Diagnostic Accuracy of Biomarkers for Early Multiple Organ Dysfunction in Critically Ill Patients: A Multicenter Prospective Observational Study

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Abstract

Background

Shock and organ damage occur in critically ill patients in the emergency department because of biological responses to invasion, and cytokines play an important role in their development. It is important to predict early multiple organ dysfunction (MOD) because it is useful in predicting patient outcomes and selecting treatment strategies. This study examined the accuracy of biomarkers, including interleukin (IL)-6, in predicting early MOD in critically ill patients compared with that of quick sequential organ failure assessment (qSOFA).

Methods

This observational study was conducted at five universities from 2016 to 2018. Data of adult patients with systemic inflammatory response syndrome who presented to the emergency department or were admitted to the intensive care unit were prospectively evaluated. qSOFA score and each biomarker (IL-6, IL-8, IL-10, tumor necrosis factor-α, C-reactive protein, and procalcitonin [PCT]) level were assessed on Days 0, 1, and 2. The primary outcome was set as MOD on Day 2, and the area under the receiver operating characteristic curve (AUROC) was analyzed to evaluate qSOFA scores and biomarker levels.

Results

Of 199 patients, 38 were excluded and 161 were included. Patients with MOD on Day 2 had significantly higher qSOFA, SOFA, and Acute Physiology and Chronic Health Evaluation II scores and a trend toward worse prognosis, including mortality. The AUROC for qSOFA score (Day 0) that predicted MOD (Day 2) was 0.728 (95% confidence interval [CI]: 0.651−0.794). IL-6 (Day 1) showed the highest AUC among all biomarkers (0.790 [95% CI: 0.711−852]). The combination of qSOFA (Day 0) and IL-6 (Day 1) showed improved prediction accuracy (0.859 [95% CI: 0.792−0.907]). The combination model using qSOFA (Day 0) and IL-6 (Day 1) also showed a higher AUROC (0.889 [95% CI: 0.828−0.929]).

Conclusions

The addition of serum IL-6 level to qSOFA scores improved the accuracy of early MOD prediction.

Introduction

Excessive immune response with the overproduction of inflammatory mediators leads to systemic inflammatory response syndrome (SIRS), which is crucial for the development of multiple organ dysfunction (MOD) [1]. MOD is an independent prognostic factor for intensive care unit (ICU) mortality [2]. Patients with MOD have longer ICU stays and higher mortality rates [3, 4]. The early detection of MODS may help identify patients at a risk of prolonged illness and death. Therefore, predicting early MOD can improve patient outcomes and quality of care.

Sequential organ failure assessment (SOFA) is a scale used to score organ failure and predict mortality by determining disease severity [5]. However, blood tests, including those of arterial blood gases, are essential to assess SOFA. In contrast, quick SOFA (qSOFA) was designed as a simple tool that can be used in the emergency department (ED) and can be used without performing blood tests [6]. qSOFA is considered a useful index for identifying patients with high mortality and those requiring systemic management in the ICU and is highly convenient in primary care [7]. In addition, the in-hospital mortality predictive effectiveness of qSOFA was statistically higher than that of SOFA in cases of suspected infection outside the ICU [8]. However, qSOFA is affected by the severity of infection and quality of the health care system, and factors such as biomarkers that correlate with systemic inflammation are not included in the score. Therefore, the addition of simple blood tests, including those of cytokines, as in the present study, may improve the diagnostic accuracy of qSOFA for sepsis [9, 10, 11].

Interleukin (IL)-6 is a proinflammatory cytokine released by immune cells and reflects the degree of hypercytokinemia involved in systemic inflammatory changes [12]. IL-6 peaks at 6 h after invasion and is induced earlier than C-reactive protein (CRP) and procalcitonin (PCT). Furthermore, IL-6 enables earlier diagnoses of SIRS, and IL-6 levels reflect the severity and outcome of sepsis [13, 14, 15]. In this study, we investigated whether adding biomarkers such as IL-6 to qSOFA would provide a more accurate prediction of early MOD in critically ill patients.

