

Received: 2020.08.04  
Accepted: 2020.12.28  
Published: 2021.02.01

# The Levels of Lactate, Troponin, and N-Terminal Pro-B-Type Natriuretic Peptide Are Predictors of Mortality in Patients with Sepsis and Septic Shock: A Retrospective Cohort Study

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ADEF 1 **Harith Alataby**  
AE 1,2 **Jay Nfonoyim**  
E 1,2 **Keith Diaz**  
EF 3 **Amna Al-Tkrit**  
A 3 **Shahnaz Akhter**  
EF 3 **Sharoon David**  
B 1 **Vishnuveni Leelaruban**  
B 1 **Kara S. Gay-Simon**  
B 1 **Vedatta Maharaj**  
B 1 **Bruce Colet**  
B 1 **Cherry Hanna**  
B 1 **Cheryl-Ann Gomez**

1 Department of Medicine, Richmond University Medical Center, Staten Island, NY, U.S.A.  
2 Department of Pulmonary and Critical Care, Richmond University Medical Center, Staten Island, NY, U.S.A.  
3 Department of Clinical Research, Richmond University Medical Center, Staten Island, NY, U.S.A.

**Corresponding Author:** Harith Alataby, e-mail: [Harith\\_adnan\\_89@yahoo.com](mailto:Harith_adnan_89@yahoo.com)  
**Source of support:** Departmental sources

**Background:** Serum lactate, troponin, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have been proposed to be useful prognostic indicators in patients with sepsis and septic shock. This study aimed to evaluate the predictive ability of these biomarkers and assess how their prognostic utility may be improved by using them in combination.

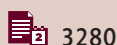
**Material/Methods:** A retrospective review of the medical records of 1242 patients with sepsis and septic shock who were admitted to the Richmond University Medical Center between June 1, 2018, and June 1, 2019, was carried out; 427 patients met the study criteria and were included in the study. The primary outcome measures included 30-day mortality, APACHE II scores, length of hospital stay, and admission to the Medical Intensive Care Unit (MICU).

**Results:** High levels of lactate (>4 mmol/L), troponin (>0.45 ng/mL), and NT-proBNP (>8000 pg/mL) were independent predictors of 30-day mortality, with an adjusted odds ratio of mortality being 3.19 times, 2.13 times, and 2.5 times higher, respectively, compared with corresponding reference groups, at 95% confidence intervals. Elevated levels of lactate, troponin, and NT-proBNP were associated with 9.12 points, 7.70 points, and 8.88 points in higher APACHE II scores, respectively. Only elevated troponin levels were predictive of a longer length of hospital stay. In contrast, elevated lactate and troponin were associated with an increased chance of admission to the MICU.

**Conclusions:** Elevated levels of serum lactate, troponin, and NT-proBNP are independent predictors of mortality and higher APACHE II scores in patients with sepsis and septic shock.

**Keywords:** **Decision Support Techniques • Lactic Acid • Natriuretic Peptide, Brain • Prognosis • Sepsis • Troponin**

**Full-text PDF:** <https://www.basic.medscimonit.com/abstract/index/idArt/927834>



## Background

Sepsis is a syndrome involving the development of multiple physiologic, pathologic, and biochemical anomalies and is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” [1]. Septic shock is considered to be a subset of sepsis in which the circulatory and metabolic derangements are severe enough to result in a significant increase in mortality [1]. Over the years, significant advancements have been made in understanding the complex pathophysiology of sepsis; however, sepsis remains a major cause of morbidity and mortality worldwide. It has been estimated that more than 30 million people develop sepsis annually worldwide, resulting in around 6 million fatalities [2].

Early recognition and early administration of intravenous fluids and antibiotics have been associated with an increased likelihood of survival in patients with sepsis [3]. Biomarkers can be of great importance in this regard, as a reliable, sensitive, and specific biomarker can be a valuable tool in the early identification of sepsis. In addition, biomarkers can help monitor the progression of the disease and can help identify patients who are at an increased risk of developing complications and, therefore, they can act as important prognostic indicators in patients with sepsis.

Several serum biomarkers have been proposed as biomarkers for sepsis; lactic acid, troponin, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are 3 such biomarkers. Elevated serum lactate levels may be a manifestation of organ dysfunction, which, in turn, may be associated with mortality in patients who are septic [4]. Similarly, an increased level of troponins in the setting of sepsis may serve as an indicator of underlying myocardial dysfunction, which has been found to be a common complication of sepsis [5]. NT-proBNP levels have also been associated with an increased severity of global tissue hypoxia and myocardial dysfunction and mortality in patients with severe sepsis [6]. These 3 biomarkers, may therefore act as useful adjuncts in the detection, stratification, and prognostication of high-risk patients.

