Serum lactate dehydrogenase improves significantly quick-Sequential Organ Failure Assessment score as a predictor of mortality in patients with thoracic empyema: A retrospective analysis

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ABSTRACT

INTRODUCTION One of the most recent scoring systems, quick-Sequential Organ Failure Assessment (qSOFA), shows lack of sensitivity as outcome predictor in various clinical settings including thoracic empyema. We aimed to evaluate our new prognostic score Lactate Dehydrogenase-qSOFA (LDH-qSOFA) as a better predictor of death than qSOFA alone, in patients with empyema.

METHODS This single-center retrospective study, of 84 patients with thoracic empyema, was conducted in the Clinic of Thoracic Surgery of the University Hospital at Stara Zagora, for the period January 2021–October 2023. LDH levels, SIRS and qSOFA were assessed at admission. We analyzed area under receiver operating characteristics (AUROC) curves of SIRS, qSOFA and LDH-qSOFA, and performed a comparison of their prognostic performance.

RESULTS Of the total of 84 patients, nine (10.7%) died during hospitalization. The new LDH-qSOFA score showed the best prognostic ability in comparison to qSOFA alone (AUROC=0.851 vs 0.747) and SIRS (AUROC=0.851 vs 0.676). As predictor of fatal outcome LDH-qSOFA at optimal threshold ≥2 points was observed with higher sensitivity compared to qSOFA ≥2 (62.5% vs 44.4%).

CONCLUSIONS In patients with thoracic empyema a combination of qSOFA and LDH demonstrated better prognostic performance than qSOFA alone.

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INTRODUCTION

Thoracic empyema is defined as a collection of pus in the pleural cavity, gram-positive, or pleural fluid culture[1]. Usually, it is associated with pneumonia, but can also develop after surgery or trauma. Every year in the USA and Great Britain, 65000 patients suffer from empyema, which leads to huge financial costs (US$500 million) and a 20–30% mortality rate[2]. Nearly one-third of the affected patients require additional surgery within the first year after developing an empyema.

The early prognostic assessment of empyema gives the possibility of differentiating the high-risk patients and a chance for a timely and adequate change of the therapeutic approach, which in turn can affect the unfavorable outcome. Various prognostic factors have been developed over the years, but none has shown the necessary qualities so far. Most are complex and difficult to calculate, require many clinical and laboratory parameters and can rarely be used outside intensive care units (ICUs).

In 2016, a working group created the current Sepsis-3 definitions and removed the concept of systemic inflammatory response syndrome (SIRS) from the definition of sepsis[3]. The same group introduced the quick-Sequential Organ Failure Assessment (qSOFA) as a prognostic score that can immediately identify which patients with suspected infection are likely to have a prolonged ICU stay or die in hospital. An important advantage of qSOFA is its easy calculation, without the need for any laboratory tests. Following the task force's recommendations, many hospitals are implementing qSOFA in the rapid assessment of high-risk patients. There are studies that show the superiority of qSOFA over SIRS criteria in predicting the final outcome[4,5]. However, in surgical patients, there is evidence that qSOFA has a lack of sensitivity in predicting mortality[6,7].

Based on the lack of sensitivity of qSOFA to predict an unfavorable outcome, we decided to add a fourth criterion to improve the prognostic performance of this scoring system. Our choice was serum lactate dehydrogenase (LDH) levels and we called this combination the LDH-qSOFA score. We chose LDH, because nowadays this biomarker has been used as an indicator of cellular injury and death in different clinical settings[8-10], and its higher concentrations show promising

diagnostic and prognostic qualities in various pulmonary diseases[11-13].

The aim of this study was to demonstrate the prognostic superiority of our new score LDH-qSOFA compared to qSOFA alone, in patients with thoracic empyema.

METHODS

We conducted a single-center retrospective study in the Clinic of Thoracic Surgery (CTS) of the University Hospital 'Prof. Dr. Stoyan Kirkovich', at Stara Zagora. All adult patients who underwent emergency surgery due to thoracic empyema between January 2021 and October 2023 were included. Our exclusion criteria were those aged <18 years and who used immunosuppressive drugs; however, none of the patients met them, and finally 84 patients were included in this analysis. The diagnosis empyema was made based on collection of pus in the pleural cavity or pleural fluid culture[1]. No intra-pleural fibrinolytic therapy was used in the management of empyema.