Materials And Methods

Settings

This prospective observational study was conducted using data from EDs and ICUs from 5 university hospitals in Japan as a secondary analysis of a study. This study was approved by the Institutional Review Board of the University of Occupational and Environmental Health (approval number H28-120).

Study population

This study included patients with SIRS between September 2016 and September 2018. The inclusion criteria were patient emergency admission (ICU or ED), age ≥ 20 years at the time of obtaining consent, patients predicted to undergo hospitalization > 48 h, and patients with a diagnosis of SIRS according to the American College of Chest Physicians/Society of Critical Care Medicine criteria on admission. Patients with trauma were included if they had multiple injuries (≥ 2 injured area) and had a predicted Injury Severity Score ≥ 10, and patients with burns were included if they had a Burn Index ≥ 15. Patients who received steroids, immunosuppressive drugs, or preparations that affected serum IL-6 concentration within 1 week before emergency transport or ICU admission, those with HIV infection, those who were pregnant, or those considered ineligible for enrollment were excluded.

Data collection

The patient information included demographic characteristics, etiology of admission, comorbidities, presence of hemodynamic instability, and history of treatment in the ED/ICU. Blood samples were

collected 6 h after admission (Day 0) and the following morning (Day 1). Blood samples on Day 2 were collected during the morning period. The inflammatory biological markers included CRP, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, and PCT; serum CRP levels were measured immediately using commercially available assays at each hospital; IL, TNF-α, and PCT levels were measured 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). MOD was defined as more than two organs with a SOFA score ≥ 2. qSOFA and SOFA scores were recorded on Days 0, 1, and 2. The Acute Physiology and Chronic Health Evaluation (APACHE) II scores were recorded on admission.

Statistical analysis

The outcome as an early MOD was assessed on Day 2 because reversible derangements induced by the inciting event or incomplete resuscitation may be reflected 24 h after admission. To evaluate the accuracy of predicting MOD by adding biomarkers to qSOFA, we developed a baseline model to predict MOD (Day 2) using a logistic regression analysis. We calculated the area under the receiver operating characteristic curve (AUROC) by drawing an ROC curve for the blood concentration of each biomarker on Days 0 and 1 to determine which biomarker and time points were most predictive of MOD on Day 2. The biomarkers and days with the highest AUROC were used in the model added to qSOFA to evaluate whether the model improves the accuracy of predicting MOD. ROC curves were drawn, and AUROC values were compared between the baseline model and the model with the biomarker added to qSOFA. We calculated the net reclassification improvement (NRI) to compare each model and presented the values with 95% confidence intervals (CIs). The results were compared using Mann-Whitney U tests and chi-square tests. P-values < 0.05 were considered statistically significant. All statistical analyses were performed using R version 3.5.3 and JMP 13.2.1.

Results

Of 199 patients included in this study, the following patients were excluded: 5 who withdrew their consent, 4 who were on steroids before admission, 7 who died within 48 h of admission, 1 who was discharged within 48 h of admission, and 21 who had deviated from the protocol for biomarker testing and SOFA score calculation. Of 161 eligible patients, 96 patients had MOD on Day 2 (Figure 1). Patients with MOD had significantly higher qSOFA, SOFA, APACHE II scores, mortality rates, fewer ICU-free days, ventilator-free days, renal replacement therapy (RRT)-free days (Table 1).

The ROC analysis of each biomarker on Days 0 and 1 was performed to assess MOD on Day 2. The results showed that IL-6 on Day 1 had the highest AUC (AUC: 0.790; 95% CI: 0.711−0.852) (Table 2). Next, as a baseline model, the predictive accuracy of MOD on Day 2 using Day 0 qSOFA scores was evaluated by logistic regression analysis (AUC: 0.728; 95% CI: 0.651−0.794). We analyzed the predictive accuracy of MOD (Day 2) in a model that added IL-6 (Day 1) to qSOFA (Day 0). The AUROC was significantly higher in this additional model than in the baseline model (AUC: 0.859; 95% CI: 0.792−0.907; NRI: 0.80) (Table 3/Figure 2). This model was also significantly improved with the model with the addition of IL-6 (Day 0)

(AUC: 0.776; 95% CI: 0.697–0.837; NRI: 0.562). Changing qSOFA in this model from Day 0 to Day 1 and analyzing it in the same manner resulted in a significant improvement in AUROC (AUC: 0.889; 95% CI: 0.828–0.929; NRI: 0.712).