Therefore, the aim of our study was to demonstrate the prognostic role of these biomarkers by answering 2 main questions. First, are serum lactate, troponin, and NT-proBNP useful prognostic biomarkers in patients with severe sepsis and septic shock? Second, can the measurements of these biomarkers be combined to improve their prognostic utility?

## Material and Methods

### Study Population

We conducted a retrospective review of the medical records of patients admitted to the Richmond University Medical Center

with sepsis (ICD-10 code A41.9), severe sepsis without septic shock (ICD-10 code R65.20), severe sepsis with septic shock (ICD-10 code R65.21), and sepsis, unspecified organism (ICD-10 code A41.9). Data were retrieved from patients who were admitted between June 1, 2018, and June 1, 2019. The patients were included in the study if they met the definition of sepsis, with or without the presence of septic shock, and if they had serum lactate, troponin, and NT-proBNP levels measured within the first 24 h of hospital admission. Sepsis was identified by an increase in the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more, in response to an infection. Septic shock was identified as having persistent hypotension requiring the administration of vasopressors to maintain the mean arterial pressure  $\geq 65$  mmHg and having a serum lactate level  $>2$  mmol/L (18 mg/dL), despite adequate volume resuscitation [1]. We excluded patients who failed to meet the diagnostic criteria for sepsis and septic shock or in whom any of the above-mentioned laboratory biomarkers were not obtained in a timely manner.

This study was reviewed and approved by the Richmond University Medical Center’s institutional review board (IRB).

### Number of Patients

This was a retrospective review of patients admitted to the Richmond University Medical Center. Patients were screened using electronic medical records and included in the study if they met the inclusion criteria. The records were retrospectively reviewed by using ICD-10 codes. We matched the study enrollment criteria for the duration of the study. The approximate number of patients was anticipated using *R* version 3.6.0. (RStudio, Inc, Boston, MA, USA). Assuming a standard normal distribution, with a margin of error to be 0.05 at a 95% confidence interval (CI), and assuming the probability that a patient would die (mortality rate) was 0.35, the required sample size was anticipated to be 350 patients.

Based on the inclusion and exclusion criteria, 427 patients were included in the study.

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects, and IRB approval was collected.

### Data Collection

The following data were collected from the electronic medical records: patient demographics; patient outcome measures, which were defined as the initial levels of lactate, troponin, and NT-proBNP that were collected during the first 24 h of hospital admission; length of stay in the hospital; admission to the Medical Intensive Care Unit (MICU); mortality rate (if the patient died within

30 days from the time of hospital admission); and the calculated Acute Physiology and Chronic Health Evaluation (APACHE) II score.

### Statistical Analysis

Statistical analysis was done using R 3.6.0. For categorical data, multivariate logistic regression was performed. Variables were reported as adjusted odds ratios (aOR) with a 95% CI. For continuous variables, multivariate linear regression was implemented. For both regressions, a probability value of  $P < 0.05$  was considered statistically significant. Variables that retained statistical significance were reported with 95% CIs.

## Results

### Characteristics of the Study Population

A total of 427 patients were included in the study, 243 men and 184 women. The baseline characteristics of the patients are shown in **Table 1**.

Patients were classified into 3 groups according to their lactate levels ( $\leq 2$  mmol/L, 2 to 4 mmol/L, and  $\geq 4$  mmol/L). Patients were classified into 2 groups according to their troponin levels ( $\leq 0.045$  ng/mL and  $\geq 0.045$  ng/mL). Patients were classified into 3 groups according to their NT-proBNP levels ( $\leq 4000$  pg/mL, 4000 to 8000 pg/mL, and  $\geq 8000$  pg/mL).

It must be noted that multiple groups with different NT-proBNP levels were established and evaluated to find significant correlations with the outcomes of interest. We found that NT-proBNP levels of  $\leq 4000$  pg/mL, 4000 to 8000 pg/mL, and  $\geq 8000$  pg/mL were significantly correlated with the outcomes and, thus, served the aim of our study.

Of the 427 patients, 171 (40%) had a normal serum lactate level of  $\leq 2$  mmol/L, 154 (36.1%) had an elevated lactate level of 2 to 4 mmol/L, and 102 (23.9%) had a highly elevated lactate of level  $\geq 4$  mmol/L. Troponin levels were found to be in the normal range of less than 0.045 ng/mL in 51.1% of patients, whereas 48.9% of patients had elevated troponin levels above 0.045 ng/mL. In total, 293 patients (68.6%) had an NT-proBNP level below 4000 pg/mL, while the NT-proBNP levels were found to be over 8000 pg/mL in only 35 patients (8.2%).

