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Original Article

Serum platelet and bilirubin levels as potential predictors of septic shock in adults with sepsis admitted to the intensive care unit

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Abstract: Objective: Early identification of septic shock is critical for effective treatment. This study aimed to investigate the potential of different diagnostic and prognostic sepsis biomarkers as indicators for sepsis and septic shock. Methods: The study involved 47 patients with sepsis, including 11 patients with septic shock. Seventeen biochemical, hemostatic, and inflammatory markers as well as blood and Deep Throat Aspiration (DTA) cultures were tested. ELISA was used to measure blood levels of biomarkers. Results: The platelet count (PLT), and plasma bilirubin were significantly associated with septic shock. The cultures showed no growth in 9.1% (septic shock) and 11.1% (sepsis) of the cultured samples, P = 0.10, with *Acinetobacter* significantly lower (0% vs. 38.9%), P = 0.02, and *Candida* significantly higher (45.5% vs. 13.9%), P = 0.039 in septic shock patients. Conclusion: The study showed that PLT and plasm bilirubin are potential markers for septic shock, supported by the dominance of *Candida* and scarcity of *Acinetobacter* in pathogen cultures.

Keywords: Sepsis, septic shock, ICU, biomarkers, bilirubin, blood and DTA culture

Introduction

Sepsis is characterized by intense systemic inflammation, which can progress to a fatal condition which is septic shock, therefore, early identification of sepsis and septic shock is a life-saving matter. Despite advances in management, sepsis mortality rates remain high between 20% and 36% in the world's best hospitals primarily due to the progression of sepsis to septic shock [1, 2]. Several biomarkers have been proposed for early detection and prognosis of sepsis. However, there is not yet a clear optimal approach for sepsis and septic shock prediction [2-4].

To better comprehend sepsis and its complications, it is necessary to define the terms used in the literature, including sepsis, septicemia, and septic shock. The definition of sepsis is not consistent in all settings, the world health organization (WHO) defines sepsis as a serious condition that happens when the body's immune system has an extreme response to an infection, with consequent damage to its tissues and organs. This is consistent with an earlier definition by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), which defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection [5]. Septic shock is defined as sepsis with circulatory, cellular, and metabolic dysfunction, associated with a higher risk of mortality [6]. Septicemia is not synonymous with sepsis, as the former is an invasion of the bloodstream by bacteria which may trigger a strong systemic immune response [6]. Regardless, sepsis and/or septicemia cause inflammation throughout the body, which can cause blood clots and oxygen depletion in vital organs, resulting in organ failure. When organ failure occurs with low

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blood pressure and vasodilatation, the term septic shock is used, which is a more fatal condition [5].

While there is no single ideal biomarker for diagnosing sepsis, several simple diagnostic criteria exist such as heart rate (HR), respiratory rate (RR), and blood pressure (BP) [7]. However, it is worth noting that RR and BP are not always recorded in patients on artificial ventilation (AV) or those who have unrecordable BP due to septic shock, respectively. White blood count (WBC) is one lab-based parameter performed routinely or in cases of suspected bacterial infection in a hospital setting [8]. In addition, inflammatory markers such as c-reactive protein (CRP), and procalcitonin (PCT), along with the clinical presentation remain the most widely used method for sepsis diagnosis [3, 9]. PCT has been approved for sepsis diagnosis and was shown to be a more reliable indicator of sepsis than CRP [9]. Finally, lactate, the metabolic marker for anaerobic metabolism due to hypoxia or ischemia, is also widely accepted as a reliable circulating marker for sepsis severity [10] and was added to the list of diagnostic parameters in 2016 [5]. However, none of these parameters described are specific to infection or are used to predict the progression of sepsis to septic shock.

Some of the most widely investigated biomarkers for sepsis are; interleukin-6 (IL-6) and interleukin-8 (IL-8) [11, 12], soluble triggering receptor expressed on myeloid cells 1 (TREM-1) [13], Soluble urokinase-type plasminogen activator receptor (suPAR) [14] and presepsin. The suPAR is reported to be important in the diagnosis and prognosis of sepsis and septic shock [15]. However, there is currently no approved biomarker for tracking sepsis development and progression into the more severe and fatal septic shock [16].

