤14	61 (10.6%)	50 (82%)	11 (18%)	6.47 (2.87–14.58)	< 0.001
GCS score*	15 (15–15)	15 (15–15)	15 (14–15)	0.78 (0.69-0.87)	< 0.001
sBP ≤100 mmHg	128 (22.1%)	114 (89.1%)	14 (10.9%)	3.82 (1.77-8.25)	< 0.001
sBP [mmHg]*	120 (103-138)	120 (104–138)	101 (81-138)	0.98 (0.97-1.00)	0.011
Respiration rate ≥22/min	275 (47.6%)	254 (92.4%)	21 (7.6%)	3.50 (1.46-8.36)	0.003
Respiration rate [/min]*	21 (15–25)	21 (15–25)	24 (18-30)	1.04 (1.00-1.08)	0.025
qSOFA 0 pts	249 (43.1%)	243 (97.6%)	6 (2.4%)	0.34 (0.14-0.86)	0.018
qSOFA 1 pts	220 (38.1%)	213 (96.8%)	7 (3.2%)	0.53 (0.22-1.26)	0.144
qSOFA 2 pts	83 (14.4%)	77 (92.8%)	6 (7.2%)	1.68 (0.66-4.26)	0.274
qSOFA 3 pts	26 (4.5%)	17 (65.4%)	9 (34.6%)	14.85 (5.87–37.59)	< 0.001
qSOFA ≥2 pts	109 (18.9%)	94 (86.2%)	15 (13.8%)	5.60 (2.58–12.15)	< 0.001

sBP, systolic blood pressure; qSOFA, quick sequential organ failure assessment score; BMI, body mass index; 95% CI, 95% confidence interval; pts, points; \*, Values are medians (interquartile ranges (IQR)); \*\*, Pearson  $\chi^2$  or Mann-Whitney U test.

TABLE 2. Primary and Secondary Outcome Analysis Stratified According qSOFA and qadSOFA

		Mortality		ICU Admission		Ventilation	
		n/n	Proportion (95% CI)	n/n	Proportion (95% CI)	n/n	Proportion (95% CI)
qSOFA	0	6/249	2.4% (1%-4.9%)	26/249	10.4% (7.1%–14.7%)	15/249	6.0% (3.6%–9.5%)
	1	7/220	3.2% (1.4%–6.1%)	46/220	20.9% (15.9%–26.6%)	29/220	13.2% (9.2%-18.1%)
	2	6/83	7.2% (3.1%–14.3%)	32/83	38.6% (28.6%–49.3%)	25/83	30.1% (21.1%-40.5%)
	3	9/26	34.6% (18.7%–53.7%)	21/26	80.8% (62.9%–92.3%)	20/26	76.9% (58.5%–89.7%)

		Mortality		ICU admission		Ventilation	
		n/n	Proportion (95% CI)	n/n	Proportion (95% CI)	n/n	Proportion (95% CI)
qadSOFA	0	1/151	0.7% (0.1%-3.1%)	3/151	2.0% (0.6%-5.2%)	1/151	0.7% (0.1%-3.1%)
	1	2/158	1.3% (0.3%–4%)	16/158	10.1% (6.1%–15.5%)	6/158	3.8% (1.6%–7.7%)
	2	1/126	0.8% (0.1%-3.6%)	26/126	20.6% (14.3%–28.3%)	15/126	11.9% (7.1%–18.4%)
	3	5/70	7.1% (2.8%–14.9%)	29/70	41.4% (30.4%–53.1%)	22/70	31.4% (21.5%-42.9%)
	4	9/40	22.5% (11.8%–37.1%)	22/40	55.0% (39.7%–69.6%)	17/40	42.5% (28.1%–57.9%)
	5	5/22	22.7% (9.2%–42.9%)	19/22	86.4% (67.9%–96.0%)	18/22	81.8% (62.4%–93.5%)
	6	2/5	40.0% (9.4%–79.1%)	4/5	80.0% (37.1%–97.7%)	4/5	80.0% (37.1%–97.7%)
	7	3/6	50.0% (16.7%–83.3%)	6/6	100.0% (100%–100%)	6/6	100.0% (100%–100%)