Of the 427 patients, 278 patients survived and 149 died (non-survival). The 30-day mortality rate in our study was 34.9%.

### Prognostic Use of Lactate, Troponin, and NT-proBNP Levels

High levels of serum lactate ( $>4$  mmol/L), troponin ( $>0.45$  ng/mL), and NT-proBNP ( $\geq 8000$  pg/mL) were predictive of

**Table 1.** Clinical characteristics of patients involved in the study.

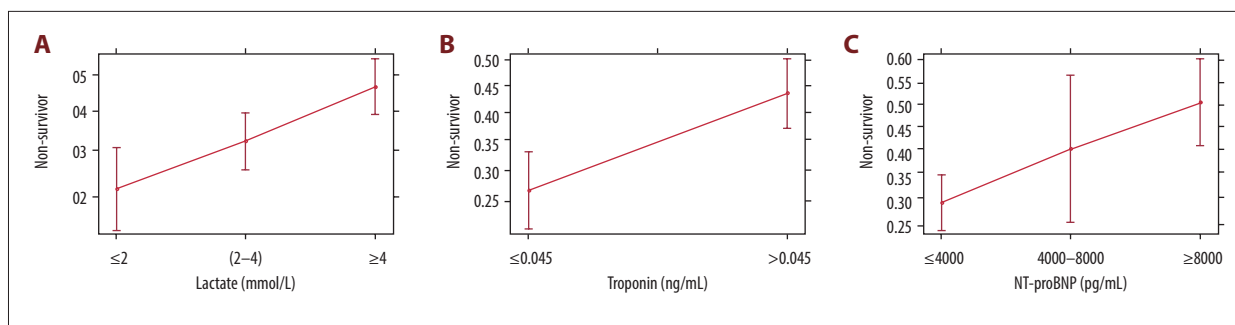
Character	N
Male	243
Female	184
Survivors	278
Non-survivors	149
Lactate (mmol/L)	
0-2	171
2-4	154
$>4$	102
Troponin (ng/mL)	
$<0.045$	218
$>0.045$	209
NT-ProBNP (pg/mL)	
$<4000$	293
4000-8000	99
$>8000$	35

30-day mortality. We found that the mortality rate associated with sepsis and septic shock was higher in patients who had higher levels of either lactate, troponin, or NT-proBNP (**Figure 1A-1C, Table 2**).

For the group of patients with lactate levels  $>4$  mmol/L, the aOR of non-survival was found to be 3.19 times (95% CI 1.98-5.14,  $P=0.00006$ ) greater than that of the reference group (lactate  $\leq 2$  mmol/L). Similarly, for the group with troponin levels  $>0.045$  ng/mL, the aOR of non-survival was 2.13 times (95% CI, 1.51-2.99,  $P=0.00027$ ) higher than the aOR of the reference group (troponin  $\leq 0.045$  ng/mL). Compared with the reference group (NT-proBNP  $\leq 4000$  pg/mL), the aOR of non-survival was 2.5 times (95% CI 1.69-3.70,  $P=0.00013$ ) higher in patients in the group with NT-proBNP levels  $\geq 8000$  pg/mL.

The results of the regression analyses for elevated lactate and NT-proBNP levels were statistically significant, whether observed separately or in combination with the other variables. Compared with the reference group (lactate  $\leq 2$  mmol/L), the group with lactate levels  $\geq 4$  mmol/L had an aOR that was 3.01 times (95% CI 1.82-4.97,  $P=0.0003$ ) higher, while keeping the other 2 variables constant, whereas for the group with NT-proBNP levels  $\geq 8000$  pg/mL, the aOR was 2.35 times (95% CI 1.55-3.58,  $P=0.00076$ ) higher as compared with the reference group (NT-proBNP  $\leq 4000$  pg/mL), while keeping the other 2 variables constant.

Of note, the results of the regression analysis for troponin alone (as mentioned in **Table 2**) and the regression analysis



**Figure 1.** Correlation between serum biomarkers and 30-day mortality rate. **(A)** The highest level of lactate (>4 mmol/L) was correlated with a higher mortality rate. **(B)** The higher level of troponin (>0.045 ng/mL) was associated with a higher mortality rate. **(C)** The higher level of NT-proBNP (>8000 pg/mL) was correlated with a higher mortality rate.

**Table 2.** Higher biomarker levels were associated with higher possibility of death as a predictor of 30-day mortality.

