Accuracy for mortality prediction with additive biomarkers including interleukin-6 in critically ill patients: a multicenter prospective observational study

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Research

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Abstract

Background: Several inflammation markers have been reported to be associated with unfavorable clinical outcomes in critically ill patients. We aimed to elucidate whether serum IL-6 concentration considered with sequential organ failure assessment (SOFA) score can better predict mortality in critically ill patients.

Methods: A prospective observational study was conducted at five university hospitals in 2016–2018. Critically ill adult patients who met ≥2 systemic inflammatory response syndrome criteria on admission were included, and those who died or discharged within 48 hours were excluded. Inflammatory biomarkers including interleukin (IL) -6, -8, and -10, tumor necrosis factor-α, and procalcitonin were blindly measured daily for 3 days. Area under the receiver operating characteristic curve (AUROC) for SOFA score at Day 2 according to 28-day mortality was calculated as a baseline. Combination models of SOFA score and additional biomarkers were developed using logistic regression, and AUROC calculated in each model was compared with the baseline.

Results: Among 161 patients included in the study, 18 (11.2%) did not survive at Day 28. Univariate analysis for each biomarker identified that the IL-6 (Days 1–3), IL-8 (Days 0–3), and IL-10 (Days 1–3) were higher in non-survivors versus survivors. Analyses of 28-day mortality prediction by a single biomarker showed IL-6, -8, and -10 at Days 1–3 had a significant discrimination power, and the IL-6 at Day 3 had the highest AUROC (0.766 [0.656–0.876]). Baseline AUROC for SOFA score predicting 28-day mortality was 0.776 (0.672–0.880). The combination model using additional IL-6 concentration at Day 3 had higher AUROC than baseline (AUROC = 0.844, AUROC improvement = 0.068 [0.002–0.133]), whereas other biomarkers did not improve accuracy in predicting 28-day mortality.

Conclusions: Accuracy for 28-day mortality prediction was improved by adding serum IL-6 concentration to SOFA score.

Trial registration: N/A (This study did not include any health-related interventions)

Background

Most critically ill patients experience significant morbidity or mortality despite receiving intensive care by a multidisciplinary medial team [1, 2]. The ability to accurately predict mortality for critically ill patients can help health care providers optimize care and provide valuable information for patients and caregivers [3, 4]. Various prognostic indices have been proposed, and several scoring system to calculate the severity of organ dysfunction have been externally validated and are globally used [4–7].

The sequential organ failure assessment (SOFA) score is one of the well-accepted scales to quantify organ function and predict in-hospital mortality [4]. Use of the SOFA score to assess patient status changes over time in the intensive care unit (ICU) has been validated to represent better mortality prediction [8]. Both the European Society of Intensive Care Medicine and Society of Intensive Care Medicine have proposed that acute changes in SOFA score may be used to define organ dysfunction

among patients with infection and to diagnose sepsis [9, 10]. However, the SOFA score, as well as other prognostic scales such as acute physiology and chronic health evaluation (APACHE) II and simplified acute physiology score, do not include biological markers correlated with systemic inflammation as a variable for score calculation [5, 6, 8]. Notably, such inflammation markers, including cytokines/chemokines and acute phase proteins, are associated with unfavorable clinical outcomes [11–13].

Interleukin-6 (IL-6) is a cytokine released by immune cells and plays a role in systemic inflammatory changes caused by infection or tissue injury [14]. Several studies have reported that serum IL-6 concentration is associated with disease severity, adverse events, and overall mortality among patients with sepsis, burn and trauma injury, cardiovascular diseases, and hemodialysis [15–19]. However, diagnostic accuracy for sepsis using IL-6 has been inconclusive, despite extensive analysis [13], and the clinical feasibility of IL-6 for mortality prediction in critically ill patients remains unclear [11, 20, 21]. This study sought to elucidate whether serum IL-6 concentration can be a valid component of the SOFA scoring system to better predict mortality in critically ill patients. The hypothesis is that the addition of serum IL-6 concentration to SOFA score can provide better mortality prediction in this population.

Methods

Study design and setting

This prospective observational study used emergency department (ED) and ICU data from 5 university hospitals in Japan. All hospitals received individual local institutional review board approval for conducting research with human subjects. The Ethics Committee at the Keio University School of Medicine approved this study (approval number 16-03-007). Informed consent was obtained from all patients for being included in the study.

