

Original Article



Prediction of mortality in sepsis with biomarkers and qSOFA score combination: An observational study in a tertiary care centre of western India

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Abstract

Introduction: In any clinical set up, the laboratory biomarkers are very important and can serve in determining the suitable treatment course. In this study, we assumed that considering a combination of biomarkers rather than individual items like lactate, C-reactive protein (CRP) and procalcitonin (PCT) along with qSOFA (quick sequential organ failure assessment) score would be better for predicting 28-day mortality in patients diagnosed with sepsis.

Methods: A prospective observational study was conducted in a tertiary care centre in Jaipur, Rajasthan (western India) including 160 participants who were admitted in the intensive care unit (ICU) and diagnosed as sepsis. Detailed history and examination were performed, followed by blood investigations and qSOFA score calculations. Written informed consent was obtained from all participants and institutional ethics committee approval was taken at the beginning of the study. Statistical analysis was done after adequate data collection.

Results: Mean CRP [mg/L] was 9 ± 1.41 , mean PCT [ng/mL] was 1.6 ± 0.56 , mean lactate [mmol/L] was 2.1 ± 1.97 among the study subjects. In this study, specificity (%) of qSOFA + biomarkers (serum lactate, CRP, PCT) was 98.9%, that was more than sensitivity of qSOFA score alone i.e., 40.62%. Although sensitivity (%) of qSOFA was 45.31% that was almost similar to the specificity of qSOFA + biomarkers i.e., 46.8%. Positive predictive value and negative predictive value was also higher in the qSOFA + Biomarker group.

Conclusion: The predictive rate of combined method was better than that of qSOFA score alone.

Introduction

Any lethal organ malfunction due to an unsynchronized response of the host is called sepsis.^{1,2} It is the foremost reason of bereavement among those who are critically ill, with a total mortality of 30%.^{3,4}

Septic shock and sepsis impair the host's ability to control any infection, which can result in organ failure (also known as "multiorgan dysfunction") and eventual death. Since the early 1990s, there have been numerous adjustments made to the definition of sepsis.⁵ The term "systemic inflammatory response syndrome" (SIRS), which develops as a reaction to any pathogenic cause, was coined by the International Consensus Panel in 1992 to describe sepsis. The term "severe sepsis" was suggested by the panel to describe situations in which organ failure and sepsis coexist. The term "septic shock" refers to sepsis that has been worsened by either hypotension that is resistant to fluid therapy or high serum lactic acid levels.⁶ A second consensus panel described the symptoms of SIRS in 2003

as tachycardia or bradycardia, fever or hypothermia; and an increased or decreased total leucocyte counts. Since SIRS is no longer usually caused by an infection, it is no longer included in the definition of sepsis. The definitions of sepsis and septic shock have been updated by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. A subdivision of sepsis in which circulatory, cellular, and metabolic abnormalities are associated with a higher risk of mortality than sepsis alone, is how septic shock is characterized now. The clinical criterion of hypotension requiring vasopressor therapy to maintain mean blood pressure of 65 mm Hg or above and having a serum lactate level of more than 2 mmol/L following satisfactory fluid resuscitation can be used to classify patients as having septic shock.⁷ Sepsis is typically diagnosed at the patient's bedside based on symptoms and indications of organ failure as well as clinical suspicion of an underlying infection. The diagnosis of sepsis is also aided by laboratory, radiographic, physiological,

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and microbiologic factors. Though it is possible to have sterile cultures and still have sepsis, which is typically true, antibiotics are only partially administered before culture samples are collected. Sepsis cannot be accurately diagnosed with any gold standard technique, and there is no reliable system to forecast consequences.⁸ Numerous scores have been developed for use in sepsis. Sequential organ failure assessment (SOFA) and fast sequential organ failure assessment (qSOFA) scores were employed in this investigation.

SOFA score is calculated as follows (Table 1)²:

The maximum score is 24 points, a score more than 16 depicts 90% mortality.

qSOFA is a shorter and quicker version of SOFA, it is calculated as follows (Table 2)⁹:

The maximum score is 3 points which suggests high risk of poor outcome.