While blood culture remains an indispensable diagnostic tool for the detection of septicemia, it has major limitations such as long turnaround time, or failure of microbial growth in patients who received antimicrobials such as antibiotics, and failure to detect slow-growing and obligatory intracellular pathogens [17]. In this study, we aimed to identify potential septic shock detection markers in sepsis patients that can be investigated later for septic shock prediction. Considering the lack of any single ideal biomolecule for diagnosing septic shock, it is prudent to determine the best combination of such biomarkers to allow for early diagnosis and risk assessment, with improved sensitivity and specificity. Hence, the present study was envisaged to serve as an initiative for the development of better diagnostic markers for septic shock, and risk assessment in septicemic patients.

Materials and methods

Study type and site: This is a cross-sectional hospital-based study, conducted at Salmaniya Medical Complex (SMC) in Bahrain.

Study subjects: A total of 47 patients with sepsis were admitted to the intensive care unit (ICU). This included 11 patients who developed septic shock. Inclusion criteria were any patient (18 years or above) diagnosed with sepsis, who is admitted to the ICU at SMC and provided informed consent to participate. Patients with other conditions that could interfere with the marker levels such as chronic inflammatory conditions were excluded. Pregnant or lactating women, patients under 18 years of age, and those who did not sign an informed consent were all excluded from the study.

Ethical issues

This study proposal was approved by the Research and Ethics Committee of the College of Medicine and Medical Sciences (CMMS), Arabian Gulf University (AGU), Bahrain. Informed consent was obtained from patients/guardians, for inclusion in the study and publication of the data.

Clinical diagnosis

Sepsis diagnosis was largely based on the WHO and the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee (ACCP/SCCM), Sepsis 1-2 criteria. These include a body temperature above 38°C or below 36°C, heart rate (HR) >90/minute, respiratory rate (RR) >20/minute, white blood count (WBC) >12000/mm^3 or <4000/mm^3 [7], in addition to CRP, PCT, and lactate measurement. Artificial ventilation (AV), was considered as a marker for severity.

Blood sampling

Blood samples were collected by venipuncture in plain and EDTA tubes, on the day of diagno-

sis, before the commencement of treatment. Plasma was separated by centrifugation for 15 min at 1000×g (at 2°C-8°C), within 30 min of blood collection, and stored at -80°C until use.

Laboratory investigations

1. Diagnostic parameters: The WBC, CRP, PRC, and lactate were measured using automated machines in the SMC central lab, clinical chemistry section. 2. Para-diagnostic parameters: Hemostasis markers; platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, international normalization ratio (INR), and D-dimer, were measured in the hematology section of the central lab using automated hemo-analyzers. For the organ dysfunction markers (ODM), bilirubin was measured using an automated chemo-analyzer.

Enzyme-linked immunosorbent assay (ELISA)

Solid-phase sandwich ELISA analysis using Invitrogen ELISA kits was used for measurement of IL-6 (EH2IL6), IL-8 (KHC0081), TREM-1 (EHTREM1), uPAR (EHPLAUR), and presepsin (MBS766136), following the protocols provided with the kits, as previously described [18].

Blood culture

Blood culture was conducted to identify the causative pathogen for sepsis. This was conducted following aseptic techniques, and both the venipuncture site and tops of the culture bottles were disinfected with 70% isopropyl alcohol to minimize the likelihood of any contamination. Subsequently, 10 ml of the patient's blood was collected via a sterile needle into aerobic and anaerobic blood culture bottles. The blood culture bottles were incubated in a BACTEC blood culture instrument at 37°C. The instrument automatically reports positive blood culture or the presence of microbial pathogens. Further subcultures and proper bacterial identification were carried out as needed [19].

Deep throat aspiration (DTA) cultures

Deep tracheal aspirates (DTA) were collected and sent to the microbiology lab for culture and assessment. The DTA samples were cultured according to a previously reported standard procedure at SMC [20].