Study Population

The study enrolled critically ill patients admitted to the participating centers between September 2016 and September 2018. Inclusion criteria were: age ≥ 20 years; ≥2 systemic inflammatory response syndrome (SIRS) criteria of the American College of Chest Physicians/Society of Critical Care Medicine on ED/ICU admission [22]; expected ICU stay ≥ 48 hours. In addition to meeting these criteria, burn patients were included with burn index ≥ 15 and trauma patients with injuries in ≥ 2 body regions on the abbreviated injury scale coding system and with Injury Severity Score ≥ 10. Exclusion criteria were: current medications that affect serum IL-6 concentration (e.g., corticosteroids, immunosuppressants) within 1 week before study inclusion; discharge or death within 48 hours after admission; deviation from study protocol for biomarker tests and SOFA score calculation; HIV infection; pregnancy; and any other condition precluding suitability for enrollment in the investigators' opinion.

Data Collection And Definitions

Patient information included: demographic characteristics; admission source; comorbidities; medications administered within 1 week before study inclusion; etiology on admission; episode of cardiac arrest before study inclusion; presence of hemodynamic instability defined as vasopressor requirement or persistent hypotension despite fluid resuscitation; and any ED/ICU treatments.

Blood samples were obtained within 6 hours after ED/ICU admission (Day 0) and the next morning (Day 1). Blood tests were then performed daily from Days 2–3 and as need until 7 days after admission. These inflammatory biological markers were: C-reactive protein (CRP), IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, and procalcitonin (PCT). Serum CRP was measured immediately with commercially available assays at each hospital; ILs, TNF-α, and PCT were measured blindly to treating physicians at an outside facility after serum samples were frozen and stored at − 20 °C (IL-6, PCT, Roche Diagnostics, Mannheim, Germany; IL-8, IL-10, BioSource Europe, Nivelles, Belgium; TNF-α, R&D Systems, Minneapolis, MN, USA).

Arterial blood gas analysis and other blood tests for calculating each SOFA score component were performed at each hospital at the same time of blood sampling for biological markers. The SOFA score was recorded daily until Day 3 and as needed until Day 7; APACHE II score was also calculated on ED/ICU admission.

Outcome Measures

Primary outcome was 28-day all-cause mortality. Secondary outcome was ICU-free days, defined as the number of days alive and out of the ICU between admission and Day 28.

Statistical analysis

To assess improved accuracy for mortality prediction by adding a biomarker test to SOFA score, a baseline model was developed using logistic regression analysis to predict 28-day mortality, in which SOFA score at Day 2 was chosen as a sole explanatory variable. The Day 2 score was chosen because the original SOFA score validation study showed that the SOFA score at 48 hours post-admission had a high discrimination power for predicting ICU mortality [8]. To identify the best time for each biomarker to predict mortality, receiver operating characteristic (ROC) curves were drawn for serum concentration of each biomarker at Days 0–3 based on 28-day mortality, and area under the ROC curve (AUROC) was calculated. The day with the highest AUROC was considered as best time point for each biomarker.

Logistic regression analyses to predict 28-day mortality were performed again to derive the linear combination of the baseline model (Day 2 SOFA score) and an additional biomarker as measured based on the best time point just described. Some biomarkers were analyzed with sex as suggested in other studies [23, 24]. The ROC curves were drawn and AUROC was compared between the baseline model and combination model developed with the additional biomarker. Improvement of AUROC from baseline was shown with 95% confidence interval (CI). Sensitivity and specificity of each model were also obtained at a best cutoff point defined as the Youden index(25). To assess optimism of the combination model using the additional biomarker, a corrected AUROC was calculated with bootstrap analysis (resampling the

model 1000 times) [26]. The combination models with additional biomarkers were also examined in linear regression analyses to predict ICU-free days. The clinical applicability of biomarker was then assessed by calculating observed 28-day mortalities in subgroups classified as SOFA score and the biomarker dichotomized at the median value.