In any clinical set up, the laboratory biomarkers are of analytical and predictive importance and can serve in determining the suitable management course. There are more than 100 such laboratory biomarkers that have been suggested to be useful for sepsis diagnosis and prognostication.¹⁰ One of these biomarkers, serum lactate, has been associated with 28-day mortality in sepsis and septic shock patients.^{11,12} Even procalcitonin (PCT) has been a very useful biomarker in diagnosing sepsis.^{13,14} C-reactive protein (CRP) is an acute phase reactant and a sensitive marker of sepsis.¹⁵ In this study, we hypothesised that qSOFA score and a combination of biomarkers rather than individuals would be more effective at predicting 28-day death in patients with sepsis.

Methods

A prospective hospital-based observational study was conducted in the Department of General Medicine at a tertiary care centre in Jaipur, Rajasthan (western India) over a period of 15 months.

Patients who were admitted in intensive care unit (ICU) and diagnosed as sepsis, underwent a detailed medical history and a thorough physical examination followed by blood investigations. Institute Ethics Committee approval was taken before the start of study. Written and informed consent of the patients was obtained from all participants

before enrolment into the study. 160 patients were included in the study on the basis of following criteria:

Inclusion criteria

- Age more than 18 years.
- Patients who gave consent for the study.
- Diagnosed as sepsis:
 1. Temperature > 38 °C or < 36 °C
 2. Pulse above 90 beats/min
 3. Tachypnoea with rate > 20/min or PaCO₂ < 32 mm Hg
 4. Total leucocyte count (TLC) > 12000/cmm, < 4000/cmm or > 10% immature neutrophils 'band'
 5. Evidence of organ failure.

Exclusion criteria

- Those who did not give consent for study.
- Pregnancy.
- Patients with malignancy.
- Patients with any underlying comorbid illness.

The focus of infection was identified, appropriate laboratory investigations – complete blood counts, CRP, lactate, and PCT were performed. This data was obtained and entered in excel worksheet. Statistical tests were used to find significant correlation and predict mortality. T-test was used to find statistical significance and sensitivity and specificity was calculated. A true positive was patient who survived with qSOFA of 1, or a patient who expired with qSOFA of 2-3, PCT > 10 ng/mL, lactate > 4 mmol/L, CRP > 50 mg/L.

Results

The present study comprised of 160 patients suffering from sepsis, admitted in the ICU. Out of 160 subjects, 98 (61.25%) were males and 62 (38.75%) were females. Mean age of the study subjects was 54.91 ± 13.58 years (Table 3, Figure 1).

Out of 160 subjects, 5 (3.125%) were in 18-30 years age group, 19 (11.875%) were in 31-40 years age group, 31 (19.375%) were in 41-50 years age group, 47 (29.375%) were in 51-60 years age group, 39 (24.375%) were in 61-70 years age group, 18 (11.25%) were in 71-80 years age group, and 1 (0.625%) was in 81-90 years age group. Mean age of the

Table 1. SOFA score

System	0	1	2	3	4
Respiratory PaO ₂ /FiO ₂	>400	<400	<300	<200	<100
Coagulation Platelets (x10 ³ /uL)	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
Cardiovascular system	No hypotension	MAP < 70	On dopamine < 5 or Dobutamine (any dose) *	Dopamine > 5 or Noradrenaline < 0.1*	Dopamine > 15 or Norepinephrine > 0.1*
CNS Glasgow Coma Scale (GCS)	15	13-14	10-12	6-9	< 6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 < 500	>5.0 < 200

*Dose in ug/kg/min for at least 1 hour.

Table 2. qSOFA score

System		Points
CNS	Altered mental status GCS < 15	1
Respiratory	Tachypnoea > 22 breaths/ min	1
Cardiovascular	Systolic blood pressure < 100 mm Hg	1

Table 3. Gender and age distribution among the study subjects

Characteristics	
Gender, No. (%)	
Male	98 (61.25)
Female	62 (38.75)
Total	160 (100)
Age (y), Mean ± SD	
	54.91 ± 13.58

study subjects was 55 ± 25.5 years (Table 4, Figure 2).