Demographic information and clinical outcome were determined from the patients' medical records at admission to CTS. All patients were divided into two groups according to outcome (in-hospital mortality) – survivors and non-survivors (Table 2).

SIRS criteria were defined as follows: heart rate (HR) > 90/min, respiratory rate (RR) > 20/min, temperature (T) <36°C or >38°C, and white blood cell count (WBC) <4×10⁹/L or >12×10⁹/L. A positive result was defined as ≥2 out of 4

possible signs[14].

Renal, Age, Purulence, Infection source, and Dietary factors (RAPID) score[15] was calculated based on five risk indicators (Table 1).

The qSOFA was determined using the following criteria, each equal to 1 point: systolic blood pressure (SBP) ≤100 mmHg, respiratory rate (RR) ≥ 22/min, and Glasgow Coma Scale (GCS) <15. A score of ≥2 out of a possible 3 points was defined as positive[3].

One point for LDH >752U/L was added to the qSOFA (0 to 3 points), which we established as an optimal cut-off level for prediction of fatal outcome in ROC curve analysis. We named this combination Lactate Dehydrogenase-quick-SOFA (LDH-qSOFA) score with a range of 0 to 4 points.

All clinical and laboratory parameters necessary were extracted from each patient's data at admission to the clinic. The parameters WBC, SBP, HR, RR, GCS, SIRS and qSOFA were determined for all 84 patients, while serum C-reactive protein levels for 81 patients (missing data in 3 medical records), RAPID for 74 patients (missing data in 10 medical records), neutrophil count (Neu) for 68 patients (missing data in 16 medical records), and LDH and LDH-qSOFA for 63 patients (missing data in 21 medical records).

Statistical analysis

Sensitivity, specificity, and areas under the curves (AUROC) for predicting mortality were calculated for each scoring system. Categorical variables are presented as frequency (%) and were analyzed by Pearson χ^2 test or Fisher's exact test. Continuous variables are presented as mean with standard deviation (SD) and compared by Student's t-test or median with interquartile range (IQR) and compared by Mann-Whitney U test. A p<0.05 was considered statistically significant. For statistical analysis, we used statistical software SPSS (IBM, Chicago, Illinois, USA).

RESULTS

Patients' characteristics

Of the 84 patients included, nine (10.7%) died during the hospital stay. Their median age was higher than the survivor group, but was not statistically significant (68 vs 61 years, p=0.186). No ability to discriminate non-survivors from survivors was found also for sex (p=0.194), blood type (p=0.092), length of hospitalization (p=0.302), location of infection (0.298) and comorbidity (p=1.00). In contrast, the type of surgical approach showed significant association with outcome, whereas patients who required video-assisted thoracoscopic surgery (VATS) had a higher chance of survival (p=0.031) (Table 2).

Laboratory findings, clinical parameters, and prognostic scores

No significant differences were observed in serum levels of WBC, Neu and CRP at admission between patients who died and those who survived p = 0.452, 0.18 and 0.663

Table 1. RAPID score (0–7)

Parameter	Score
Renal urea (mmol/L)	
<5	0
5–8	1
>8	2
Age (years)	
<50	0
50–70	1
>70	2
Purulence of pleural fluid	
Yes	0
No	1
Infection source	
Community	0
Hospital	1
Dietary factors albumin (g/L)	
≥27	0
<27	1

respectively. However, non-survivors had significantly higher median concentrations of LDH than survivors (808 vs 395 U/L, p<0.0001). Poor outcome was associated with higher RR (p=0.011) and lower GCS (p=0.001), while better chance of survival had participants with higher median SBP values (p=0.019). Other prognostic factors like T (p=0.26), HR (p=0.202) and SIRS (p=0.16) could not discriminate patients according to outcome (Table 3).