Descriptive statistics are presented as the mean (standard deviation), median (interquartile range), or number (percentage). No imputation was used to estimate missing data. The improvement of predictive ability for mortality by adding biomarkers was unclear before the study, and sample size estimation was not performed for the main analysis. Sample size estimation for ROC analysis in which 0.7 of AUROC was expected for an event with 15% of incident rate indicated that 150 cases were needed with power of 80% and α error of 0.05 [27]. Results were compared using Mann-Whitney U tests, chi-square tests, or Fisher's exact tests, as appropriate. For testing all hypotheses, a two-sided α threshold of 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS, version 26.0 (IBM, Armonk, NY, USA) and R Version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among 199 patients who met all inclusion criteria, these patients were excluded: 4 had corticosteroids before inclusion, 7 died within 48 hours post-admission, and 21 deviated from protocol for biomarker tests and SOFA score calculation (**Fig. 1**). Among the 161 eligible patients, 18 (11.2%) did not survive at Day 28. **Table 1** shows the characteristics of the participant population. Most common etiology on admission was infectious disease (109 [67.7%]); >50% required mechanical ventilation (86 [53.4%]) and about 33% underwent renal replacement therapy (51 [31.7%]).

Table 1 Characteristics of study population

Case, n	161
Age, years, mean (SD)	69 (15)
Sex, male, n (%)	101 (62.7%)
Type of admission, n (%)	
Medical, infectious disease	105 (65.2%)
Medical, non-infectious disease	21 (13.0%)
Surgical, trauma/burn	23 (14.3%)
Surgical, non-trauma/burn	12 (7.5%)
Comorbidity, n (%)	
Cerebrovascular disease	23 (14.3%)
Diabetes	23 (14.3%)
Cardiovascular disease	7 (4.3%)
Chronic lung disease	9 (5.6%)
Chronic kidney disease	15 (9.3%)
Liver disease	10 (6.2%)
APACHE II score, median (IQR)	25 (19–34)
SOFA score, median (IQR)	
Day 0	7 (3–11)
Day 1	8 (4–12)
Day 2	7 (3–11)
Cardiac arrest prior to admission, n (%)	11 (6.8%)
Hemodynamic instability*, n (%)	66 (41.0%)
Mechanical ventilation, n (%)	86 (53.4%)
Renal replacement therapy, n (%)	51 (31.7%)
Length of ICU stay, days, median (IQR)	9 (5–17)
Mortality, n (%)	
7-day mortality	5 (3.1%)
28-day mortality	18 (11.2%)

SD = standard deviation, APACHE = acute physiology and chronic health evaluation, SOFA = sequential organ failure assessment, ICU = intensive care unit. *Hemodynamic instability was defined as vasopressor requirement or persistent hypotension despite fluid resuscitation.

Univariate analyses for each biomarker identified that the median IL-6 concentration at Days 1–3 was higher among non-survivors versus survivors at Day 28 (**Fig. 2, Table S1**). Similarly, median IL-8 serum concentration at Days 0–3 and IL-10 at Days 1–3 was higher among non-survivors versus survivors at Day 28. Conversely, serum CRP, RCT, and TNF-α concentrations were comparable between non-survivors and survivors until Day 3. Mortality prediction by a single biomarker on ROC analyses showed IL-6, IL-8, and IL-10 serum concentrations at Days 1–3 had a significant discrimination power to predict 28-day mortality. The best time point for mortality prediction was Day 3 for IL-6, Day 1 for IL-8, and Day 2 for IL-10. The IL-6 concentration at Day 3 had the highest discrimination power (AUROC = 0.766, 95% CI = 0.656–0.876, **Table S1**).

Accuracy in predicting 28-day mortality with SOFA score at Day 2 was assessed as the baseline model using a logistic regression analysis (AUROC = 0.776, 95% CI = 0.672–0.880). Multivariate logistic regression analyses were performed to derive combination models with SOFA score and additional

biomarkers (IL-6, CRP, PCT, TNF-α at Day 3; IL-8 at Day 1; IL-10 at Day 2). On AUROC comparison, the combination model with additional serum IL-6 concentration at Day 3 was significantly higher versus the baseline model using only the SOFA score (AUROC = 0.844, AUROC improvement = 0.068, 95% CI = 0.002–0.133, **Table 2**, **Fig. S1**). Conversely, other combination models using CRP, PCT, IL-8, IL-10, and TNF-α had comparable discrimination power with the baseline model. Improvement of accuracy for mortality prediction by adding serum IL-6 concentration to the SOFA score was maintained in bootstrap analysis that estimated optimism of the combination model (corrected AUROC = 0.815). Serum IL-6 concentrations were also associated with decreased ICU-free days in the combination model (coefficient = 2.4 days decrease, 95% CI = 0.1–4.7 days decrease, $p = 0.042$, **Table S2**), whereas models with other biomarkers were not.