Variable	Odds ratio	95% CI	P-value
Lactate 4.0	3.1929	(1.98-5.14)	0.00006
Troponin >0.045	2.12741	(1.51-2.99)	0.00027
NT-proBNP >8000	2.497	(1.69-3.70)	0.00013

NT-proBNP – N-terminal pro-B-type natriuretic peptide; CI – confidence interval.

for troponin and lactate showed that troponin was predictive of 30-day mortality, with an aOR 2.69 times (95% CI 1.65-4.39,  $P=0.0009$ ) higher than that of the reference group; however, when it was combined with lactate and NT-proBNP, troponin was not statistically significant.

As a part of determining the mortality prediction ability of these biomarkers in sepsis and septic shock, APACHE II scores were calculated and a comparison between the groups was made using linear regression. Results showed that the groups with lactate levels  $\geq 4$  mmol/L, troponin levels  $\geq 0.045$  ng/mL, and NT-proBNP levels  $\geq 8000$  pg/mL had higher APACHE II scores, which in turn were associated with a higher rate of mortality (**Table 3, Figure 2A-2C**).

For the group with lactate levels  $\geq 4$  mmol/L, the APACHE II score was 9.12 points ( $P=0.00028$ ) higher than that of the group with lactate levels  $< 2$  mmol/L. When analyzed in combination with the other variables, the group with lactate levels  $\geq 4$  mmol/L, had an APACHE II score that was 6.79 points ( $P=0.00683$ ) higher than that of the reference group, while keeping the other 2 variables constant. Compared with the group with troponin levels  $< 0.045$  ng/mL, the group with troponin levels  $\geq 0.045$  ng/mL had an APACHE II score that was 7.70 points ( $P=0.0001$ ) higher, whether observed independently or in combination with the other 2 serum biomarkers, lactate and NT-proBNP. Similarly, for the group with NT-proBNP levels  $\geq 8000$  pg/mL, the APACHE II score was 8.88 points ( $P=0.00013$ ) higher than the APACHE II score of the group with NT-proBNP  $< 4000$  pg/mL. When observed in combination with the other

variables, the group with NT-proBNP levels  $\geq 8000$  pg/mL had an APACHE II score that was 6.36 points ( $P=0.00559$ ) higher, while keeping the other 2 variables constant.

### Other Correlations and Associations

The correlation of the serum biomarkers and length of hospital stay among survivors showed that the length of stay was 3.34 days longer on average in the group with troponin levels  $\geq 0.045$  ng/mL than in the reference group (troponin  $< 0.045$  ng/mL). The other variables were not statistically significant at a 95% CI.

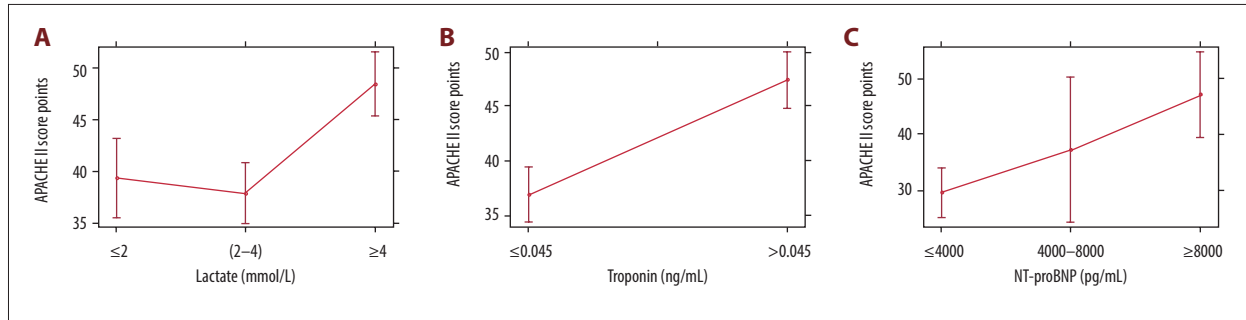
The correlation of the 3 serum biomarkers and admission to the Medical Intensive Care Unit (MICU) was analyzed only among the survivors. Results showed the group with serum lactate levels  $\geq 4$  mmol/L and the group with troponin levels  $\geq 0.045$  ng/ml had a higher chance of being admitted to the MICU. This correlation was found to be present not only when the 2 variables were studied independently, but was also present when each of the 2 variables was observed in combination with the other serum biomarkers (**Table 4, Figure 3A, 3B**).