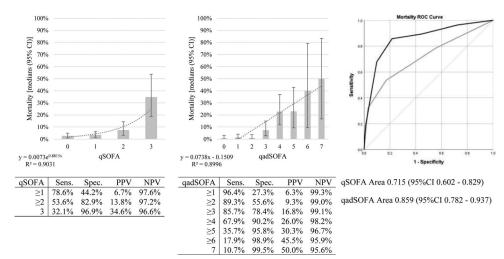


Figure 2. Diagnostic Ability and Test Performance of qSOFA vs. qadSOFA to Predict Mortality. Description: Cutoff values are calculated comparing to patients in all subgroups with lower than cutoff values, e.g. qSOFA≥1 vs. qSOFA = 0. Abbreviations: Sens., sensitivity; Spec., specificity. Color coding: black, qadSOFA; gray qSOFA.

model. A *p* value of 0.05 or less was considered statistically significant. Effect sizes were reported as odds ratio (OR) with 95% confidence intervals (CI). Different thresholds for age were assessed. The qSOFA score was modified according to the results of the multivariable regression analysis. Variables that were independently associated with the reported primary outcome were included in the modified qSOFA and weighted based on the OR.

The performance of the qSOFA and the modified qSOFA was assessed using area under the receiver operating characteristics (AUROC) curves, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Optimal cutoff values were determined on the ROC curve using the maximum Youden

index [sensitivity -(1 - specificity)]. Acceptable Youden index was defined as 50% or greater.

Statistical analysis was performed using SPSS Statistics version 25 (IBM Corporation, Armonk, NY). Reporting of this diagnostic study is undertaken in accord with the STARD guidelines (Supplemental Digital Content, http://links.lww.com/TA/C638).<sup>24</sup>

## **RESULTS**

## **Patient Population**

A total of 991 patients underwent EGS interventions for various reasons during the entire three study years. Of these, 578 patients (58.3%) were finally enrolled for further analysis

**TABLE 3.** Independent Predictors for Mortality, ICU, and Mechanical Ventilation

		OR	95% CI				
	Variables		Lower	Upper	p	Nagelkerke R <sup>2</sup>	Cox and Snell R <sup>2</sup>
Mortality	MI	15.947	5.234	48.585	< 0.001		_
	GIT perforation	4.858	1.690	13.963	0.003		
	Age ≥65 y	4.059	1.446	11.394	0.008		
	qSOFA	1.825	1.175	2.834	0.007	0.305	0.098
ICU	MI	8.564	3.590	20.426	< 0.001		
	Age ≥65 y	3.316	1.943	5.658	< 0.001		
	qSOFA	2.173	1.624	2.909	< 0.001		
	GIT perforation	1.847	1.002	3.404	0.049		
	Cholecystitis	0.277	0.131	0.586	0.001		
	Appendicitis	0.165	0.054	0.502	0.002	0.435	0.282
Ventilation	MI	24.664	10.413	58.424	< 0.001		
	Age ≥65 y	6.271	3.217	12.221	< 0.001		
	GIT perforation	4.266	2.289	7.950	< 0.001		
	qSOFA	2.503	1.802	3.478	< 0.001	0.459	0.264

Stepwise forward logistic regression analysis including all variables with p value <0.20 in univariable analysis: 65 years or older, appendicitis, cholecystitis, hernia, MI, GIT perforation (as composite/co-linearity of gastric duodenal perforation, small bowel perforation, colon perforation, anastomotic leakage), qSOFA (as composite/colinearity of: sBP  $\leq$  100 mm Hg, respiration rate  $\geq$ 22 and GCS score  $\leq$  14).

TABLE 4. Calculation of the qadSOFA

Variables	Points
Systolic blood pressure ≤100 mmHg	+1
Respiration rate ≥22 breaths per minute	+1
GCS score ≤14	+1
Age ≥65 y	+1
Disease	
Gastrointestinal perforation	+1
MI	+3
	0–7
	Systolic blood pressure ≤100 mmHg Respiration rate ≥22 breaths per minute GCS score ≤14 Age ≥65 y Disease Gastrointestinal perforation

(Fig. 1). Table 1 is showing the demographics, disease characteristics and vital signs on ED admission for the entire study population. Median age was 60 years (IQR 44–75 years). The majority were male (54.3%, 314/578). Median body mass index was 26.0 kg/m² (IQR 22.8–29.1 kg/m²). Indications for EGS included acute appendicitis (24.9%, 144/578), acute cholecystitis (24.6%, 142/578), GIT perforation (19.4%, 112/578), bowel obstruction (14.4%, 83/578), incarcerated hernia (9.5%, 55/578), and MI (7.3%, 42/578).