Out of the 160 study participants, the most common site of infection was pulmonary in 29.375%, followed by urinary in 26.25%, and then intra-abdominal in 18.125%. Blood stream infections were seen in 12.5% and CNS infections in 9.375%. Least involved sites were soft tissue in 3.125% and osteoarticular in 1.25% (Table 5, Figure 3).

Mean CRP [mg/L] was 9 ± 1.41, mean PCT [ng/mL] was 1.6 ± 0.56, mean lactate [mmol/L] was 2.1 ± 1.97 among the study subjects (Table 6).

In this study, specificity (%) of qSOFA + biomarkers (serum lactate, CRP, PCT) was 98.9%, that was more than sensitivity of qSOFA score alone (i.e., 40.62%). However, the sensitivity (%) of qSOFA was 45.31% that was almost similar to the specificity of qSOFA + biomarkers (i.e., 46.8%). Positive predictive value and negative predictive value was also higher in the qSOFA + biomarker group (Table 7, Figure 4).

Discussion

Sepsis is a serious illness with many complications. Its pathophysiology involves elements connected to both the host and the infecting pathogen. Sepsis has been characterized as an infection with at least two of the four SIRS criteria and has been featured as an inflammatory excess for more than 20 years.¹⁶ The current application of this criterion, however, might not be adequate to detect sepsis in patients. According to updated international definitions known as sepsis-3, septic shock is a subset of sepsis in which basic irregularities in the circulatory and cellular metabolism are sufficient to significantly increase mortality. Sepsis is defined as a life-threatening organ dysfunction brought on by a dysregulated host response to infection.

According to the clinical recommendations upheld by sepsis-3, patients with proven infections should have a SOFA score greater than or equal to two in order to be diagnosed with sepsis. In order to calculate SOFA, it is necessary to categorize patients as having sepsis before available laboratory test results can be used. To address

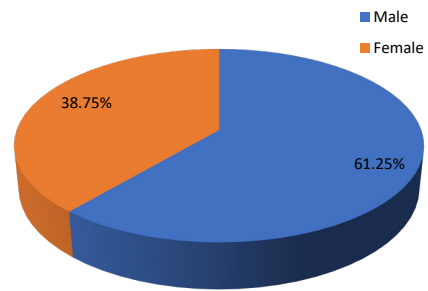


Figure 1. Gender distribution among the study subjects

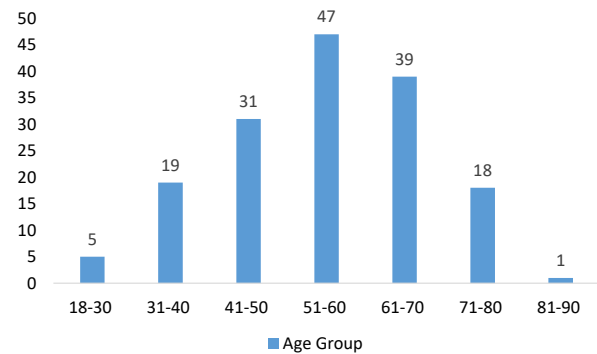


Figure 2. Age distribution among the study subjects

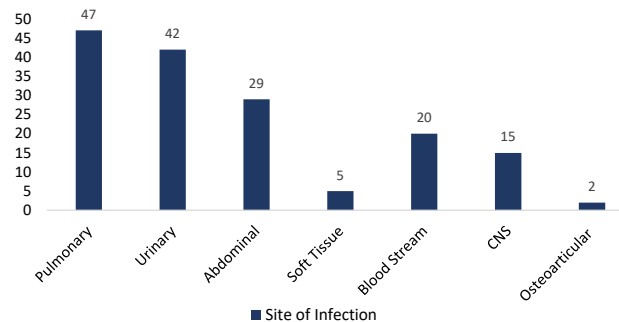


Figure 3. Site of infection among the study population

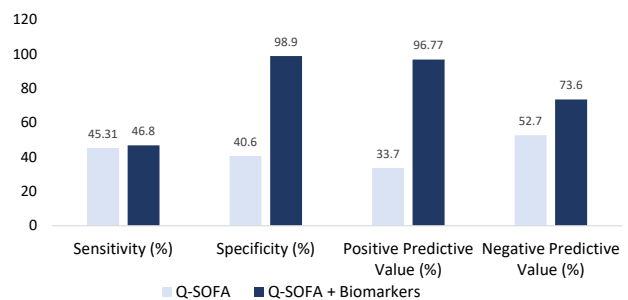


Figure 4. Diagnostic efficacy of qSOFA vs. qSOFA + biomarkers regarding screening for mortality