The group with lactate levels  $\geq 4$  mmol/L had a 2.65 times (95% CI 1.54-4.55,  $P=0.003$ ) higher aOR for being admitted to the MICU compared with its reference group (lactate  $< 2$  mmol/L). Similarly, for the group with troponin levels greater than 0.045 ng/mL, the aOR of being admitted to the MICU was 2.24 times (95% CI 1.48-3.38,  $P=0.00128$ ) higher than that of its reference group (troponin  $< 0.045$  ng/mL). The pro-BNP group did not show statistical significance at a 95% CI for MICU admission.

**Table 3.** Higher biomarker levels were associated with higher Acute Physiology and Chronic Health Evaluation (APACHE) II score.

Variable	Estimate	Std. error	P-value
Lactate 4.0	9.12	2.5	0.00028
Troponin >0.045	7.70	1.97	0.0001
NT-proBNP >8000	8.88	2.3	0.00013

NT-proBNP – N-terminal pro-B-type natriuretic peptide.

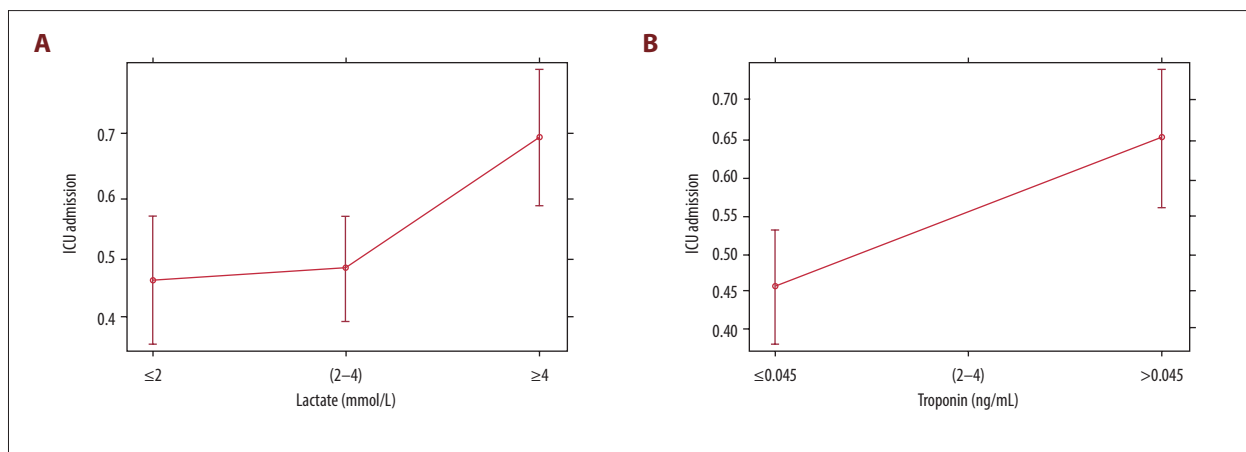


**Figure 2.** Correlation between serum biomarkers and Acute Physiology and Chronic Health Evaluation (APACHE) II score. (A) The highest level of lactate (>4 mmol/L) was correlated with a higher APACHE II score. (B) The higher level of troponin (>0.045 ng/mL) was associated with a higher APACHE II score. (C) The higher level of NT-proBNP (>8000 pg/mL) was correlated with a higher APACHE II score.

**Table 4.** Higher lactic acid and troponin levels were associated with a higher chance of Medical Intensive Care Unit (MICU) admission.

Variable	Odds ratio	95% CI	P-value
Lactate 4.0	2.65	(1.54-2.65)	0.003
Troponin >0.045	2.24	(1.48-3.38)	0.00128

CI – confidence interval.



**Figure 3.** Correlation between serum lactic acid and troponin with the medical Intensive Care Unit (MICU) admission. (A) The highest level of Lactate (>4 mmol/L) was correlated with MICU admission. (B) The higher level of troponin (>0.045 ng/mL) was associated with MICU admission.

## Discussion

We found that elevated levels of lactate, troponin, and NT-proBNP were each predictive of 30-day mortality in patients with sepsis and septic shock. Patients with high levels of all 3 biomarkers (lactate, troponin, and NT-proBNP) had a higher mortality rate. Furthermore, we demonstrated the relationship between increased levels of these serum biomarkers with higher APACHE II scores in these patients. Among survivors, elevated levels of lactate and troponin were associated with an increased chance of admission to the MICU, whereas only an elevated level of troponin was found to be prognostic of a longer length of hospital stay.

There are a few limitations to our study. First, it may be prone to sampling bias. A total of 1242 patients were found to be potentially eligible for our research. However, of these, 815 patients needed to be excluded because the 3 serum biomarkers were not measured in these patients. Therefore, the sample may not be an accurate representation of the target population, and caution must be exercised before extrapolating the results of our study to all patients with sepsis and septic shock. Nevertheless, the results obtained from our study are internally valid and are an accurate representation of actual practice carried out at a single center. Second, our study may be limited by confounding bias, as we were unable to adjust for any confounders that may have affected the outcomes of interest.