Statistical analysis

The main analytic tests were the comparison and correlation tests using Sigma Stat software. The tests were the t-test, Mann-Whitney Rank Sum Test some test (MW), One-way analysis of variance (ANOVA), Kruskal-Wallis One Way Analysis of Variance on Ranks (KW), and Chi-square test. Pearson product-moment correlation coefficient (Pearson's correlation, for short) was used in the correlation analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

The number, sex, and age of study subjects

Over the study period, a total of 47 patients with severe sepsis were admitted to the ICU, including 11 patients who had septic shock. The patients with septic shock were comparable with the remaining patients with sepsis, in terms of sex (male/female) ratio (6/5 vs. 17/19, respectively) and age (62.0, 43.0-70.0 vs. 58.0, 34.0-65.0 years, respectively, P = 0.285) (**Table 1**).

Levels of diagnostic and para-diagnostic parameters

As seen in **Table 1**, the diagnostic parameters, HR, WBC, CRP, PCT, and lactate were comparable between the two groups, the septic shock and sepsis patients, P = 0.360, P = 0.167, P = 0.976, P = 0.101, P = 128, respectively, as well as the body temperature (temp). However, of the six hemostasis parameters, only the PLT count was different between the septic shock and sepsis groups, which was significantly lower in the former group, 115.55 ± 83.67 vs. 219.72 ± 117.28, P = 0.009, T-test (**Figure 1A**).

Bilirubin was the only marker measured to assess ODM, and it was found to be significantly higher in septic shock patients, 84.0, 11.0-116.0 vs. 12.0, 7.0-30.5, P = 0.036 (**Figure 1B**). However, the AV frequency, which may serve as a sepsis severity indicator, was not significantly different between the two groups, septic shock, and sepsis, 70% (7/10) vs. 50% (17/34), P = 0.306, Chi-square test.

Levels of sepsis biomarkers

In the comparisons between septic shock patients and sepsis patients, the levels of the

Table 1. Description of patients with septic shock and sepsis patients without shock, and comparison of levels of diagnostic markers between the two groups

Variables	Septic shock patients	Sepsis patients	*p*-value (MW)
Number	11	36	
Sex/ratio (M/F)	6/5	17/19	
Age (years)	62.0, 43.0-70.0	58.0, 34.0-65.0	0.285
Others			
Temperature (°C)	36.63 ± 1.18	37.04 ± 1.31	0.363 T-test
Under AV	70% (7/10)	50% (17/34)	0.306 Chi-square
Diagnostic parameters			
HR (bpm)	110.80 ± 23.35	102.77 ± 24.71	0.360 T-test
WBC (× 10^9/L)	20.10, 15.93-31.40	16.09, 10.70-23.79	0.167
CRP (mg/L)	103.5, 22.83-176.00	100.0, 44.35-155.25	0.976
PCT (mg/L)	11.25, 1.80-35.820	2.39, 0.47-11.300	0.101
Lactate (mmol/L)	2.1, 1.6-7.8	1.7, 1.3-3.2	0.128
Hemostasis parameter			
PT (sec)	16.60, 15.00-19.80	14.95, 13.15-18.125	0.119
APTT (sec)	29.00, 22.80-45.20	27.10, 23.40-36.30	0.767
INR	1.4, 1.28-1.80	1.295, 1.107-1.415	0.102
Fibrinogen (g/L)	366.92 ± 159.08	412.27 ± 151.76	0.435 T-test
D-dimer (mg/L)	11.35, 3.308-24.555	5.35, 1.555-8.698	0.119

APTT = activated partial thromboplastin time, AV = artificial ventilation, bpm = beat per minute, CRP = c-reactive protein, HR = heart rate, INR = international normalized ratio, PCT = procalcitonin, PT = prothrombin time, WBC = white blood count.

tested biomarkers IL-6 (P = 0.499), IL-8 (P = 0.289), TREM-1 (P = 0.366), uPAR (P = 0.152), and presepsin (P = 0.466) were not significantly different between the two groups (**Table 2**).

The outcome of the blood and DTA cultures for microorganisms

The frequency of sterile blood culture for microbial growth in septic shock patients was 45.5% and in sepsis patients was 33.3%, P = 0.493, which was comparable (**Table 3**). For the positive blood cultures, the dominant pathogens were *Staphylococcus* (Staph), with a prevalence of 36.4% in the septic shock group and 27.8% in the sepsis group, P = 0.710, followed by *Acinetobacter*, 0.0% and 19.4%, respectively, P = 0.175, and then *Candida*, 9.1% and 2.8%, respectively, P = 0.417, which were all comparable between the two groups. Other detected pathogens were *E. coli* and *Enterobacter cloacae* in septic shock, *Enterococcus faecalis*, *klebsiella pneumoniae, Streptococcus gallolyticus, Propionibacterium, Escherichia coli,* and *Burkholderia cepacian* in sepsis.