Discussion

In this study, IL-6 on Day 1 was the most accurate biomarker for predicting early MOD. Furthermore, the addition of IL-6 blood levels to qSOFA was a more accurate predictor of early MOD. Although previous studies implicated that patients with MOD had poor prognosis, including increased mortality and hospitalization days [2, 3], this study also confirmed that patients with MOD on Day 2 had poor prognosis (Table 1).

Cytokine storms play an important role in the pathogenesis of MOD, and various cytokines have been assessed for their accuracy in predicting MOD. IL-6 is a cytokine involved in inflammatory responses and is released in response to tissue injuries and inflammatory stimuli, resulting in a physiological response. IL-6 acts locally and systemically and is a proinflammatory mediator and an anti-inflammatory regulator that stimulates anti-inflammatory cytokines, including IL-10 [16]. The mediators of acute inflammation and infection, such as CRP, IL-6, and PCT, have long been involved in the pathophysiology of critically ill patients and are routinely used for diagnostic, prognostic, and treatment monitoring in the ICU [16, 17, 18]. Compared with other biomarkers such as CRP and PCT, IL-6 responds more quickly to inflammatory stimuli, peaking at 3–6 h. This suggests that it has an advantage in predicting risk at admission. In this regard, several reports have shown that IL-6 is a useful biomarker for detecting early sepsis; however, CRP and PCT are still often within the reference range owing to their much slower rates [19, 20, 21]. However, the AUROC in Table 2 revealed that IL-6 peaked on Day 1, and PCT had a higher AUROC than IL-6 on Day 0. This may indicate that IL-6 levels have an early increase in the blood but remain more reflective of MOD than other biomarkers after Day 1. In a study examining various cytokine concentrations in patients with severe sepsis, IL-6 and IL-8 in the first 24 h predicted organ dysfunction on Day 3 [22]. In light of these findings, the present study shows that IL-6 may predict early MOD with greater accuracy than other biomarkers.

However, it is cumbersome to accurately predict organ failure and mortality using a single biomarker alone; therefore, a combination of biomarkers and severity scores has been proposed to provide better results. Oberholzer et al. suggested that IL-6 and APACHE II scores were correlated and showed that these combined models increased the accuracy of predicting mortality in patients with severe sepsis [23]. In addition, a study examining factors that predicted mortality 90 days after ICU admission found that combining SAPS II with IL-6 and soluble suppression of tumorigenesis-2 improved prediction accuracy [24].

The accuracy of predicting post-hospital organ failure and in-hospital mortality using qSOFA has been previously reported [25, 26]. In contrast, a previous study reported that positive qSOFA scores had high specificity but poor sensitivity for predicting in-hospital mortality, acute organ dysfunction, and ICU

admission in patients with infection outside the ICU, and the limits of qSOFA accuracy of the predictions have been reported [27]. The combination of IL-6 and qSOFA improved the accuracy of predicting early MOD in this study. Since qSOFA does not require testing, the improvement in predictive accuracy obtained without increasing healthcare costs is a major advantage. The combination in this study was qSOFA on admission and IL-6 on Day 1, which is also in line with that used in clinical practice. Typically, qSOFA is screened for sepsis on admission, and Il-6, which does not peak upon admission, is measured on Day 1.

In the future, a new scoring system that combines severity scores and biomarkers to predict MODs needs to be investigated.

Limitations

This study had some limitations. First, the sample size was small. This study included patients with a variety of diseases. Second, one of the problems with qSOFA is that it is difficult to assess consciousness in patients with cognitive impairment before the onset of infection [28].

Conclusion

We compared each biomarker as a predictor of MOD on Day 2. IL-6 on Day 1 had the highest predictive value. Furthermore, the addition of IL-6 (Day 1) to qSOFA score (Day 0) predicted MOD on Day 2 with greater accuracy. The present study showed that adding IL-6 to qSOFA could predict early MOD.