It is essential to recognize the key novel findings of our study. To date, several studies have been conducted to assess the utilization of several different serum biomarkers in patients with sepsis. However, to the best of our knowledge, this is the first study to evaluate the prognostic use of lactate, troponin, and pro-BNP in combination. The results of our study may provide valuable insight into the combined use of these biomarkers as predictive tools in patients with sepsis and septic shock.

The independent correlations of elevated levels of serum lactate, troponin, and NT-proBNP with mortality demonstrated in our study are indicative of the prognostic ability of these biomarkers. These biomarkers may aid in the risk-stratification of patients with sepsis and septic shock, and offer clinicians an opportunity to administer life-saving interventions to high-risk patients early in the disease course. Multiple studies have shown the association between elevated lactate levels and mortality in sepsis [4,7-10]. On the other hand, although some studies have shown an independent association between elevated troponin levels and mortality [11-13], other studies have not [14,15]. Similarly, a relatively unclear picture applies to the significance of NT-proBNP in predicting mortality in sepsis, with some studies finding a positive correlation between elevated NT-proBNP levels and mortality [16-18], alongside others that found no significant correlation [19,20]. This could presumably

be because of the presence of multiple causes of natriuretic peptide elevations in patients with sepsis. Indeed, the results of our study are consistent with previous data showing that elevated levels of lactate, troponin, and NT-proBNP are predictors of mortality in patients with sepsis and septic shock.

An ideal prognostic biomarker should be equal to or superior to the clinical severity scores used for the prediction of outcomes. The APACHE II score is a widely applied tool in critically ill patients and is a strong predictor of mortality in patients with sepsis [21,22]. In our study, each of the 3 biomarkers was found to have a positive correlation with higher APACHE II scores, which is indicative of the prognostic ability of these biomarkers. Several studies have demonstrated the usefulness of serum biomarkers in combination with the APACHE II score for the prediction of mortality in critically ill patients with sepsis and septic shock [23-25]. The combined use of these biomarkers and the APACHE II score may therefore serve as a useful method for the risk stratification of patients with sepsis and septic shock.

Elevated levels of serum lactate have been associated with an increased chance of admission to the ICU in patients with sepsis and septic shock [26,27]. Similarly, elevated troponin levels are frequently seen in critically ill patients admitted to the ICU [28,29]. These findings are consistent with our observation of an increased probability of MICU admission in patients with elevation of either serum lactate or troponin levels. It is interesting to note that in our study, serum lactate was independently associated with higher APACHE II scores and an increased risk of MICU admission only at levels higher than 4 mmol/L. This may be because rising lactate levels are associated with an increased severity of illness and mortality in patients with sepsis. Thus, in comparison to patients with lower lactate levels, patients with lactate levels >4 mmol/L may have a more severe illness that may be reflected by higher APACHE II scores and a greater risk of being admitted to the ICU. However, it is important to remember that the lactate expression in sepsis can vary in each individual, and patients with normal to mildly elevated lactate levels can still carry a significant risk of mortality.

Serum lactate has also been identified as a predictor of longer length of hospital stay [30]; however, there is differing evidence on the ability of troponin and pro-BNP to predict the length of hospital stay. Some studies suggest that elevated troponin levels are associated with an increased length of stay [31], whereas others do not show any such association [32,33]. Similarly, while some studies have shown the role of BNP in predicting an increased length of stay [17,34,35], others indicate the opposite [19]. Nevertheless, in our study, only elevated levels of troponin predicted an increased length of hospital stay.

Because there is no evidence of a single biomarker with high sensitivity and specificity that can be used as the ideal prognostic tool in patients with sepsis and septic shock, there has been a recent trend toward the utilization of a biomarker combination approach [36,37]. Some investigators have used a combination of interleukin-6, procalcitonin, and soluble triggering receptor expressed on myeloid cells-1 for the early detection of sepsis [38]. However, others have combined arterial lactate, NT-proBNP, and C-reactive protein for the prediction of mortality in patients with sepsis [39]. Therefore, it was interesting to find in our present study that the 3 serum biomarkers were of predictive value when used together. Therefore, the combined use of these biomarkers may provide clinicians with a more convenient method of risk stratification.