For the DTA culture, the frequency of sterile culture was 27.3% in septic shock and 33.3% in sepsis, P = 1.00, which was comparable. For the positive DTA culture, the prevalence of Staph was 18.2% in septic shock and 8.3% in the sepsis group, P = 0.578, and of the *Acinetobacter*, was 0.0% and 22.2%, respectively, P = 0.170, which were comparable between the two groups. The prevalence of *Candida* was significantly higher in septic shock (45.5%) compared to the sepsis group (13.9%), P = 0.039. However, when taking the results of both blood and DTA cultures together, the prevalence of sterile culture declined to 9.1% in septic shock and 11.1% in the sepsis groups but remained comparable between the two groups, P = 1.000. The prevalence of Staph inclined in septic shock to 45.5% and in sepsis to 30.6%, and the difference remained insignificant, P = 0.472. However, for the prevalence of *Acinetobacter* in septic shock (0.0%) and in sepsis (38.9%), P = 0.020, and of *Candida* in septic shock (45.5%) and in Se (13.9%), P = 0.039, was significantly different. The other detected pathogens in DTA cultures were *Klebsiella pneumoniae, Streptococcus pneumoniae, Stenotrophomonas maltophilia*, gram negative bacilli, in septic shock. While in sepsis, the other pathogens detected by DTA culture

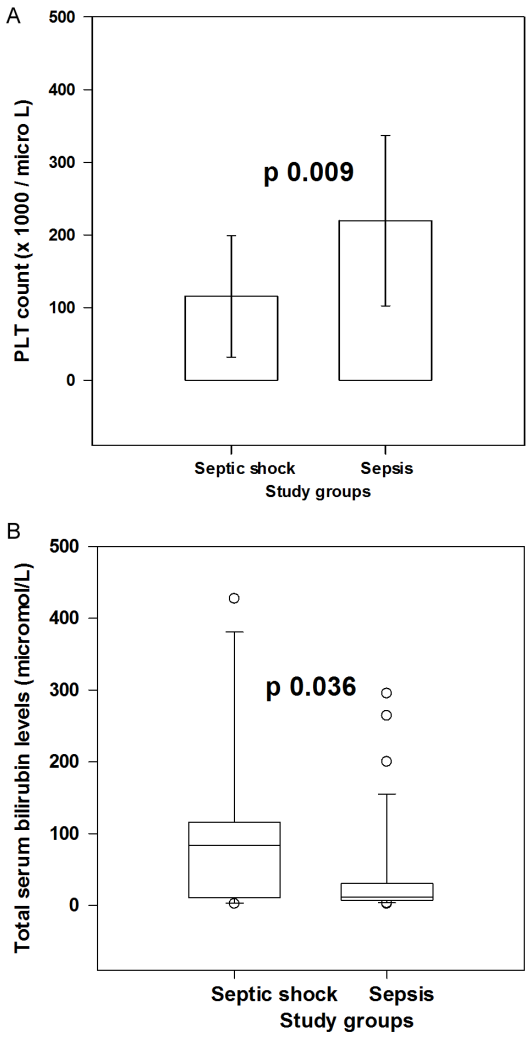

Figure 1. A. Bar Chart Column Means showing significantly lower platelet counts in patients with septic shock compared to patients with sepsis without shock, P = 0.009. B. Box plot showing higher median plasma bilirubin concentrations in patients with septic shock compared to patients with sepsis without shock, P = 0.036.

were *Pseudomonas aeruginosa, K. Pneumoniae, Klebsiella pneumoniae, Stenotrophomonas maltophilia, E. Coli,* and *Burkholderia cepacia*.