this need, the sepsis-3 introduced the quick SOFA or qSOFA, a new easily and cheap approach to measure bedside clinical score. For each of the clinical variables—respiratory rate > 22 breaths per minute, GCS < 15, and systolic blood pressure < 100 mm Hg—the qSOFA score

Table 4. Age distribution among the study subjects

Age group	No. of patients	%
18-30	5	3.125
31-40	19	11.875
41-50	31	19.375
51-60	47	29.375
61-70	39	24.375
71-80	18	11.25
81-90	1	0.625
Total	160	100%

Table 5. Site of infection among the study population

Site of infection	No. of patients	%
Pulmonary Infection	47	29.375
Urinary Infection	42	26.25
Intra-abdominal Infection	29	18.125
Soft Tissue Infection	5	3.125
Blood Stream Infection	20	12.5
CNS Infection	15	9.375
Osteoarticular Infection	2	1.25

is given, ranging from 0 to 3.⁷

Depending on the patient's baseline level of risk, the initial and extensive retrospective study that compared patients hospitalised with infection suspicion and a SOFA score of 2 found that those with a SOFA > 2 had a two- to five-fold higher risk of in-hospital mortality than those with a SOFA < 2. When compared to SOFA > 2, the in-hospital mortality rate for patients in the ICU increased by three to 11 times. Additionally, the study demonstrated that qSOFA > 2 was associated with in-hospital mortality but was unable to foretell patient mortality in the ICU.⁷ Sepsis-3 advises using the qSOFA outside the ICU as an early score to launch investigation for organ failure and to guide appropriate clinical care because it appears to be less aggressive than SOFA in the ICU.¹⁷ Due to conflicting literature, the prospective observational study was conducted in the Department of General Medicine, in a tertiary care centre in Jaipur among 160 patients admitted in ICU that were diagnosed with sepsis. The current study aimed to evaluate and compare the performance of qSOFA with biomarkers usually used in sepsis and to predict mortality. Out of 160 subjects, 98 were males and 62 were females. Most common site of infection was pulmonary in 29.375%, followed by urinary in 26.25% and then intra-abdominal in 18.125%. Blood stream infections were seen in 12.5% and CNS infections in 9.375%. Least involved sites were soft tissue in 3.125% and osteoarticular in 1.25%. Similarly, de Freitas Garbero et al reported that the most prevalent sites of infection were respiratory (51.63%), urinary (24.46%), and abdominal (10.33%).¹⁸ Song et al revealed that the most common site of infection was the respiratory system (n = 102; 63.8%), followed by

Table 6. Biomarkers among the study subjects

Parameters	Mean	SD
CRP [mg/L]	9.0	1.41
Procalcitonin [ng/mL]	1.6	0.56
Lactate [mmol/L]	2.1	1.97

SD, standard deviation.

Table 7. Diagnostic efficacy of qSOFA and qSOFA+biomarkers regarding screening for mortality

Parameter	qSOFA	qSOFA + Biomarkers
	Value	Value
Sensitivity (%)	45.31	46.8
Specificity (%)	40.62	98.9
Positive Predictive Value (%)	33.7	96.77
Negative Predictive Value (%)	52.7	73.6

the genitourinary (n = 48; 30.0%) and gastrointestinal systems (n = 13; 8.1%).¹⁹

Mean CRP [mg/L] was 9 ± 1.41 , mean PCT [ng/mL] was 1.6 ± 0.56 , mean lactate [mmol/L] was 2.1 ± 1.97 among the study subjects. Gaini et al in their study revealed approximate similar biochemical profile among the study subjects.¹⁷