Multiple organ dysfunction syndrome (MODS) is a critical illness that is characterized by the development of reversible physiological derangements in association with the simultaneous dysfunction of 2 or more organs. MODS is a major cause of morbidity and mortality, and can develop in response to sepsis, traumatic injuries, burns, or hypoperfusion. The exact pathophysiology of sepsis-induced MODS is complex and multifactorial, and has been proposed to be directly related to the host's excessive proinflammatory response toward the infection. Various prognostic indicators, including high APACHE II scores, have been identified as risk factors for the development of multiorgan failure in patients with severe sepsis admitted to

the MICU [40]. Hence, the combined use of the 3 serum biomarkers and the APACHE II score may help identify patients with sepsis who are at an increased risk of multiorgan failure, thereby promoting the use of organ-targeted treatment and preventing the occurrence and progression of MODS.

Future prospective studies should be conducted to evaluate the benefit of clinical management algorithms in which these 3 serum biomarkers, lactate, troponin, and NT-proBNP, are used for the risk stratification of patients with sepsis and septic shock. It remains to be determined whether these algorithms will benefit high-risk patients. The added costs of obtaining combined lactate, troponin, and NT-proBNP will be justified if future studies can demonstrate the advantages of using such models of prognostication.

## Conclusions

Elevated levels of serum lactate, troponin, and NT-proBNP are independently predictive of mortality and higher APACHE II scores, and may therefore be useful prognostic biomarkers in patients with sepsis and septic shock. Higher lactate and troponin levels may also help identify patients who have an increased chance of admission to the MICU. The prognostic utility of these 3 biomarkers may be further improved by using them in combination with each other.

## References:

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, 2016;315(8):8010-10
2. Gyawali B, Ramakrishna K, Dharmoon AS. Sepsis: The evolution in definition, pathophysiology, and management. *SAGE Open Med*, 2019;7:2050312119835043
3. Kim HI, Park S. Sepsis: Early recognition and optimized treatment. *Tuberc Respir Dis (Seoul)*, 2019;82(1):6-14
4. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*, 2009;37:1670-77
5. Hussain N. Elevated cardiac troponins in setting of systemic inflammatory response syndrome, sepsis, and septic shock. *ISRN Cardiol*, 2013;2013:1-7
6. Rivers EP, McCord J, Otero R, et al. Clinical utility of B-type natriuretic peptide in early severe sepsis and septic shock. *J Intensive Care Med*, 2007;22(6):363-73
7. Lee SM, An WS. New clinical criteria for septic shock: Serum lactate level as new emerging vital sign. *J Thorac Dis*, 2016;8(7):1388-90
8. Filho RR, Rocha LL, Corrêa TD, et al. Blood lactate levels cutoff and mortality prediction in sepsis-time for a reappraisal? A retrospective cohort study. *Shock*, 2016;46(5):480-85
9. Kang HE, Park DW. Lactate as a biomarker for sepsis prognosis? *Infect Chemother*, 2016;48(3):252-53
10. Chambers KA, Park AY, Banuelos RC, et al. Outcomes of severe sepsis and septic shock patients after stratification by initial lactate value. *World J Emerg Med*, 2018;9(2):113-17
11. Smith A, John M, Trout R, et al. Elevated cardiac troponins in sepsis: What do they signify? *WV Med J*, 2009;105(4):29-32
12. Bessière F, Khenifer S, Dubourg J, et al. Prognostic value of troponins in sepsis: A meta-analysis. *Intensive Care Med*, 2013;39(7):1181-89
13. Vasile VC, Chai HS, Abdeldayem D, et al. Elevated cardiac troponin T levels in critically ill patients with sepsis. *Am J Med*, 2013;126(12):1114-21
14. Mehta S, Granton J, Gordon AC, et al. Cardiac ischemia in patients with septic shock randomized to vasopressin or norepinephrine [published correction appears in *Crit Care*, 2017;21(1):98]. *Crit Care*, 2013;17(3):R117
15. Brivet FG, Jacobs FM, Colin P, et al. Cardiac troponin level is not an independent predictor of mortality in septic patients requiring Medical Intensive Care Unit admission. *Crit Care*, 2006;10(1):404
16. Varpula M, Pulkki K, Karlsson S et al, FINNSEPSIS Study Group. Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. *Crit Care Med*, 2007;35(5):1277-83
17. Singh H, Ramai D, Patel H, et al. B-type natriuretic peptide: A predictor for mortality, Intensive Care Unit length of stay, and hospital length of stay in patients with resolving sepsis. *Cardiol Res*, 2017;8(6):271-75
18. Brueckmann M, Huhle G, Lang S, et al. Prognostic value of plasma N-terminal pro-brain natriuretic peptide in patients with severe sepsis. *Circulation*, 2005;112(4):527-34
19. McLean AS, Huang SJ, Hyams S, et al. Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock. *Crit Care Med*, 2007;35(4):1019-26
20. Rudiger A, Gasser S, Fischler M, et al. Comparable increase of B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure. *Crit Care Med*, 2006;34(8):2140-44
21. Sadaka F, EthmaneAbouElMaali C, Cytron MA, et al. Predicting mortality of patients with sepsis: A comparison of APACHE II and APACHE III scoring systems. *J Clin Med Res*, 2017;9(11):907-10
22. Badrinath K, Shekhar M, Sreelakshmi M, et al. Comparison of various severity assessment scoring systems in patients with sepsis in a tertiary care teaching hospital. *Indian J Crit Care Med*, 2018;22(12):842-45