Overall, observed in-hospital mortality was 4.8% (28/578) (Table 1 and Table 2). The highest mortality rate was found in patients with MI (26.2%%, 11/42) and large bowel perforation (18.2%, 8/44). Median hospital length of stay and ICU length of stay were 5 days (IQR 3–10 days) and 3 days (IQR 1–6 days), respectively. Severe complications (Dindo-Clavien Classification ≥3a) occurred in 15.6% (90/578) of patients.

## Diagnostic Ability and Test Performance of the qSOFA

Table 1 and 2 are showing mortality rates stratified according the qSOFA. No significantly higher mortality was found when comparing patients with a qSOFA = 0 versus qSOFA = 1 [2.4% (95% CI 1.0–4.9%) vs. 3.2% (95% CI 1.4–6.1%) p=0.780] and patients with a qSOFA = 1 versus qSOFA = 2 [3.2% (95% CI 1.4–6.1%) vs. 7.2% (95% CI 3.1–14.3%) p=0.199]. The mortality rate of patients with a qSOFA = 3 was significantly higher than the rate of patients with a qSOFA = 2 [34.6% (95% CI 18.7–53.7%) vs. 7.2% (95% CI 3.1–14.3%) p<0.001].

The AUROC of the qSOFA to predict mortality, ICU admission, and the need for mechanical ventilation were 0.715 (95% CI 0.602–0.829), 0.709 (95% CI 0.655–0.763), and 0.744 (95% CI 0.684–0.804), respectively (Fig. 2 and Supplemental Digital Content Figures 1 and 2, http://links.lww.com/TA/C639). For the qSOFA score, exponential trendlines demonstrated the highest correlation  $R^2$  with regard to the observed outcomes. According the Youden Index, the optimal cutoff value for mortality was identified as qSOFA  $\geq$  2 (53.6% sensitivity, 82.9% specificity, 13.8% PPV, 97.2% NPV; Youden Index 36.5%).

# Diagnostic Ability and Test Performance of a Modified qadSOFA

Multivariable logistic regression analysis identified MI, GIT perforation, and 65 years or older as independent predictors for mortality, ICU admission and the need for mechanical ventilation (Table 3). Accordingly, the qSOFA score was modified using these three variables, leading to the age- and disease-

adjusted qSOFA (qadSOFA) score. Based on the OR of the multivariable regression analysis for mortality, 1 point was added to the score for older than 65 years, 1 point for GIT perforation, and 3 points for MI. (Table 4). If both, GIT perforation and MI were present, MI alone was entered in the score.

Figure 2 and Supplemental Digital Content Figures 1 and 2, http://links.lww.com/TA/C639, are summarizing the diagnostic ability and test performance of the qadSOFA for mortality, ICU admission and mechanical ventilation. The AUROC of the qadSOFA to predict mortality, ICU admission and the need for mechanical ventilation were 0.859 (95% CI 0.782–0.937), 0.834 (95% CI 0.795–0.874), and 0.875 (95% CI 0.837–0.913), respectively. Linear trendlines demonstrated the highest correlation  $R^2$  for the qadSOFA score with regard to the observed outcomes. According the Youden Index, the optimal cutoff value for mortality was identified as qadSOFA  $\geq$ 3 (85.7% sensitivity, 78.4% specificity, 16.8% PPV, 99.1% NPV; Youden Index 64.1%).

## **DISCUSSION**

This study validated for the first time the qSOFA to predict mortality and higher need of care in abdominal EGS patients specifically. In this group of patients, no acceptable cutoff value of qSOFA to predict mortality was identified (maximum Youden Index 36.5%), revealing its limited prognostic ability.

On the other hand, the newly developed qadSOFA score, including age, MI, and GIT perforation in addition to the variables of the qSOFA score, revealed an excellent discriminatory performance for the investigated clinical outcomes (Fig. 2 and Supplemental Digital Content Figures 1 and 2, http://links.lww.com/TA/C639, maximum Youden Index 64.1%). Moreover, the best trendlines through the observed outcomes turned from exponential for the qSOFA to linear for the qadSOFA. This finding may improve applicability and interpretation of the qadSOFA in the daily clinical use. The qadSOFA score thus is a promising new score for the prediction of outcomes in the investigated patient population.

