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Original Contribution

Added value of inflammatory markers to vital signs to predict mortality in patients suspected of severe infection

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ABSTRACT

Objective: To evaluate the added value of inflammatory markers to vital signs to predict mortality in patients suspected of severe infection.

Methods: This study was conducted at an acute care hospital (471-bed capacity). Consecutive adult patients suspected of severe infection who presented to either ambulatory care or the emergency department from April 2015 to March 2017 were retrospectively evaluated. A prognostic model for predicting 30-day in-hospital mortality based on previously established vital signs (systolic blood pressure, respiratory rate, and mental status) was compared with an extended model that also included four inflammatory markers (C-reactive protein, neutrophil-lymphocyte ratio, mean platelet volume, and red cell distribution width). Measures of interest were model fit, discrimination, and the net percentage of correctly reclassified individuals at the pre-specified threshold of 10% risk.

Results: Of the 1015 patients included, 66 (6.5%) died. The extended model including inflammatory markers performed significantly better than the vital sign model (likelihood ratio test: $p < 0.001$), and the c-index increased from 0.69 (range 0.67–0.70) to 0.76 (range 0.75–0.77) ($p = 0.01$). All included markers except C-reactive protein showed significant contribution to the model improvement. Among those who died, 9.1% (95% CI −2.8–21.8) were correctly reclassified by the extended model at the 10% threshold.

Conclusions: The inflammatory markers except C-reactive protein showed added predictive value to vital signs. Future studies should focus on developing and validating prediction models for use in individualized predictions including both vital signs and the significant markers.

1. Introduction

Sepsis, defined by Sepsis-3 as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [1], is associated with high morbidity and mortality [2]. To improve the prognosis of patients with sepsis, early detection and treatment are crucial [3].

Since changes in vital signs are often an early warning sign in critically ill patients [4,5], several screening tools of vital sign parameters have been used for early identification of infected patients at risk of death (e.g., the quick Sequential Organ Function Assessment [qSOFA] and National Early Warning Score 2) [6-10]. These tools also have been used as predictors to predict mortality in patients suspected of infection [7,9,11]. Compared with tools that include laboratory tests [12,13], those tools have the advantage of being able to immediately check on a patient's vital signs on arrival and help physicians initiate appropriate management at a very early stage [7].

Besides using vital signs, there have been several attempts to predict the prognosis of patients with infectious conditions using biomarkers like lactate and other inflammatory markers [14-28]. When evaluating the prognostic value of biomarkers, the interest is in the value that can be added to already available clinical information (e.g., history and

Abbreviations: qSOFA, quick Sequential Organ Function Assessment; TRIPOD, Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis; CRP, C-reactive protein; NLCR, neutrophil-lymphocyte ratio; MPV, mean platelet volume; RDW, red cell distribution width; IQR, interquartile range; CI, confidence interval.

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physical examination) [29]. That is, to be useful in clinical practice, a biomarker should add prognostic information to easily available existing measures, and whether they have predictive value by themselves is not the main focus [30].

Thus, in patients suspected of acute severe infection, the prognostic performance of biomarkers should be assessed in addition to at least vital signs, which are parameters commonly used for the screening of those patients, as discussed above [6-10]. Although the added value of lactate to qSOFA has been often evaluated [20,26,27], most inflammatory markers have not been adequately assessed in a sequential process in clinical practice.

We therefore quantified the added value of inflammatory markers to vital sign parameters in the prediction of poor outcome in patients suspected of severe infection. We used the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) for transparent reporting in our study [31,32].

2. Materials and methods

This study was designed as a retrospective observational study at an acute care hospital (471-bed capacity). Approval was granted by the ethics committees of the hospital. Using a structured collection form, data were collected from electronic medical records by the authors. Another author reviewed all the data and any disagreement was resolved by discussion among the authors.