23. Bao B, Li ZG, Sun XL. [Blood lactic acid level and APACHE II score on prognosis of critically ill elderly patients.] *Zhonghua Liu Xing Bing Xue Za Zhi*, 2012;33(4):428-30 [in Chinese]
24. Wang H, Li Z, Yin M, et al. Combination of Acute Physiology and Chronic Health Evaluation II score, early lactate area, and N-terminal prohormone of brain natriuretic peptide levels as a predictor of mortality in geriatric patients with septic shock. *J Crit Care*, 2015;30(2):304-9
25. Cheng H, Fan WZ, Wang SC, et al. N-terminal pro-brain natriuretic peptide and cardiac troponin I for the prognostic utility in elderly patients with severe sepsis or septic shock in Intensive Care Unit: A retrospective study. *J Crit Care*, 2015;30(3):654.e9-14
26. Yoo JW, Lee JR, Jung YK, et al. A combination of early warning score and lactate to predict Intensive Care Unit transfer of inpatients with severe sepsis/septic shock. *Korean J Intern Med*, 2015;30(4):471-77
27. Wardi G, Wali AR, Villar J, et al. Unexpected intensive care transfer of admitted patients with severe sepsis. *J Intensive Care*, 2017;5:43
28. Ostermann M, Lo J, Toolan M, et al. A prospective study of the impact of serial troponin measurements on the diagnosis of myocardial infarction and hospital and six-month mortality in patients admitted to ICU with non-cardiac diagnoses. *Crit Care*, 2014;18(2):R62
29. Markou N, Gregorakos L, Myrianthefs P. Increased blood troponin levels in ICU patients. *Curr Opin Crit Care*, 2011;17(5):454-63
30. Bou Chebl R, El Khuri C, Shami A, et al. Serum lactate is an independent predictor of hospital mortality in critically ill patients in the Emergency Department: A retrospective study. *Scand J Trauma Resusc Emerg Med*, 2017;25(1):69
31. Lim W, Qushmaq I, Devereaux PJ, et al. Elevated cardiac troponin measurements in critically ill patients. *Arch Intern Med*, 2006;166(22):2446-54
32. Abdalla M, Sohal S, Al-Azzam B, Mohamed W. Effect of troponin I elevation on duration of mechanical ventilation and length of Intensive Care Unit stay in patients with sepsis. *J Clin Med Res*, 2019;11(2):127-32
33. Tiruvoipati R, Sultana N, Lewis D. Cardiac troponin I does not independently predict mortality in critically ill patients with severe sepsis. *Emerg Med Australas*, 2012;24(2):151-58
34. Zhang Z, Zhang Z, Xue Y, et al. Prognostic value of B-type natriuretic peptide (BNP) and its potential role in guiding fluid therapy in critically ill septic patients. *Scand J Trauma Resusc Emerg Med*, 2012;20:86
35. Zhao HY, An YZ, Liu F. [Prognostic values of B-type natriuretic peptide in severe sepsis and septic shock.] *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*, 2009;21(5):293-95 [in Chinese]
36. Samraj RS, Zingarelli B, Wong HR. Role of biomarkers in sepsis care. *Shock*, 2013;40(5):358-65
37. Sandquist M, Wong HR. Biomarkers of sepsis and their potential value in diagnosis, prognosis and treatment. *Expert Rev Clin Immunol*, 2014;10(10):1349-56
38. Dolin HH, Papadimos TJ, Stepkowski S, et al. A novel combination of biomarkers to herald the onset of sepsis prior to the manifestation of symptoms. *Shock*, 2018;49(4):364-70
39. Guo Y, Yang H, Gao W, et al. Combination of biomarkers in predicting 28-day mortality for septic patients. *J Coll Physicians Surg Pak*, 2018;28(9):672-76
40. Jenkins D, Sharfeen Qureshi R, Moinudheen J, et al. Evaluation of electronic medical record downtime in a busy Emergency Department. *Qatar Med J*, 2020;2020(1):20