The current study population comprised EGS patients with various abdominal emergencies (mean 193 patients per annum) and is comparable to other busy acute care centers. The detected mortality rate of 4.3% in the current study is comparable to the literature with the highest mortality rate for patients suffering from MI (26.2%). 1-6,25-27

In the daily clinical routine, it is of highest importance to predict outcomes at a very early stage of surgical decision making. Especially in times of reduced hospital and ICU resources, increasing frailty of EGS patients and different patients' or relatives' treatment expectations and goals, predictive scores may facilitate decision making in a timely manner. Of note, in a recent meta-analysis, frailty (relevant especially in patients with age ≥65 years) was significantly associated with mortality patients undergoing abdominal EGS (OR 4.3: 95% CI 2.25-8.19: p < 0.05]. <sup>26</sup> Similar to the study by Kennedy et al., age has been included as a variable into the qadSOFA to further improve prediction for mortality. However, scores to predict mortality need to be applicable at a very early stage of decision making, where only a limited number of variables are available. A previous study has shown that due to the complexity of data needed to calculate scores, such as the SOFA, multiple organ dysfunction

score or the Denver score, feasibility might be as low as 5.0% in EGS patient cohorts. In accordance with the findings of the mentioned study, we think that only variables that are documented routinely in daily clinical practice are useful for any predictive score. In contrast to above-mentioned scores, this does apply for the qSOFA and the proposed qadSOFA. Both scores are easy to calculate and applicable bedside in EGS patients.

In the current study, a significant increase of mortality in abdominal EGS patients was detected only in qSOFA = 2 versus qSOFA = 3 with mortality in the latter group of 34.6% (95% CI 18.7–53.7%). This finding is in contrast to previous studies on septic patients, where a cutoff value of a qSOFA  $\geq$  2 has been established. However, these studies included patients with heterogeneous sources of sepsis with no possible extrapolation to patients requiring EGS specifically. In the current study, the qSOFA revealed limited prognostic value with an AUROC of 0.715 (95% CI 0.602–0.829) and a maximal PPV for mortality of 34.6% with the maximum Youden Index less than 50%.

The qadSOFA remains clinically applicable as it includes solely additional variables that are available at a very early stage of hospital care. Age is a throughout available variable. The disease or pathology of the patient is identified either preoperatively by imaging (e.g., contrast-enhanced computed tomography scan) or, at the latest, during surgery. In the current study, the qadSOFA was available for 100% of patients.

#### Limitations

Because of the retrospective design of the current study there is a possible selection and attribution bias. Moreover, due to the single-center design at a tertiary university hospital, the reproducibility of study results might be limited at other centers. In addition, the current analysis is lacking a validation of the newly developed qadSOFA score to other cohorts of patients undergoing EGS. A post hoc power calculation for mortality rates in qSOFA = 3 versus qadSOFA = 7 with a type I/II error rate alpha 0.05 results in 10.6% power.

## **CONCLUSION**

This is the first study investigating the qSOFA score as a predictor for clinical outcomes specifically in patients undergoing EGS. Based on the characteristics of this specific patient population, the modified age and disease adjusted qSOFA (qadSOFA) score was developed. Compared with the qSOFA score, the new qadSOFA revealed an excellent predictive power for clinical outcomes. Nevertheless, in clinical practice, a qSOFA = 3 is worrisome and postoperative higher level of care needs to anticipated. Future validation of the qadSOFA on different datasets is warranted.

#### **AUTHORSHIP**

C.T.J.M. participated in the data analysis, data interpretation, writing, literature review, drafting, critical revision. T.H. participated in the data analysis, data interpretation, drafting, critical revision. J.-B.D. participated in the data collection, drafting, critical revision. A.O. participated in the data collection, drafting, critical revision. S.W. participated in the data collection, drafting, critical revision. D.C. participated in the data interpretation, drafting, critical revision. B.S. participated in the study design, data interpretation, writing, drafting, critical revision.

#### DISCLOSURE

The 1964 Helsinki declaration and its later amendments and comparable ethical standards were obeyed. There were no animal studies performed by any of the authors for this study.

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