2.1. Patients

We included consecutive outpatients aged 18 years or older who presented to either ambulatory care or the emergency department of our hospital with suspicion of acute severe infection, from April 2015 to March 2017, and in whom at least two sets of blood culture were ordered. We included patients who presented not only to the emergency department but also to ambulatory care since walk-in patients with acute illness in our hospital are seen in ambulatory care during the daytime. As in previous studies, we used the physicians' decision to order blood cultures as a surrogate marker for a patient at risk of severe infection [33-36]. We focused on this target population since the prediction of poor prognosis is more important in those highly suspected of severe infection than in those less suspected of severe infection. Exclusion criteria were as follows: duration of illness was unknown or longer than 1 week (because the target population was patients suspected of acute severe infection), and a past history of blood disorders (some of the inflammatory markers used as candidate predictors were indices of blood cells, and were therefore not reliable in these patients).

2.2. Candidate predictors

We a priori determined to study the three well known vital sign parameters of systolic blood pressure, respiratory rate, and mental status at presentation, which are all included in the qSOFA score [1].

Further, we studied the added prognostic value of the following blood biomarkers which are previously described as predictors of the prognosis of patients with infectious conditions: C-reactive protein (CRP) [25], neutrophil-lymphocyte ratio (NLCR) [15,17], mean platelet volume (MPV) [18,19], and red cell distribution width (RDW) [14,16,21,24]. CRP levels were measured using an automated analyzer (7700; Hitachi High-Technologies Corporation, Tokyo, Japan). Complete blood count with differential, RDW and MPV were measured using an automated hematology system (XN-3100; Sysmex, Hyogo, Japan). NLCR was calculated as absolute neutrophil count divided by absolute lymphocyte count [15,17]. We explicitly did not study the value of inflammatory markers that were not routinely measured in our hospital, such as procalcitonin and other newly developed markers such as mid-regional pro-adrenomedullin [28].

2.3. Outcomes

The primary outcome of this study was 30-day in-hospital mortality [37].

2.4. Statistical analysis

There were some missing values in the predictors. As shown in Table 1, these were not missing completely at random. Since ignoring these missing data can lead to biased results [38,39], missing values were multiply imputed using chained equations [40,41]. Missing data on predictors were imputed using all available information including the outcome [42]. Twenty-five imputed datasets were created and subsequently analyzed in accordance with methodological recommendations [41,43].

To assess the predictive value of vital signs combined, we fitted a logistic regression model including systolic blood pressure, respiratory rate, and mental status as predictors and 30-day in-hospital mortality (yes/no) as the outcome (vital sign model). Next, we fitted an extended logistic regression model by adding the four inflammatory markers (CRP, NLCR, MPV and RDW) simultaneously to the vital sign model (extended model). The functional form of all continuous variables (systolic blood pressure, respiratory rate, and all inflammatory markers) was evaluated using restricted cubic splines with three knots (two degrees of freedom), and incorporated as such in case of significant non-linearity [44,45]. The vital sign model and the extended model were compared by means of a likelihood ratio test using a p-value of 0.05.

Although the aim of this study was to quantify the added predictive value of inflammatory markers to vital signs and not to develop a novel prediction model to be used for individualized predictions in future patients, we did assess the calibration and discrimination of the vital sign and extended models. Calibration plots were constructed and discrimination was assessed using the c-index [32]. Also, we estimated the net percentage of correctly reclassified individuals after adding the inflammatory markers to the vital sign model, at the cut-off point of risk probability of 10%. This cut-off was predefined in accordance with the optimum threshold for starting immediate management in patients with suspected infection in Sepsis-3 [1]. For sensitivity analysis, we also assessed reclassification using a threshold of 5%, since a 10% risk of 30-day mortality could be considered too high for certain patients (e.g., when informing on relatively non-invasive treatment decisions). Because of the high mortality of severe infection and the relatively low risk of treatment, it is considered more important to correctly reclassify those who died than those who were alive. The confidence interval (CI) of the net percentage of correctly reclassified individuals was obtained using the percentile method with 2000 bootstrap samples.

All analyses were performed with R statistical software (version 3.4.4; R foundation for Statistical Computing, www.R-project.org) [46].