Table 2 Accuracy for mortality prediction with additive biomarkers

	AUROC	Improvement of AUROC (95% CI)	Optimism	Corrected AUROC	Sensitivity	Specificity
SOFA score at Day 2	0.776				82.4%	70.1%
SOFA with IL-6	0.844	0.068 (0.002, 0.133)	0.029	0.815	94.1%	64.2%
SOFA with CRP	0.783	0.008 (−0.038, 0.055)	0.020	0.763	64.7%	86.4%
SOFA with PCT	0.776	0.000 (−0.012, 0.012)	0.008	0.769	82.4%	71.6%
SOFA with IL-8	0.799	0.031 (−0.028, 0.089)	0.034	0.765	82.4%	74.4%
SOFA with IL-10	0.828	0.061 (−0.057, 0.179)	0.040	0.788	81.8%	73.5%
SOFA with TNF-α	0.773	−0.002 (−0.010, 0.007)	0.015	0.758	82.4%	72.2%

AUROC = area under the receiver operating characteristic (ROC) curve, CI = confidence interval, IL = interleukin, CRP = C-reactive protein, PCT = procalcitonin, TNF = tumor necrosis factor.

Logit-transformed predictive mortality rate was calculated in each model as follows*:

SOFA score at Day 2 (baseline model): SOFA score at Day 2 × 0.190 − 3.871

SOFA with IL-6: SOFA score at Day 2 × 0.102 + IL-6 at Day 3 × 1.226 + male × 1.011 − 6.381

SOFA with CRP: SOFA score at Day 2 × 0.211 − CRP at Day 3 × 0.867 − 3.167

SOFA with PCT: SOFA score at Day 2 × 0.181 + PCT ad Day 3 × 0.134 − 0.3862

SOFA with IL-8: SOFA score at Day 2 × 0.146 + IL-8 at Day 1 × 0.471 + male × 0.834 − 5.000

SOFA with IL-10: SOFA score at Day 2 × 0.155 + IL-10 at Day 2 × 2.180 + male × 0.372 − 6.096

SOFA with TNF-α: SOFA score at Day 2 × 0.189 − TNF-α at Day 3 × 0.023 − 3.856

* Log-transformed values of biomarker levels were entered in the calculation.

On subgroups analysis of observed 28-day mortalities classified with SOFA score at Day 2 and serum IL-6 concentration at Day 3, low IL-6 concentration (≤74 pg/dL) was associated with mortality ≤10% among patients with SOFA scores ≤11 (**Fig. 3**). For high IL-6 concentrations (>74 pg/dL), the mortality rate averaged >20% in patients with SOFA scores 8–11 and 25.8% with SOFA scores >11.

Discussion

This multicenter observational study examined the accuracy of mortality prediction with additive biomarkers and found that serum IL-6 concentration had the highest discrimination power to predict 28-day mortality in critically ill patients. The improvement of accuracy for mortality prediction by adding serum IL-6 concentration at Day 3 to SOFA score was identified as increased AUROC from baseline that used only SOFA score. Higher serum IL-6 concentration was also associated with longer ICU stay when used as an additional inflammation biomarker with SOFA score.

Several pathophysiologic mechanisms for the high prediction ability of IL-6 may be considered based on previous studies [14, 28, 29]. Interleukin-6 activates target genes involved in host defense mechanisms and are major players in pro- and anti-inflammatory responses to infection and injury [28]. Because IL-6 is synthesized in a local lesion in the initial stage of inflammation or infection and then moves to the liver where acute phase proteins such as CRP are rapidly induced, incrementation of serum IL-6 concentration usually precedes elevation of other inflammatory biomarkers and also clinical signs such as fever [14, 29]. In addition, removal of the inflammation source is quickly followed by cessation of IL-6 mediated cascade and degradation of IL-6 mRNA [29]. Therefore, alteration of serum IL-6 concentration closely reflects the degree or severity of systemic inflammation. Furthermore, persistent IL-6 production with high serum concentration has been identified in patients with severe SIRS who experience cytokine storm [30], suggesting dysregulated IL-6 abnormally accelerates inflammatory pathways and organ insult [14, 30]. Considering that serum IL-6 concentrations at Day 3 versus Days 0–2 had the highest discrimination in predicting mortality, persistent systemic inflammation would be detected by high IL-6 value at Day 3 among critically ill patients.