Both qSOFA and LDH-qSOFA demonstrated significant prognostic qualities, whereas higher median scores were indicative for fatal outcome (1 vs 0 points, p=0.003 for qSOFA; and 2 vs 0 points, p<0.0001 for LDH-qSOFA). Positive qSOFA ≥2 and LDH-qSOFA ≥2 were observed more frequently in non-survivors than survivors (44.4% vs 8%, p=0.01 for qSOFA; and 62.5% vs 7.3%, p=0.001 for LDH-qSOFA) (Table 3).

Table 2. Characteristics of patients in the study

| Characteristics	Total n (%)	Survivors (N=75) n (%)	Non-survivors (N=9) n (%)	p
Age (years), median (IQR)	62.5 (47–70.5)	61 (45–69)	68 (58–74.5)	0.186
Sex				0.194
Male	66 (78.6)	57 (76.0)	9 (100)	
Female	18 (21.4)	18 (24.0)	0 (0)	
Hospital stay (days), median (IQR)	10 (7–14)	10 (8–14)	7 (3.5–18)	0.302
Blood type				0.092
A+	30 (35.7)	29 (38.7)	1 (11.1)	
A-	7 (8.3)	5 (6.7)	2 (22.2)	
B+	9 (10.7)	6 (8.0)	3 (33.3)	
B-	2 (2.4)	2 (2.7)	0 (0)	
O+	27 (32.1)	25 (33.3)	2 (22.2)	
O-	3 (3.6)	3 (4.0)	0 (0)	
AB+	6 (7.1)	5 (6.7)	1 (11.1)	
AB-	0 (0)	0 (0)	0 (0)	
Location				0.298
Left hemithorax	44 (52.4)	41 (54.7)	3 (33.3)	
Right hemithorax	40 (47.6)	34 (45.3)	6 (66.7)	
Surgical approach				**0.031**
Chest tube drainage	21 (25.0)	18 (24.0)	3 (33.3)	
VATS	54 (64.3)	51 (68.0)	3 (33.3)	
Thoracotomy	9 (10.7)	6 (8.0)	3 (33.3)	
Comorbidity	59 (70.2)	53 (70.7)	6 (66.7)	1.000
Cardiovascular	41 (48.8)	36 (48.0)	5 (55.6)	0.735
Respiratory	9 (10.7)	6 (8.0)	3 (33.3)	0.052
Oncological	11 (13.1)	8 (10.7)	3 (33.3)	0.091
Endocrine	15 (17.9)	13 (17.3)	2 (22.2)	0.659
Neurological	5 (6.0)	5 (6.7)	0 (0)	1.000
Excretory	5 (6.0)	5 (6.7)	0 (0)	1.000
Digestive	2 (2.4)	2 (2.7)	0 (0)	1.000
Hematological	1 (1.2)	1 (1.3)	0 (0)	1.000

IQR: interquartile range.

Table 3. Laboratory findings, clinical parameters, and prognostic scores of study patients

| Variable	Total Median (IQR)	Survivors Median (IQR)	Non-survivors Median (IQR)	p
WBC (×10⁹/L)	14.35 (10.48–22.7)	14.1 (10.47–20.7)	16.4 (11.02–25.04)	0.452
Neu (×10⁹/L)	11.95 (8.35–18.55)	11.8 (7.94–17.85)	19.8 (8.63–22.97)	0.18
CRP (mg/L)	188 (107.7–299.5)	184.65 (112.23–285-7)	316.8 (74.6–338.6)	0.663
LDH (U/L)	413 (328–587)	395 (308–504)	808 (768–943.5)	**<0.0001**
LDH (>752 U/L), n (%)	12 (19.0)	5 (9.1)	7 (87.5)	**<0.0001**
SBP (mmHg)	120 (110–130)	120 (110–130)	110 (95–120)	**0.019**
HR (beats/min)	86 (80–99)	86 (80–99)	100 (79–101)	0.202
RR (breaths/min)	19 (18–21)	19 (17–21)	23 (19.5–25)	**0.011**
T >38°C, n (%)	28 (33.3)	27 (36.0)	1 (11.1)	0.26
GCS (points)	15 (15–15)	15 (15–15)	15 (14–15)	**0.001**
SIRS (points)	2 (1–2)	1 (1–2)	3 (1.5–3)	0.074
SIRS ≥2, n (%)	44 (52.4)	37 (49.3)	7 (77.8)	0.16
RAPID (points)	2 (1–3)	2 (1–3)	3 (3–4.75)	**0.007**
RAPID >2, n (%)	28 (37.8)	21 (31.8)	7 (87.5)	**0.004**
qSOFA (points)	0 (0–1)	0 (0–1)	1 (0–3)	**0.003**
qSOFA ≥2, n (%)	10 (11.9)	6 (8.0)	4 (44.4)	**0.01**
LDH-qSOFA (points)	0 (0–1)	0 (0–1)	2 (1–3.75)	**<0.0001**
LDH-qSOFA ≥2, n (%)	9 (14.3)	4 (7.3)	5 (62.5)	**0.001**