3. Results

3.1. Patient characteristics

Of the 1256 potentially eligible patients, we excluded 45 with unknown illness duration, 177 with illness duration longer than 1 week, and 19 with past history of blood disorders, leaving a total of 1015 included study patients. The basic characteristics of these 1015 patients are shown in Table 1. Median age was 81 years (interquartile range [IQR] 66–87) and 48.8% were men. Respiratory infection was the most common clinical diagnosis (37.9%). Sixty-six patients (6.5%) died in

Table 1
Demographic characteristics, vital signs, and inflammatory markers

Patients characteristics	The number of patients with missing information, n (%)	Patients with at least one missing value (n = 195)	Complete cases (n = 820)	p[a]	Overall[b] (n = 1015)
Age (year), median (IQR)	0 (0.0)	77 (63, 86)	82 (67, 88)	0.004	81 (66, 87)
Male sex, n (%)	0 (0.0)	86 (44.1)	409 (49.9)	0.171	495 (48.8)
Presented to the emergency department, n (%)	0 (0.0)	62 (31.8)	373 (45.5)	0.001	435 (42.9)
Clinical diagnosis, n (%)	0 (0.0)			0.01	
Respiratory		53 (27.2)	332 (40.5)		385 (37.9)
Urinary		21 (10.8)	99 (12.1)		120 (11.8)
Abdominal		40 (20.5)	90 (11.0)		130 (12.8)
Cutaneous		18 (9.2)	34 (4.1)		52 (5.1)
Neurological		2 (1.0)	5 (0.6)		7 (0.7)
Bone and joints		3 (1.5)	4 (0.5)		7 (0.7)
Others		137 (29.8)	564 (31.2)		701 (69.0)
Systolic blood pressure, (mmHg), median (IQR)	11 (1.0)	126.0 (107, 146.3)	123.0 (107.0, 141.3)	0.304	123.0 (107.0, 143.0)
Diastolic blood pressure, (mmHg), median (IQR)	11 (1.0)	71.0 (60.8, 81.0)	70.0 (59.8, 81.0)	0.576	70.0 (60.0, 81.0)
Heart rate (beats/min), median (IQR)	13 (1.3)	96.0 (80.0, 110.0)	95.0 (82.0, 109.0)	0.916	95.0 (82.0, 109.0)
Respiratory rate (breaths/min), median (IQR)	162 (16.0)	24.0 (20.0, 25.0)	22.0 (19.0, 25.0)	0.138	22.0 (20.0, 25.0)
Consciousness disturbance, n (%)	0 (0.0)	31 (15.9)	210 (25.6)	0.006	241 (23.7)
CRP (mg/dL), median (IQR)[c]	7 (0.7)	5.3 (1.3, 14.4)	5.6 (1.5, 13.0)	0.715	5.5 (1.4, 13.2)
NLCR, median (IQR)	33 (3.3)	8.8 (5.2, 15.4)	8.6 (4.6, 16.3)	0.808	8.6 (4.6, 16.2)
MPV (fL), median (IQR)	8 (0.8)	9.8 (9.0, 10.8)	9.9 (9.2, 10.6)	0.371	9.9 (9.2, 10.6)
RDW, median (IQR)	6 (0.6)	13.5 (12.8, 15.1)	13.5 (12.8, 14.5)	0.299	13.5 (12.8, 14.6)
Death, n (%)	0 (0.0)	14 (7.2)	52 (6.3)	0.791	66 (6.5)

IQR = interquartile range, CRP = C-reactive protein, NLCR = neutrophil-lymphocyte ratio, MPV = mean platelet volume, RDW = red cell distribution width.
[a] Comparison between patients with at least one missing value and complete cases.
[b] Data includes imputed data for missing values.
[c] To convert CRP to nmol/L, multiply values by 9.524.

the hospital within 30 days. The mortality rate in those presented to ambulatory care, walk-in patients in the emergency department, and those taken to the emergency department by ambulance was 3.3% (8/243), 4.5% (15/337), and 9.9% (43/435), respectively.