Abbreviations

AUROC: area under the receiver operating characteristic curve

qSOFA: quick sequential organ failure assessment

IL: interleukin

CRP: C-reactive protein

PCT: procalcitonin

TNF: tumor necrosis factor

sST2: solublesuppressionoftumorigenesis-2

MOD: multiple organ dysfunction

NRI, net reclassification improvement

SIRS, systemic inflammatory response syndrome

APACHE II: Acute Physiology and Chronic Health Evaluation II

ICU: intensive care unit

Declarations

Ethics approval and consent to participate

The study was approved by the Clinical Research Ethics Committee of University of Occupational Environmental Health (Application number is H28-120), and all subjects provided informed consent, and written informed consent was obtained from all subjects prior to participation.

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

Authors' contributions

S.I., Y.T., H.O., and M.T., 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.

Acknowledgements

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Tables

Table1. Characteristics and clinical outcomes in patients with or without multiple organ dysfunction on Day2

	MOD (n=96)	without MOD (n=65)	p value
Characteristics			
Age, years	70 (59-78)	72 (64-85)	0.145
Male sex, n(%)	59 (61.5)	42 (64.6)	0.684
Etiology of SIRS, (%)			
Infection	63 (65.6)	46 (70.8)	0.493
Post-surgery	8 (8.3)	4 (6.2)	0.605
Trauma	14 (14.6)	8 (12.3)	0.680
Burn	1 (1.0)	0 (0.0)	0.409
Acute pancreatitis	6 (6.3)	3 (4.6)	0.658
Others	10 (10.4)	6 (9.2)	0.805
APACHE Ⅱ score on admission	29 (23-37)	19 (13-22)	< 0.001*
qSOFA on admission			< 0.001*
0	1	14	-
1	33	29	-
2	35	21	-
3	26	1	-
qSOFA≧2 on admission, n(%)	61 (64.2)	22 (33.8)	< 0.001*
SOFA score on admission			
Total SOFA score	10 (7-13)	3 (2-5)	< 0.001*
Respiration, (%)	72 (75.0)	23 (37.1)	< 0.001*
Coagulation, (%)	29 (30.2)	4 (6.2)	< 0.001*
Liver, (%)	14 (14.7)	4 (6.2)	0.092
Cardiovascular, (%)	58 (60.4)	3 (4.6)	< 0.001*
Central Nervous System, (%)	67 (69.8)	9 (13.8)	< 0.001*
Renal, (%)	46 (47.9)	9 (13.8)	< 0.001*
Outcome			
In hospital 28day mortality	16 (16.7)	2 (3.1)	0.007*

ICU free days	13 (0-20)	26 (23-28)	< 0.001*
Ventilator free days	16 (1-24)	28 (28-28)	< 0.001*
RRT free days	25 (11-28)	28 (28-28)	< 0.001*

MOD, multiple organ dysfunction; SIRS, systemic inflammatory response syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; qSOFA, quick Sequential Organ Failure Assessment; ICU, intensive care unit; RRT, renal replacement therapy.

Data are presented as median and interquartile range for continuous variables and *exact number (%) for categorical variables.* *P*-values were calculated using Pearson's chi-square test or the Wilcoxon test. For APACHE II score, n=93 with MOD and n=37 without MOD.

Table 2. Receiver operating characteristic curve analysis for prediction of multiple organ dysfunction on day 2 for various biomarkers on day 0,1.

	AUROC	95%CI
Day-0		
Interleukin-6	0.647	0.558-0.727
Procalcitonin	0.728	0.644-0.800
C-reactive protein	0.603	0.513-0.686
White blood cell	0.733	0.648-0.804
Interleukin -8	0.717	0.631-0.790
Interleukin-10	0.619	0.527-0.704
Tumor necrosis factor-α	0.633	0.540-0.717
Day-1		
Interleukin-6	0.790	0.711-0.852
Procalcitonin	0.705	0.618-0.780
C-reactive protein	0.610	0.519-0.693
White blood cell	0.769	0.687-0.835
Interleukin -8	0.789	0.711-0.850
Interleukin-10	0.751	0.669-0.817
Tumor necrosis factor-α	0.635	0.544-0.716

AUC, area under the curve; CI, confidence interval.