IQR: interquartile range.

Figure 1. ROC curves of SIRS, RAPID, qSOFA and LDH-qSOFA
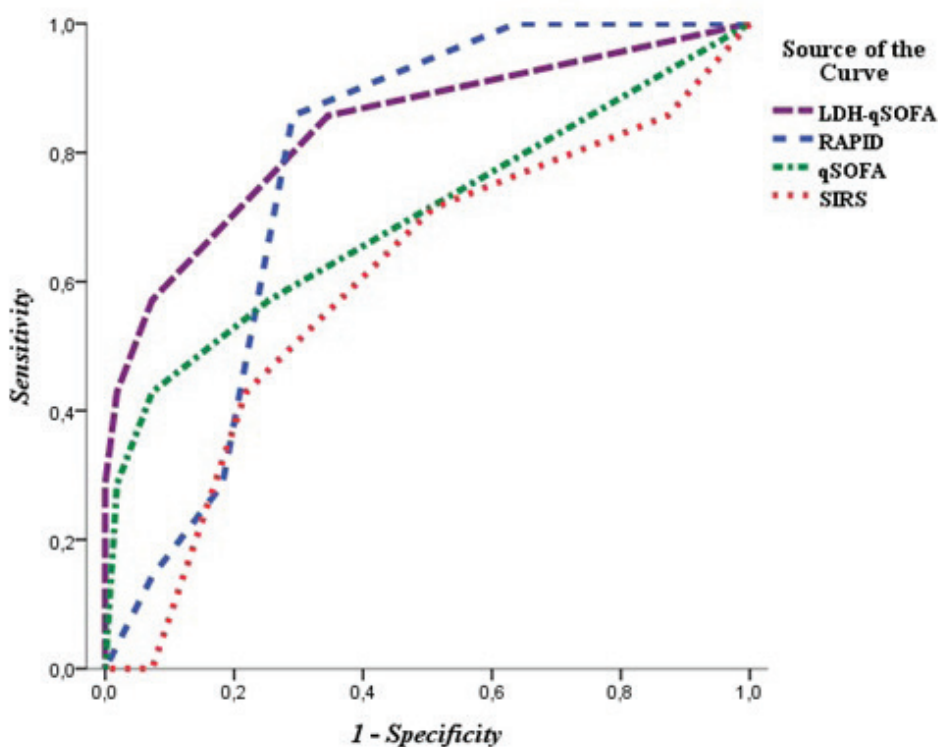
Table 4. Sensitivity, specificity and AUROCs of SIRS, RAPID, qSOFA and LDH-qSOFA scores

Variable	Cut-off	Sensitivity %	Specificity %	AUROC	p
SIRS	≥2	77.8	50.7	0.676	0.085
RAPID	>2	87.5	68.2	0.786	**0.009**
qSOFA	≥2	44.4	92.0	0.747	**0.016**
LDH-qSOFA	≥2	62.5	92.7	0.851	**0.001**