3.2. Vital sign model and extended model

The vital sign model and extended model are shown in Table 2. Systolic blood pressure and RDW were incorporated into the models using restricted cubic splines with three knots to account for the non-linear relationship with the outcome. In the vital sign model, respiratory rate and consciousness disturbance were significant, while systolic blood pressure was not. In the extended model, all inflammatory markers except CRP were significant. Accordingly, model fit improved when adding all inflammatory markers (likelihood ratio test $p < 0.001$). The vital sign model showed slight over-prediction at lower predicted probabilities (below 0.05), which improved when extending the model with inflammatory markers (Fig. 1). Fig. 2 shows the change in probability between the vital sign model and the extended model. The improvement in estimated probability was relatively large in the higher deciles among patients who died, while it was small among patients who were alive after 30 days. The c-index of the vital sign model and the extended model was 0.69 (range 0.67–0.70) and 0.76 (range 0.75–0.77), respectively ($p = 0.01$).

Table 2
Formula of the vital sign model and the extended model.

Intercept and predictors in the model	Vital sign model			Extended model		
	Coefficient	Standard error	p	Coefficient	Standard error	p
Intercept	−2.580	1.258	0.041	−13.352	4.066	0.001
Systolic blood pressure 1	−0.013	0.010	0.344[a]	−0.012	0.011	0.501[a]
Systolic blood pressure 2	0.011	0.013		0.012	0.014	
Respiratory rate	0.043	0.020	0.037	0.037	0.022	0.091
Consciousness disturbance	1.029	0.264	<0.001	0.862	0.274	0.002
CRP				0.006	0.013	0.650
NLCR				0.019	0.008	0.018
MPV				0.330	0.101	0.001
RDW 1				0.525	0.278	0.004[a]
RDW 2				−0.450	0.347	

CRP = C-reactive protein, NLCR = neutrophil-lymphocyte ratio, RDW = red cell distribution width, MPV = mean platelet volume.
[a] Since the variable was transformed using restricted cubic splines to account for the nonlinearity, there were two estimated coefficients for the variable. The p value is the pooled estimate of the two coefficients.

3.3. Reclassification

Among 66 patients who died within 30 days, 9.1% (95% CI −2.8–21.8) were correctly reclassified by the extended model at a risk threshold of 10%, while 1.3% (95% CI −1.2–3.6) of the 949 patients who were alive at 30 days were correctly reclassified (Table 3). At the threshold of 5%, the corresponding values of those who died within 30 days and those who were alive at 30 days were 15.2% (95% CI 1.7–27.3) and 1.8% (95% CI −1.2–5.6), respectively (Table A.1).

3.4. Analysis per inflammatory marker

The models in which each inflammatory marker was separately added to the vital sign model are shown in Table A.2 and showed similar results. All inflammatory markers other than CRP were significant; CRP did not show a significant contribution even when the other inflammatory markers were not included in the model. However, when added as a single marker, none of the markers significantly improved the c-index of the vital sign model (Table A.3).

4. Discussion

We quantified the added value of inflammatory markers to vital signs in the prediction of 30-day in-hospital mortality in patients suspected of severe infection. When adding the four inflammatory