Table 3. Predictive diagnostic accuracy of MOD on day 2 with qSOFA and additional Interleukin-6

	AUROC(95%CI)	Improvement of AUROC	P-value	NRI (95%CI)	P-value
qSOFA（Day-0）	0.728 (0.651-0.794)				
qSOFA（Day-0）＋ IL-6 （Day-0）	0.776 (0.697-0.837)	0.047 (0.107-0.012)	p=0.116	0.562 (0.267-0.857)	p<0.001
qSOFA（Day-0）＋ IL-6 （Day-1）	0.859 (0.792-0.907)	0.131 (0.063-0.199)	p<0.001	0.801 (0.520-1.084)	p<0.001
qSOFA（Day-1）	0.801 (0.723-0.861)				
qSOFA（Day-1）＋ IL-6 （Day-1）	0.889 (0.828-0.929)	0.088 (0.035-0.140)	p=0.001	0.712 (0.423-1.001)	p<0.001

AUROC, area under the receiver operating characteristic (ROC) curve; CI, confidence interval; IL, interleukin; NRI, net reclassification improvement; qSOFA, quick squential organ failure assessment.

If the NRI is positive and the 95%CI does not straddle zero, the predictive ability of the new model is considered to be significantly improved from the baseline model.

Figures

Figure 1