In our study, out of 160 subjects, 60% survived and 40% expired. De Freitas Garbero et al found that overall sample mortality was 51.63%, which was approximately similar to our study.¹⁸

In our study mean serum lactate, CRP, and PCT were suggestively more in expired subjects in comparison to survivors. Lactate is the most common and valued biomarker for estimation of mortality in sepsis. However, according to two more investigations, the biomarker lactate alone only had a mediocre ability to predict 28-day death.^{20,21} In sepsis, PCT also exhibited a modest predictive value, although the individual worth of the biomarkers was low. While this is going on, numerous research has looked into the prognostic utility of mixed biomarkers in predicting mortality due to the drawbacks of the single marker approach. The combination biomarker strategy had a stronger prognostic value than the single marker technique, which is in line with the findings of the current investigation.^{22,23}

In this study, specificity (%) of qSOFA+biomarkers (serum lactate, CRP, PCT) was 98.9%, that was more than sensitivity of qSOFA score alone i.e., 40.62%. Although sensitivity (%) of qSOFA was 45.31% that was almost similar to the specificity of qSOFA+biomarkers i.e., 46.8%. Positive and negative predictive values were also higher in the qSOFA+biomarker group. Our findings matched those of Anami et al²⁴ and Rosa et al,²⁵ who reported similar findings in acute care units in Brazil. Greater SOFA scores have been linked to greater in-hospital mortality rates, both in the ICU setting and in emergency rooms, according to the literature. Despite

the deadline for mortality analysis, several studies that assessed the sensitivity of the admission score for the same outcome came to the same conclusions. Rodriguez et al²⁶ found a sensitivity of 64.4% within 72 hours of hospitalisation; Tugul et al²⁷ found a sensitivity of 68% for mortality within 48 hours; and Hwang et al²⁸ found a sensitivity of 39% within 28 days of admission, demonstrating the brittleness and ineffectiveness of its use for an early recognition of critically ill patients. There have been questions raised concerning the qSOFA score's limited sensitivity when used as a sepsis screening tool, as was the case in our study. In a study, de Freitas Garbero et al discovered that the sensitivity for death was 93.7% and that the relative risk of death associated with the admission of a positive SOFA was 5.17 (95% CI: 2.11-12.87).¹⁸ A positive qSOFA at admission was associated with a relative risk of mortality of 1.83 (95% CI: 1.39-2.44) and a sensitivity of 56.8% for death.¹⁸

Conclusion

The specificity, positive predictive value and negative predictive value of combined qSOFA score and biomarker i.e., lactate, CRP, PCT was more than that of qSOFA score alone. So, the combination biomarker method including CRP, PCT, and lactate showed higher performance in predicting 28-day death among the sepsis patients. This method's predictive value outperformed that of the qSOFA score on its own. Biomarkers can thereby improve the qSOFA score for predicting mortality.

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Author's Contribution

Conceptualization: Pallaavi Goel.

Data curation: Pallaavi Goel.

Study Highlights

What is current knowledge?

- As far as we know, there is no superior biomarker or score for prediction of mortality in sepsis patients. This study aimed at a combined approach including biomarkers and Q-SOFA score for better prognostication.

What is new here?

- The combined biomarker approach using CRP, PCT and lactate depicted a better performance in predicting 28-day mortality among the patients diagnosed with sepsis. The prognostic value of this approach was superior to that of the Q-SOFA score alone. Therefore, biomarkers can be an enhancement to the Q-SOFA score for foreseeing mortality.

Formal analysis: Puneet Rijhwani.

Investigation: Srishti S. Jain.

Methodology: Puneet Rijhwani.

Project administration: Puneet Rijhwani.

Resources: Srishti S. Jain.

Supervision: Puneet Rijhwani.

Validation: Pallaavi Goel.

Visualization: Pallaavi Goel.

Writing—original draft: Pallaavi Goel.

Writing—review & editing: Pallaavi Goel.

Competing Interests

The authors declare no conflicts of interest concerning the authorship and/or publication of this article.

Ethical Approval

This study was approved by the Ethics Committee of Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan, India (Ethics No. MGMCH/IEC/JPR/2021/355). Consent was explained and obtained from all the subjects.

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