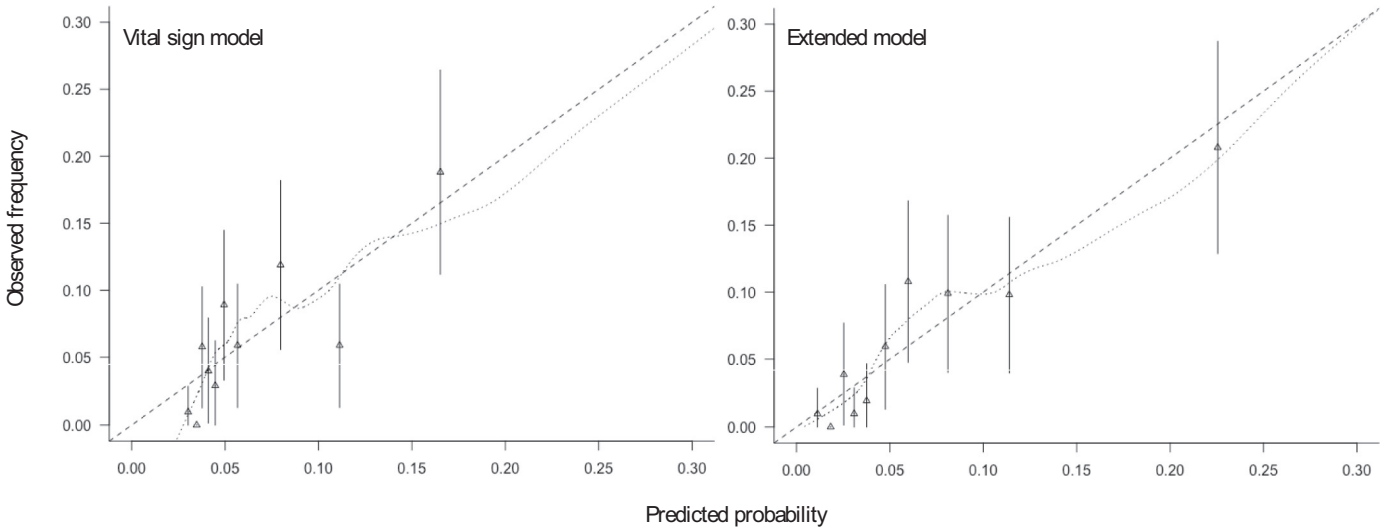

Fig. 1. Calibration plots of the vital sign model and the extended model. Ideally, all groups of predicted probabilities fit close to the dashed diagonal line (perfect calibration). Vertical lines in each group represent 95% confidence intervals of estimated probability.

markers to the vital sign model, the model improved significantly. While NLCR, MPV, and RDW contributed to the improvement of the model, CRP did not. These findings were consistent when each marker was separately added to the vital sign model. More accurate prediction of poor outcome can be expected by adding NLCR, MPV, and RDW to vital sign parameters.

We also estimated the net percentage of correctly reclassified individuals after adding the inflammatory markers to the vital sign model. Among patients who died within 30 days, the net percentage of those correctly reclassified was 9.1% at the thresholds of 10% (this prevented misclassification of 91 per 1000 patients who died within 30 days). At the threshold of 5%, more patients who died were correctly reclassified (15.2%). Among those who were alive at 30 days, very few patients were correctly reclassified: however, the improvement among those who died is more crucial in clinical practice of patients suspected of severe infection, a fatal condition.

When assessing the utility of inflammatory markers in patients with suspected severe infection, the fact that it requires time to obtain the results of the markers should be considered. Turnaround time for a complete blood count including NLCR, MPV, and RDW is around 30 min, and it takes longer for quantitative measurement of CRP [47]. Given this and the fact that our study showed nonsignificant predictive contribution of CRP, we recommend the use of markers included in a complete blood count, and not CRP. The 2018 updated version of the Surviving Sepsis Campaign has integrated its 3-hour and 6-hour bundles into a single-hour bundle [3]. It emphasizes starting treatment immediately in patients with sepsis and septic shock. Thus, 30 min is precious in the management of septic patients. As our analyses did not incorporate this negative aspect of inflammatory markers, the effect of delaying the treatment by waiting for the result should be considered separately.

Among the inflammatory markers, CRP showed much poorer performance than the others, both in isolation and in combination with other markers. This is consistent with the results of previous studies that showed NLCR and RDW predict mortality better than CRP in patients with infectious conditions [16,17]. However, these studies compared the performance of each marker as a sole predictor, not in the sequential