Although several mortality-prediction models have been developed, most used clinical and physiological parameters on admission or within the first 24 hours in the ICU [5–7]. Although useful to predict early consequences such as ICU adverse events, ignoring deteriorations and improvements of patient status as a result of initial responses to treatment limits projecting later clinical outcomes, such as 28-day mortality. Furthermore, some prediction models involving IL-6 concentrations did not include clinical parameters [11, 12, 19]. Given that use of both clinical and biological parameters would better capture patient status, Day 2 SOFA score and Day 3 serum IL-6 concentration, representing the patient condition altered by early treatment, would be feasible to predict 28-day mortality. A very high sensitivity (94.1%) for mortality was detected with the combination model using SOFA score and serum IL-6.

Clinical applicability of serum IL-6 concentration was assessed, and survival at 28 day will likely be predicted in patients with SOFA score < 7 at Day 2 when IL-6 concentration is ≤ 74 pg/dL at Day 3. This point is significant because a retrospective study reported patients with initial or highest SOFA score of 6–7 had ICU mortality of about 20% [8]. Among patients with SOFA score of 8–11, 28-day mortality almost doubled when IL-6 was > 74 pg/dL at Day 3, suggesting such persistent elevation of serum IL-6 concentration would warn of unfavorable clinical consequences.

The results of this study must be interpreted in the context of the design. First, it did not develop a new scoring scale using serum IL-6 concentration nor did it elucidate a cutoff value of IL-6 concentration to predict 28-day mortality. Although results suggested that adding IL-6 concentration to SOFA score would be valuable to develop a better prediction system, and that patients with IL-6 ≤ 74 pg/dL at Day 3 would be expected to survive even with SOFA score ≤ 7, more cases are required to derive and validate a new scale using IL-6.

Another limitation was that the study population included patients with various diseases. Given that another biomarker, such as PCT, was extensively examined among patients with bacterial infection [31], mortality of such population would be better predicted by PCT rather than IL-6. Although the small sample size precluded subgroup analyses, a disease-specific prediction model should be further examined.

Finally, the study did not collect data regarding long-term mortality nor functional outcomes, including physical impairment and cognitive function, which may be more important than 28-day mortality among critically ill patients. Although serum IL-6 concentration at Day 3 was associated with length of ICU stay, further study on long-term and/or functional outcomes should be performed.

Conclusions

In this multicenter observational study, accuracy for 28-day mortality prediction was improved by adding serum IL-6 concentration to the SOFA score. Persistent high IL-6 concentration until 3 days after admission would predict longer ICU stay and higher probability of mortality at Day 28. Further study is needed to develop a new scoring scale using both SOFA score and serum IL-6 concentrations.

List Of Abbreviations

APACHE: acute physiology and chronic health evaluation; AUROC: Area under the receiver operating characteristic curve; CRP: C-reactive protein; ED: emergency department; ICU: intensive care unit; IL: interleukin IL; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment; TNF: tumor necrosis factor

Declarations

Ethics approval and consent to participate

Before initiating the study, all collaborating hospitals obtained individual local institutional review board approval for conducting research with human subjects. This specific study was approved by Ethics Committee at the Keio University School of Medicine (Application number is 16-03-007). Informed consent was obtained from all patients for being included in the study.

Consent for publication

This manuscript, including tables and figures, has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with submission.

Availability of data and materials

The data of this study are available from the authors, but restrictions apply to the availability of these data, which are not publicly available. However, data are available from the authors upon reasonable request.

Competing interests

Authors T.S., T.N., T.S., H.O., M.N., and T.M. received honoraria for advisory board from Roche Diagnostics K.K., and authors J.S., T.M., O.T., K.M., and S.O received honoraria for advisory board and research funding for this study from Roche Diagnostics K.K. Authors R.Y. and Y.T. declare no conflict of interests for this article.

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Authors' contributions

R.Y., T.S., and J.S., conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, and revising the manuscript critically for important intellectual content. All other authors, acquisition of data, interpretation of data, and revising the manuscript critically for important intellectual content.