Figure 2. Sensitivity and specificity of RAPID, qSOFA and LDH-qSOFA
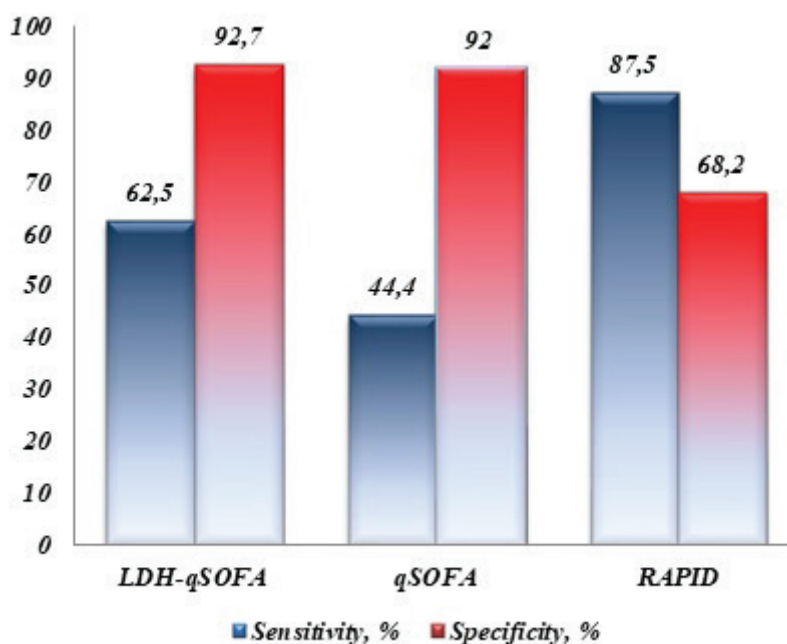
Sensitivity, specificity and AUROCs

In prediction of mortality, qSOFA showed superiority to SIRS (AUROC=0.747; 95% CI: 0.546–0.947 vs AUROC=0.676; 95% CI: 0.481–0.871). Positive qSOFA demonstrated excellent specificity of 92% at the expense of low sensitivity (44.4%). The new score LDH-qSOFA fulfilled the idea of its creation by showing the best prognostic ability (AUROC=0.851; 95% CI: 0.687–1.000) (Figure 1). While maintaining the excellent specificity of qSOFA, we found a significantly higher sensitivity of LDH-qSOFA (62.5%) (Table 4 and Figure 2).

DISCUSSION

Empyema thoracis is one of the oldest and most severe pleural diseases, about which Hippocrates wrote: 'If the empyema does not break through, death ensues'. Despite the evolution in management including advanced imaging methods, antibiotics, fibrinolytic drugs, and minimally invasive surgery, the morbidity and mortality remain high[16].

Early prognostic assessment of empyema is crucial to determine disease severity and aggressiveness of conservative therapy and surgical management. Multiple variables have been described that affect prognosis, including patient-related and pleural space characteristics, as well as experience of general/thoracic surgeons and resources of hospital. Many researchers are still trying to deal with these problems focusing on the predictive reliability of different scoring systems.

Over the years, various prognostic scores have been recommended, of which the Sequential Organ Failure Assessment (SOFA) score has proven to be the most accurate and has even been included in the new Sepsis-3 definitions[3]. SOFA showed better prognostic ability than qSOFA and SIRS in ICU patients with suspected infection[17]; however, it is complex and difficult to assess in a timely manner, especially outside an ICU, and its calculation requires many laboratory parameters. In such cases, the qSOFA, designed for rapid and easy recognition of sepsis and high

risk of in-hospital mortality, can be used.

SIRS eventually gave way to qSOFA, as it failed as a prognostic tool in patients with empyema, as also indicated by the results of the present study where almost half of the survivors (49.3%) and more than three-quarters of the deceased (77.8%) had clinical evidence of systemic inflammation (p=0.16). ROC curve analysis confirmed these findings – we observed low AUROC value for SIRS as predictor of death (0.676) with lack of significance (p=0.085). No other study investigating prognostic ability of SIRS in empyema was found.