Patient selection flow diagram A total of 199 patients were enrolled in the present study and screened for eligibility. Of those patients, 161 met the inclusion criteria. Overall, 96 (59.6%) patients experienced MOD on Day 2. MOD, multiple organ dysfunction.
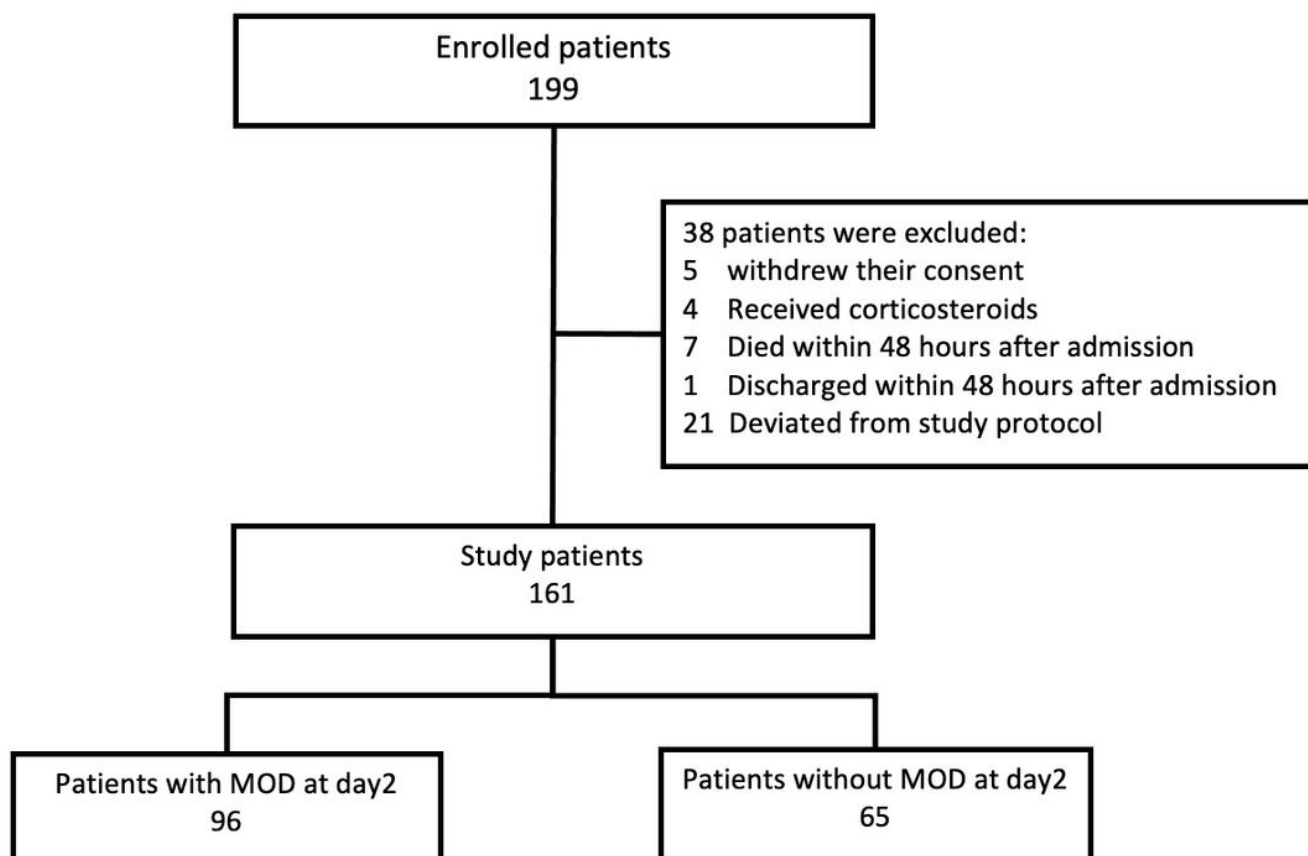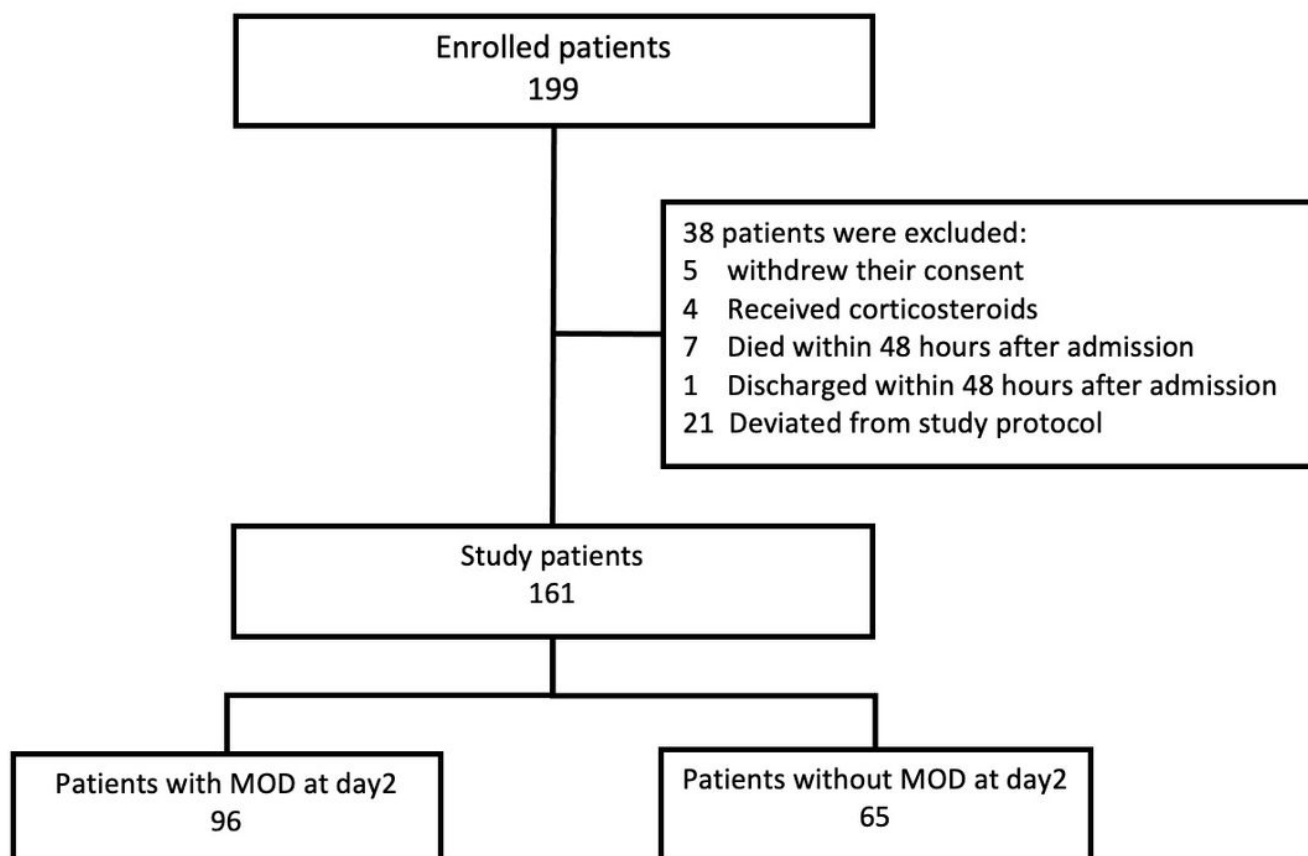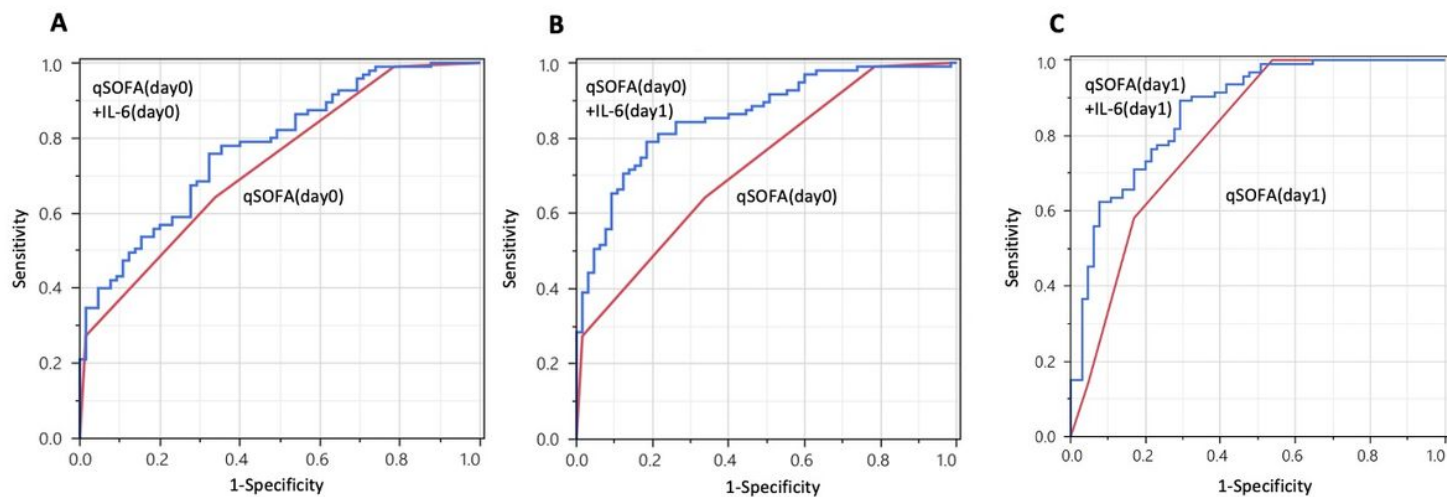
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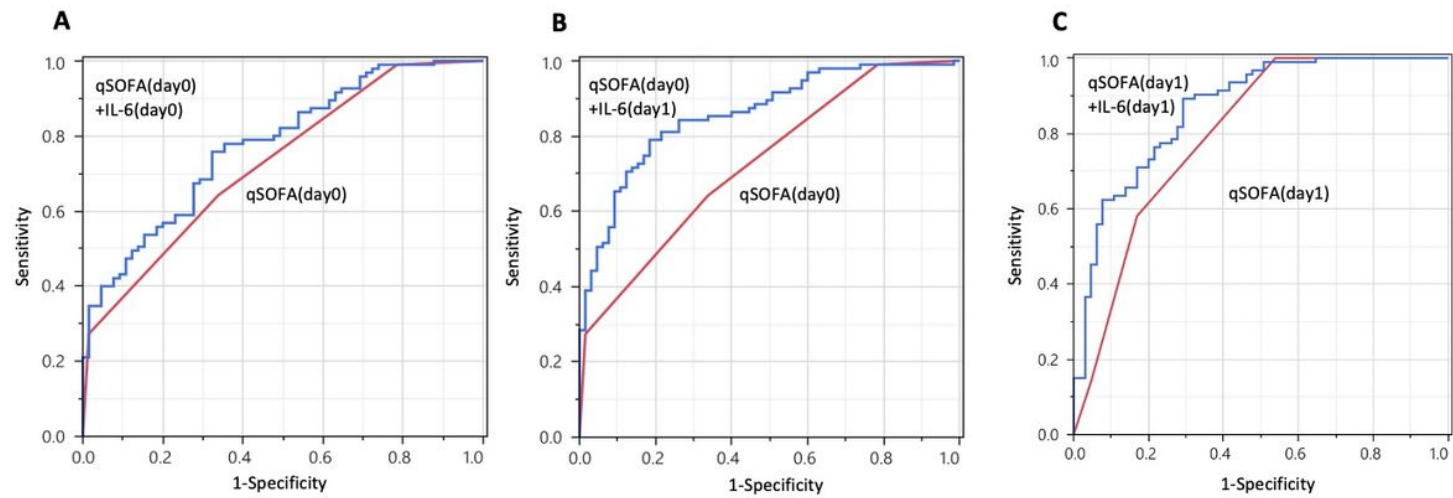