Discussion

This study aimed to identify potential biomarkers of septic shock. The study identified two non-clinical markers of septic shock, the PLT count and plasma bilirubin. These markers showed strong statistical significance, suggesting that these might be genuine biomarkers for septic shock. Unexpectedly, the other diagnostic and para-diagnostic parameters of sepsis failed to distinguish septic shock from sepsis. Age and sex are known to influence sepsis development and progression [21], however, in this study, both age and sex were less likely to be confounders as they were statistically comparable (**Table 1**).

The drop in PLT count is one of the most well-established markers associated with infection, including sepsis. It is considered an earlier marker detected in both conditions and may contribute to clinical diagnostic processes [22, 23]. PLTs are small, anucleate cells with hemostatic, inflammatory, and immune-mediating properties; therefore, sepsis is described as a thrombo-inflammatory disorder [24]. PLTs are found to express Toll-like receptors (TLR) genes, that recognize bacteria, viruses, parasites, and protozoa ligands, and may accordingly function as pathogen “sensors” [25]. In the current study, PLT count was shown to be the only hematological parameter that was strongly associated with septic shock. This is in line with a previous study that suggested that PLT count is a reliable tool for diagnosing septic shock during the first week of ICU hospitalization [26]. The other hemostasis parameters, PT, APTT, fibrinogen, INR, and D-dimer, which were used as sepsis para-diagnostic parameters, failed to detect septic shock in patients with sepsis in this study, even though coagulopathy is a cardinal feature of both sepsis and septic shock [27].

The second marker for septic shock in this study was bilirubin, which was used as an ODM. Plasma concentrations of bilirubin were significantly higher in patients with septic shock compared with sepsis patients. Accordingly, a rise in plasma bilirubin may help in predicting septic shock in patients admitted to the ICU. From another perspective, raised bilirubin can be interpreted as an indicator of liver dysfunction in septic shock, however, this remains to be explored. One mechanism of liver dysfunction in septic shock patients may be liver hypoxia secondary to hypovolemia [28]. Alternatively, bacteria, toxins, and/or cytokines of sepsis, may contribute to liver injury, as suggested before [29]. Similar to PLT count, bilirubin levels are not specific for sepsis and are recognized in several non-infectious disorders, therefore, their validity in detection/prediction of septic

Table 2. Plasma concentration of tested biomarkers in sepsis patients with and without septic shock

Tested biomarker	Septic shock patients	Sepsis patients	*p*-value (MW)
IL-6	41.72, 4.63-237.79	31.14, 0.68-64.19	0.499
IL-8	-44.97, -72.95-47.487	-62.43, -74.64 - -26.686	0.289
TREM-1	-393.07, -437.21-268.46	-338.34, -412.59 - -227.50	0.366
uPAR	1923.606 ± 991.580	1453.962 ± 914.443	0.152
Presepsin	13.27, 7.94-23.46	13.45, 3.86-18.66	0.466

Note: All values are arbitrary units, therefore negative readings are of comparative value only.

Table 3. Microbial growth detection pattern in septic shock and sepsis, in blood culture (BC), deep throat aspiration (DTA) culture, and all cultures

Type of culture	Pathogens	Septic shock	Sepsis	Fisher Exact Test *p*-values
Blood culture	No growth (sterile)	45.5% (5/11)	33.3% (12/36)	0.493
	Staphylococcus (Staph)	36.4% (4/11)	27.8% (10/36)	0.710
	Acinetobacter	0.0% (0/11)	19.4% (7/36)	0.175
	Candida	9.1% (1/11)	2.8% (1/36)	0.417
	Others	BC^{Ssh}	BC^{Se}	
DTA culture	No growth (sterile)	27.3% (3/11)	33.3% (12/36)	1.000
	Staph	18.2% (2/11)	8.3% (3/36)	0.578
	Acinetobacter	0.0% (0/11)	22.2% (8/36)	0.170
	Candida	**45.5% (5/11)**	**13.9% (5/36)**	**0.039**
	Others	DTA^{Ssh}	DTA^{Se}	
All culture	No growth (sterile)	9.1% (1/11)	11.1% (4/36)	1.000
	Staph	45.5% (5/11)	30.6% (11/36)	0.472
	Acinetobacter	**0.0% (0/11)**	**38.9% (14/36)**	**0.020**
	Candida	**45.5% (5/11)**	**13.9% (5/36)**	**0.039**