In predicting fatal outcome, qSOFA was found to be superior to SIRS criteria[4,5]. However, some authors reported a lack of sensitivity of qSOFA as mortality predictor in sepsis (37%)[18], acute infectious diseases (38.1%)[19], and complicated intra-abdominal infections (cIAIs): 46% by Jung et al.[6], 32% by Dimitrov et al.[20] and 37% by Tolonen et al.[21].

Only one study (to the best of our knowledge) investigated prognostic performance of qSOFA score in thoracic empyema exclusively. In 2022, Asai et al.[7] conducted a retrospective analysis evaluating qSOFA in 53 patients with acute empyema. The authors reported a sensitivity of 43%, specificity of 91%, and no prognostic ability (AUROC=0.563, p=0.539). The ROC curve analysis performed by us revealed a similar sensitivity of 44.4% and specificity of 92%; however, we found better prognostic performance (AUROC=0.747) with a significant value (p=0.016), which may be due to the larger sample size in our study.

Several researchers have already tried to improve the predictive ability of qSOFA by combining with it elevated serum lactate or CRP levels. Shetty et al.[22] and Jung et al.[6] added lactate to qSOFA in emergency department (ED) and cIAIs patients, respectively, to successfully achieve their goal (Lactate-qSOFA vs qSOFA: 65.5 % vs 47.6%, and 72% vs 46%, respectively). By adding CRP to the score, Kim et al.[23] in ED patients and Dimitrov et al.[24] in cIAIs patients, improved the expected sensitivity (qSOFA-CRP vs qSOFA: 76.9% vs 53.8%, and 60% vs 35%, respectively).

To improve the sensitivity of qSOFA, we studied several combinations of qSOFA and biomarkers, such as white blood cells, neutrophils, C-reactive protein, and lactate dehydrogenase. The analysis revealed that the optimal combination was qSOFA and LDH.

LDH is a cytoplasmic enzyme expressed in nearly all types of cells of the body and is released into blood when the cells experience injury or death. Many researchers suggested LDH as an important predictor of cellular injury and death[10]. First, Ewig et al.[12] reported about the association between this biomarker and unfavorable outcome in community-acquired pneumonia (NS=399 U/L vs S=254 U/L). Mortality was also higher in sepsis patients with elevated serum LDH according to Lu et al.[25] (NS=328.39 vs S=200.13 U/L), Zein et al.[26] (NS=656 vs S=369 U/L) and Wang et al.[27] (NS=300 vs S=258.5 U/L). Increased levels were associated with higher risk of death in patients with coronavirus disease[28] and

critically ill patients with acute kidney injury[29].

In our study LDH discriminated non-survivors from survivors with highly significant value (p<0.0001) and death was more likely in patients with higher serum levels (808 vs 395 U/L). The identified threshold >752 U/L was observed in 87.5% of patients who died and in only 9.1% of those with favorable outcome. The new LDH-qSOFA score showed significantly higher sensitivity than qSOFA (62.5% vs 44%). In our study group, we found that LDH-qSOFA had a better prognostic ability than qSOFA (AUROC=0.851 vs 0.747).

Our new score also showed a better prognostic performance than the RAPID score (AUROC=0.851 vs 0.786), which was introduced and validated in patients with pleural infection[15]. We suggest that one of the reasons for the lower predictive power of RAPID is a consequence of the fact that it was designed to predict 3-month mortality, while we use LDH-qSOFA to assess in-hospital mortality, which in our study did not exceed 28 days.

This is the first study (to our knowledge) to evaluate the combination of qSOFA and LDH as a predictor of mortality. With four criteria and improved sensitivity and prognostic accuracy, the new score could differentiate patients at high risk of fatal outcome who were previously incorrectly defined as non-severe and treated as such.

Limitations

Limitations of the study are the single-center setting, the small sample size, and the retrospective nature of the analysis. Future larger prospective multicenter studies could overcome these limitations and provide a definitive answer regarding the utility of the LDH-qSOFA score in clinical practice.

CONCLUSIONS

The combination of a quick-SOFA score and elevated serum lactate dehydrogenase levels shows a higher sensitivity and a better prognosis of a fatal outcome than quick-SOFA alone, in patients with thoracic empyema.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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