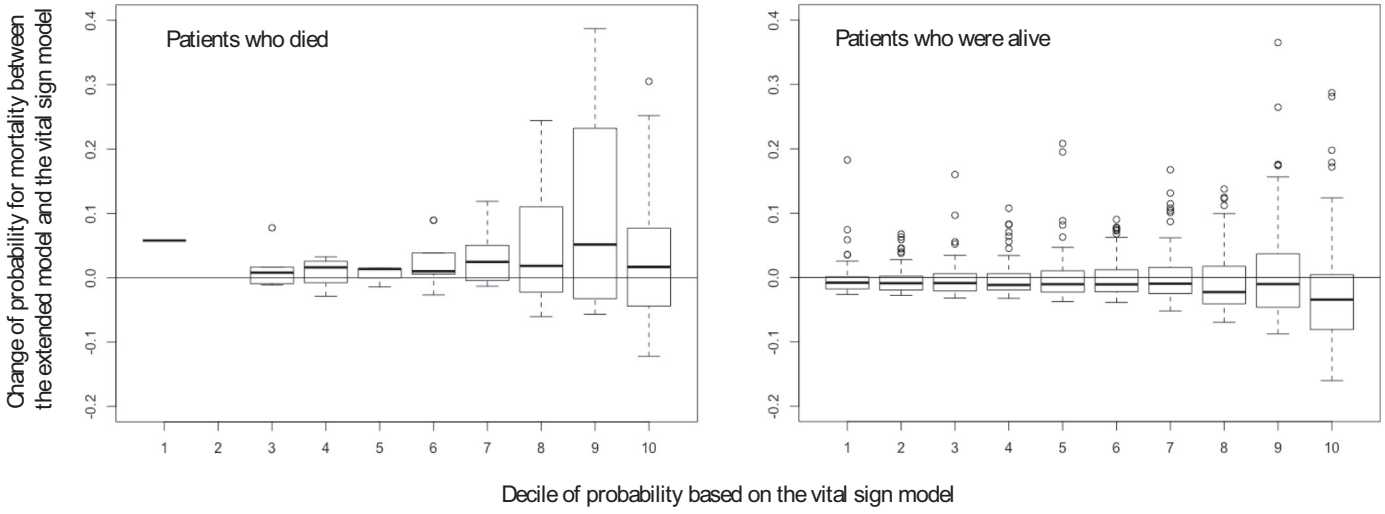

Fig. 2. Change of probability for in-hospital mortality between the vital sign model and the extended model within decile of probability estimated by the vital sign model. The left panel is for those who died within 30 days, and the right panel is for those who were alive at 30 days. It is preferable that the change of probability is positive (>0) for those who died within 30 days, while it is negative (<0) for those who were alive at 30 days.

Table 3
Reclassification by adding the inflammatory markers to the vital sign model at the threshold of 10%.

Vital sign model	Extended model	
	<10% risk	≥10% risk
In 66 patients who died		
<10% risk	30	12
≥10% risk	6	18
In 949 patients who were alive		
<10% risk	719	62
≥10% risk	74	94

The net percentage of correctly reclassified individuals was calculated as (12–6)/66 = 9.1% for patients who died within 30 days, and (74–62)/949 = 1.3% for patients who were alive at 30 days.

process of clinical practice. Since patient examinations usually start with history taking and physical examination, the usefulness of subsequent tests that include inflammatory markers should be assessed by quantifying the added value of the test to the information obtained beforehand [29].

Our study had several limitations. First, to evaluate the added value of the inflammatory markers, we derived the vital sign model and extended model. While those models were used to quantify the added value of the markers, they were not developed for actual implementation in clinical practice. Additional research is required for the aim of developing an optimum prediction model that incorporates the inflammatory markers. Second, we did not capture data on treatments received and could therefore not include this information in the models. Since treatment could have been chosen based on vital sign parameters and the inflammatory markers, the predictive performance of those variables could have been underestimated [48]. Third, as a rule of thumb, a sample size of at least 10 patients with the outcome events per candidate predictor is recommended to build a reliable logistic regression model [32]. Since there were nine parameters included in the extended model (seven candidate predictors, of which two continuous predictors were modeled flexibly using an extra degree of freedom), it was desirable to have 90 patients with an event: however, there were only 66 events in our study. This also caused the wide confidence intervals of the net percentage of reclassification for the patients who died within 30 days. Also, this issue of small sample size could explain nonsignificant effect of systolic blood pressure in both the vital sign and extended models. Thus, our findings should be further validated in studies with a larger sample size. Fourth, we could not evaluate the performance of lactate and newly developed markers since we did not routinely measure them in all patients who underwent blood cultures. It has been reported that lactate improves the predictive performance of qSOFA in patients with suspected sepsis in emergency department settings [26]. Evaluation of the added value of lactate compared to the studied inflammatory markers remains an interesting topic of further investigation. On the other hand, among newly developed markers, mid-regional pro-adrenomedullin has been reported to improve the predictive performance of qSOFA in older patients with infectious conditions [22]. Although this study was conducted in a very small cohort and was limited to older subjects, such newly developed markers have potential to support physicians' decision making. Finally, we did not integrate patients' history as predictors into the model. This was because the aim of this study was to focus on the additive value of inflammatory markers to vital sign parameters, that are commonly advocated and used for screening in patients with suspected infectious conditions. In future studies, it would be also relevant to evaluate the added value of inflammatory markers to physicians' judgement based on the information available prior to blood tests.