Figure 2

Prognostic value of a combined approach of IL-6 and baseline qSOFA A, AUROC for baseline qSOFA (Day 0) with IL-6 (Day 0) B, AUROC for baseline qSOFA (Day 0) with IL-6 (Day 1) C, AUROC for baseline qSOFA (Day 1) with IL-6 (Day 1) Comparison of AUROC revealed that the combination model using additional serum IL-6 concentration on Days 0 and 1 had a significantly higher AUROC than the baseline model that uses only the qSOFA score. AUROC = area under the receiver operating characteristic curve, qSOFA = quick sequential organ failure assessment, IL = interleukin.
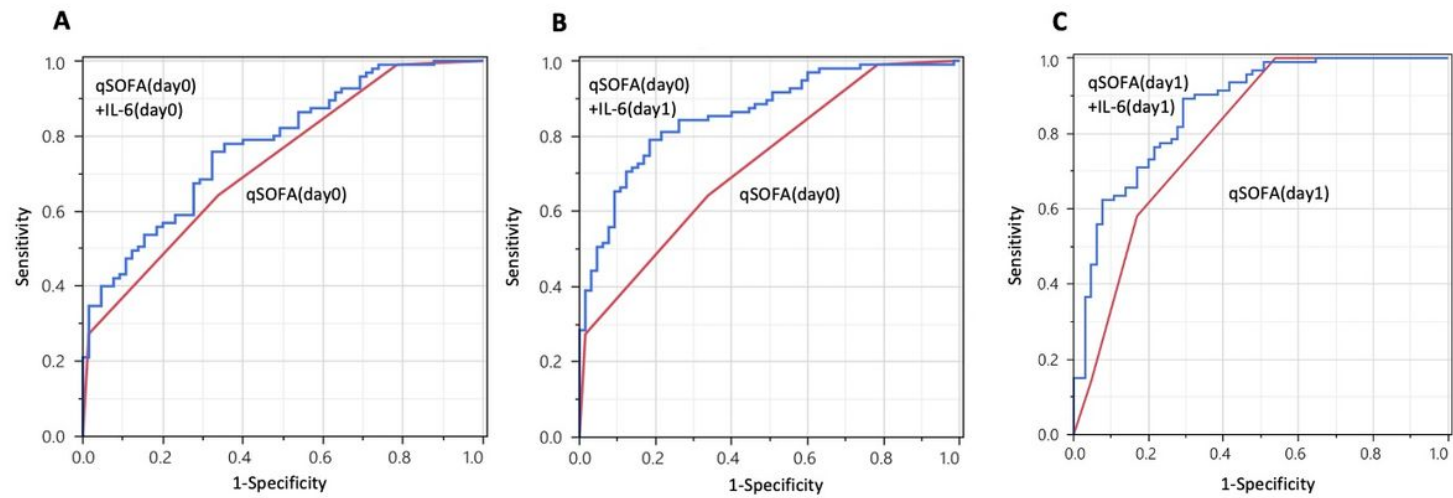

Figure 2

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