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Figures

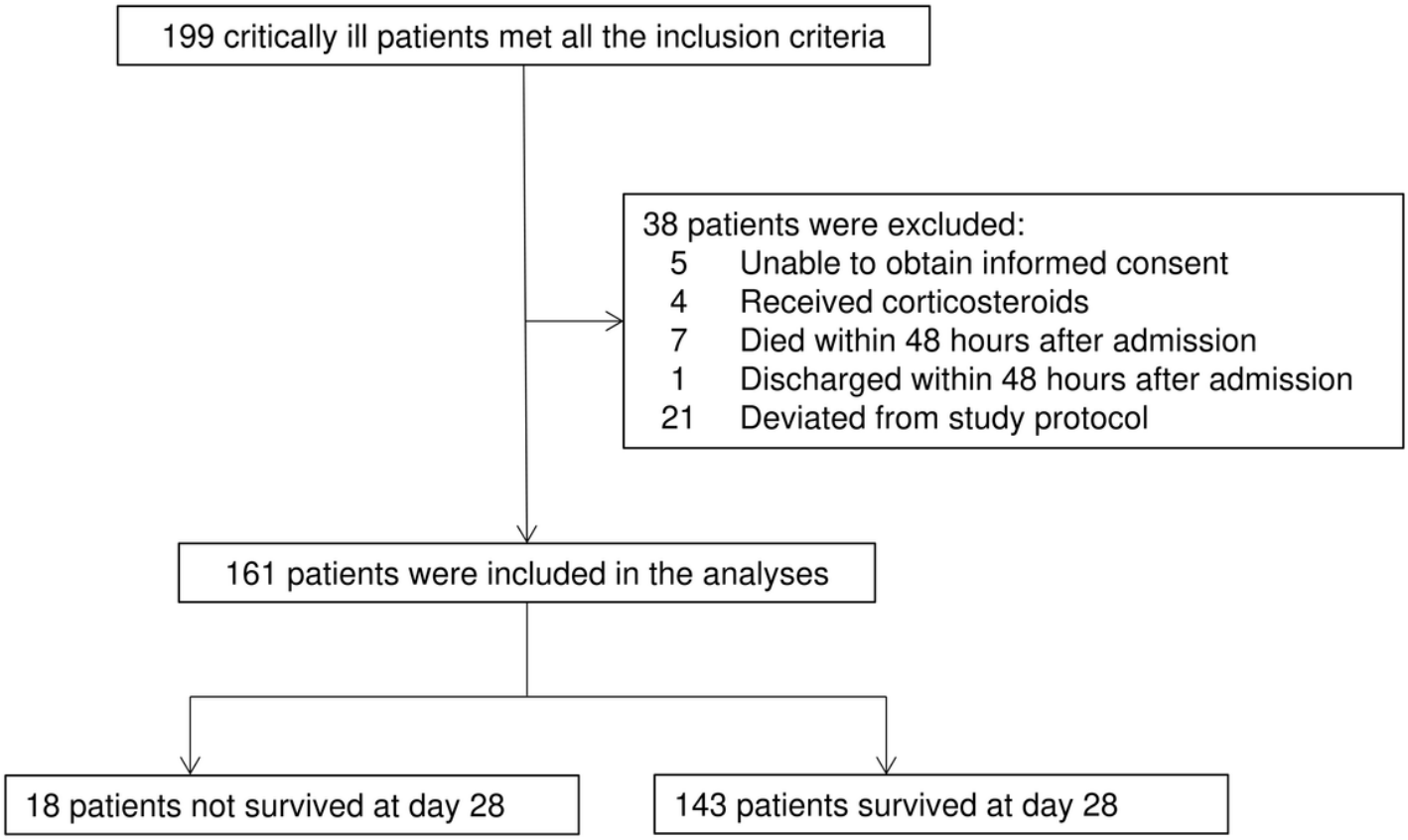

Figure 1

Study flow diagram. Among 199 patients who met the inclusion criteria, these patients were excluded: 4 had received corticosteroids before inclusion; 7 died within 48 hours post-admission, and 21 deviated from study protocol regarding biomarker tests and sequential organ failure assessment score calculation. Among 161 patients eligible for the analysis, 18 (11.2%) did not survive at Day 28. Abbreviations: SOFA, sequential organ failure assessment.