Note: In one patient more than one pathogen could be detected, therefore the total is not equivalent to 100%. Ssh = sseptic shock, Se = sepsis. Bolded rows stand for statistically significant differences. BC^{Ssh} = E. coli, Enterobacter cloacae, DTA^{Ssh} = Klebsilla pneumone, Streptococcus pneumoniae, Stenotrophomonas maltophilia, gram negative bacilli. BC^{Se} = Enterococcus faecalis, klebsilla pneumoniae, Streptococcus gallolyticus, Propionibacterium, HIV, Escherichia coli, Burkholderia cepacian, DTA^{Se} = Pseudomonas aeruginosa, K. Pneumoni, Stenotrophomonas maltophilia, E. Coli, Klebsiella pneumoniae, Burkholderia cepacian.

shock is also dependent on the clinical context.

All of the following sepsis diagnosis parameters; HR, WBC, CRP, PCT, and lactate, failed to predict or diagnose septic shock in patients with sepsis in the present study, even though CRP [27], PCT [9, 31], and lactate [10, 32], were previously shown as sepsis prognostic and severity scaling markers. Furthermore, the levels of classic well-known sepsis biomarkers, were all comparable between septic shock and sepsis patients, although a cytokine network of IL-6, and IL-8, among others, was previously shown to play a pivotal role in the acute phase of sepsis and disease prognosis [33]. Similarly, TREM-1 was previously reported as a prognostic marker in sepsis [34], and levels of suPAR have previously been shown to predict the progression of sepsis to septic shock [14, 35]. Also, presepsin has previously been reported as a promising prognostic biomarker in sepsis [34, 36]. However, all the tested biomarkers in this study, including presepsin, were comparable between sepsis patients and patients with septic shock. Since the tested markers fail to serve as detectors, they are unlikely to be predictors for septic shock, at least in this setting. However, the sample size was relatively small.

The results of microbial culture showed that blood culture was sterile in 45.5% of patients with septic shock, which was comparable with sepsis patients who were not in shock, at

33.3%. This is similar to other studies which showed that sterile culture was found in approximately 30% of patients with sepsis, a condition that is known as culture-negative sepsis [37, 38]. Interestingly, when the blood culture was coupled with DTA culture less than 10% of patients showed sterile culture, as more pathogens were revealed in the DTA culture. The most common pathogens detected by blood and DTA were the *Staphylococcus* (Staph) genus of Gram-positive bacteria, *Acinetobacter*, and *Candida*, with the majority of infected patients showing infection with more than one organism. Another observation was that the prevalence of Staph was comparable between the two groups, while the prevalence of *Acinetobacter* was nil in patients with septic shock, and it was significantly higher in patients with sepsis without shock (39%). A possible explanation is that *Acinetobacter* has a low virulence [39]. This is in contrast to previous studies which showed that *Acinetobacter* bacteremia is associated with septic shock and a high mortality rate attributed to multiple drug resistance [40]. *Candida* is one of the most common fungal infections in sepsis patients [3]. Candidemia in sepsis patients was previously reported to be associated with higher mortality [41]. In the present study, candida was significantly more frequently detected in cultures obtained from patients with septic shock compared to those with sepsis only. Finally, despite the importance of the pathogen culture as a gold standard in sepsis diagnosis and management, the delay of results restricts its clinical usefulness [37]. Future studies on larger samples with diverse patients and more biomarkers are needed to validate the preliminary findings of this current study. Future research should aim to study septic shock pathophysiology as a guide for appropriate and specific biomarkers.

Conclusion

This study emphasized the importance of identifying biomarkers for septic shock, which are currently not available. Sepsis patients' stratification and septic shock case selection remain largely based on clinical findings and criteria. Out of 18 diagnostic and para-diagnostic parameters analyzed in this study, only low PLT count and high plasma bilirubin levels were associated with septic shock in patients with sepsis admitted to the ICU. The presence of *candida* and the absence of *Acinetobacter* in *culture* has further findings in septic shock. While these findings substantiate the clinical diagnosis of septic shock, more comprehensive studies are suggested to validate these results and to discover new specific biomarkers for septic shock.

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Disclosure of conflict of interest

None.

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