5. Conclusions

Of the investigated inflammatory markers, NLCR, MPV, and RDW showed significantly added value to vital sings in the prediction of mortality in patients suspected of severe infection, while CRP did not. Future studies should focus on developing and validating prediction models for individualized predictions including both vital signs and the significant markers from our study.

Author contributions

T Takada had full access to all of the data in the study and takes responsibility for integrity of the data and the accuracy of the data analysis. T Takada contributed to study design, data collection, interpretation of data, and writing the manuscript. JH and KGMM contributed to data analysis, interpretation of data, and writing the manuscript. TY, KF, RF contributed to study design, data collection, interpretation of data, and writing the manuscript. JM, T Takeshima, MH, TA contributed to study design, data analysis, interpretation of data, and writing the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

None.

Appendix A

Table A.1
Reclassification by adding the inflammatory markers to the vital sign model at a threshold of 5%

Vital sign model	Extended model	
	<5% risk	≥5% risk
In 66 patients who died		
<5% risk	8	15
≥5% risk	5	38
In 949 patients who were alive		
<5% risk	445	109
≥5% risk	126	269

The net percentage of correctly reclassified individuals was calculated as (15–5)/66 = 15.2% for patients who died within 30 days, and (126–109)/949 = 1.8% for patients who were alive at 30 days.

Table A.2
Formula of the model with each inflammatory marker added separately

Intercept and predictors in the model	Model CRP			Model NLCR			Model MPV			Model RDW		
	Coefficient	Standard error	p	Coefficient	Standard error	p	Coefficient	Standard error	p	Coefficient	Standard error	p
Intercept	−2.810	1.274	0.028	−2.737	1.280	0.033	−6.384	1.709	<0.001	−9.770	3.801	0.010
Systolic blood pressure 1	−0.012	0.010	0.471[a]	−0.014	0.010	0.399[a]	−0.010	0.010	0.464[a]	−0.014	0.010	0.328[a]
Systolic blood pressure 2	0.011	0.013		0.014	0.013		0.008	0.013		0.013	0.013	
Respiratory rate	0.038	0.021	0.066	0.037	0.021	0.076	0.038	0.021	0.068	0.044	0.020	0.031
Consciousness disturbance	1.031	0.265	<0.001	0.944	0.268	<0.001	1.012	0.266	<0.001	0.943	0.268	<0.001
CRP	0.019	0.012	0.107									
NLCR				0.022	0.008	0.004						
MPV							0.358	0.102	<0.001			
RDW 1										0.535	0.270	0.006[a]
RDW 2										−0.484	0.334	

CRP = C-reactive protein, NLCR = neutrophil-lymphocyte ratio, MPV = mean platelet volume, RDW = red cell distribution width
[a] Since the variable was transformed using restricted cubic splines to account for the nonlinearity, there were two estimated coefficients for the variable. The *p* value is the pooled estimate of the two coefficients.

Table A.3
Performance of the model with each inflammatory marker added separately

	The *p* value of the likelihood ratio test	AUC (range)	The *p* value for comparison of AUC with the vital sign model
CRP	0.118	0.701 (0.691, 0.707)	0.345
NLCR	0.007	0.707 (0.694, 0.715)	0.276
MPV	<0.001	0.714 (0.724, 0.724)	0.197
RDW	0.006	0.717 (0.701, 0.726)	0.243

AUC = Area under the curve, CRP = C-reactive protein, NLCR = neutrophil-lymphocyte ratio, MPV = mean platelet volume, RDW = red cell distribution width.

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