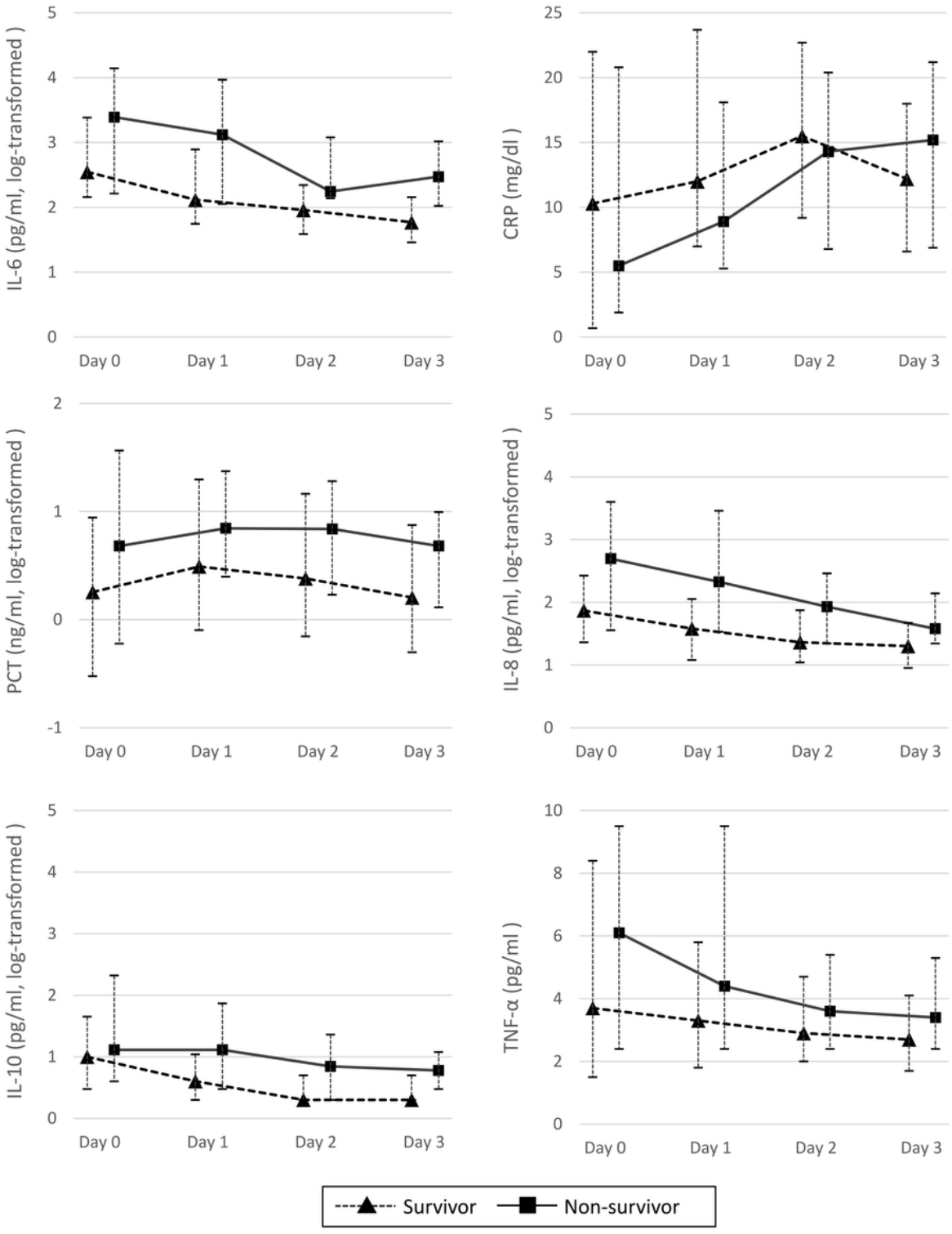

Figure 2

Biomarkers in survivors and non-survivors. Univariate analyses for each biomarker identified that the median interleukin-6 concentration at Day 1–3, interleukin-8 at Day 0–3, and interleukin-10 at Day 1–3 were higher in patients who did not survive at Day 28 after admission compared with survivors. Conversely, serum concentrations of C-reactive protein, procalcitonin, and tumor necrosis factor -α were comparable between survivors and non-survivors until Day 3. The interleukin-6 concentration at Day 3

had the highest discrimination power. Abbreviations: IL, interleukin; CRP, C-reactive protein; PCT, procalcitonin; TNF, tumor necrosis factor.

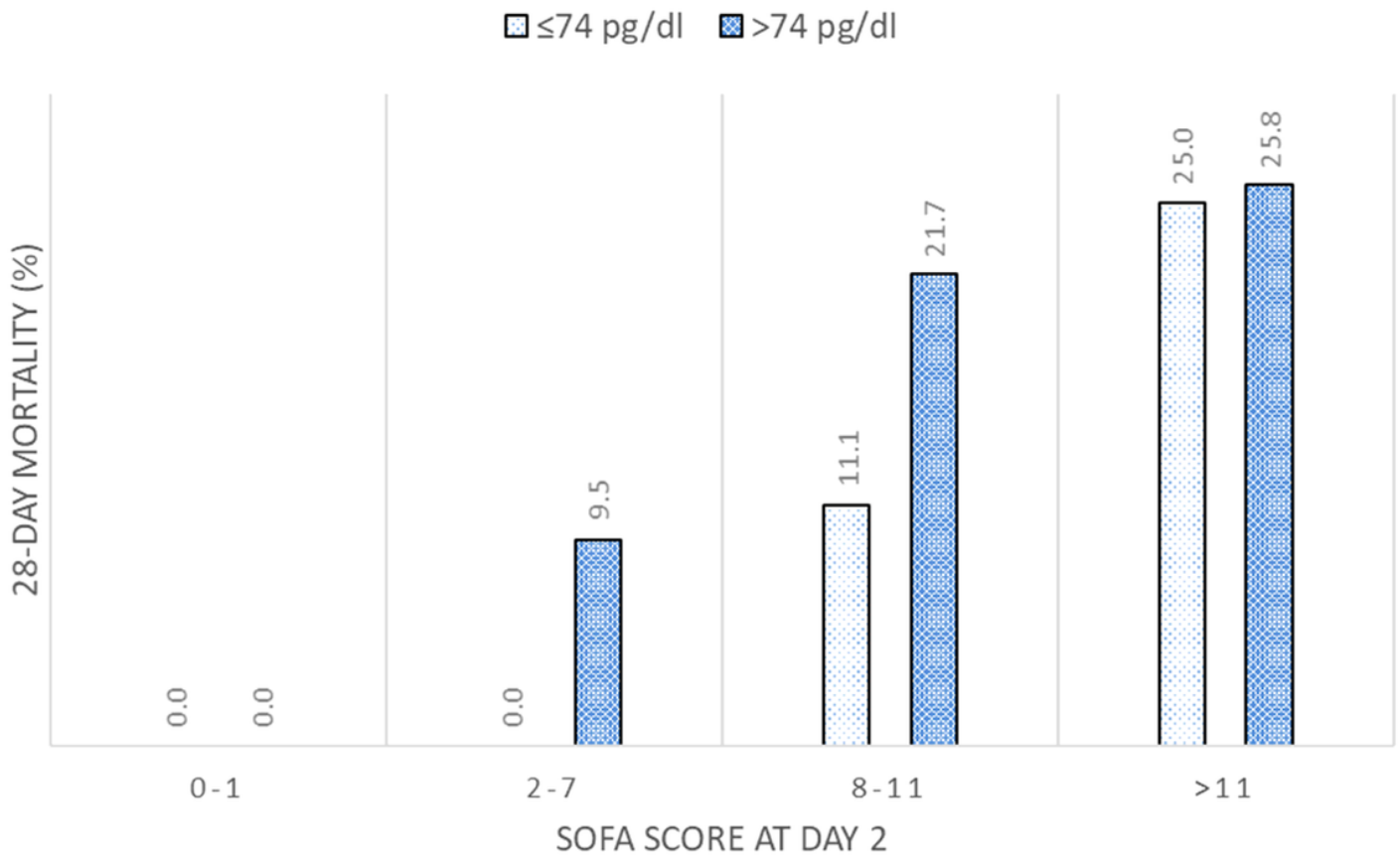

Figure 3

Mortalities in subgroups classified by with sequential organ failure assessment score and interleukin-6 concentration. Observed 28-day mortalities were calculated in the subgroups that were divided with sequential organ failure assessment score at Day 2 and serum interleukin-6 concentration at Day 3. Low interleukin-6 concentrations (≤74 pg/dL) were associated with mortality rate of ≤10% among patients with SOFA score ≤11. Conversely, when interleukin-6 concentrations were high (>74 pg/dL), the mortality rate averaged >20% in patients with sequential organ failure assessment of 8–11 and 25.8% with sequential organ failure assessment score >11.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigS1.tiff
- IL6SupplementalTablesRY090820.docx