Journal of Critical Care 43 (2018) 163–168

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Sepsis mortality score for the prediction of mortality in septic patients

Wan Fadzlina Wan Muhd Shukeri, MD [a,b], Azrina Md Ralib, PhD [a], Nor Zamzila Abdulah, MD [c], Mohd Basri Mat-Nor, MD [a,*]

[a] Department of Anaesthesiology and Intensive Care, Kulliyyah of Medicine, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia
[b] Department of Anaesthesiology and Intensive Care, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia
[c] Department of Basic Medical Sciences, Kulliyyah of Medicine, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia

ARTICLE INFO

Keywords:
Sepsis
Leukocytes count
Interleukin-6
Procalcitonin
Paraoxonase-1
Mortality

ABSTRACT

Purpose: To derive a prediction equation for 30-day mortality in sepsis using a multi-marker approach and compare its performance to the Sequential Organ Failure Assessment (SOFA) score.
Methods: This study included 159 septic patients admitted to an intensive care unit. Leukocytes count, procalcitonin (PCT), interleukin-6 (IL-6), and paraoxonase (PON) and arylesterase (ARE) activities of PON-1 were assayed from blood obtained on ICU presentation. Logistic regression was used to derive sepsis mortality score (SMS), a prediction equation describing the relationship between biomarkers and 30-day mortality.
Results: The 30-day mortality rate was 28.9%. The SMS was [elogit(p)/(1 + elogit(p))] × 100; logit(p) = 0.74 + (0.004 × PCT) + (0.001 × IL-6) − (0.025 × ARE) − (0.059 × leukocytes count). The SMC had higher area under the receiver operating characteristic curve (95% CI) than SOFA score [0.814 (0.736–0.892) vs. 0.767 (0.677–0.857)], but is not statistically significant. When the SMS was added to the SOFA score, prediction of 30-day mortality improved compared to SOFA score used alone [0.845 (0.777–0.899), $p = 0.022$].
Conclusions: A sepsis mortality score using baseline leukocytes count, PCT, IL-6 and ARE was derived, which predicted 30-day mortality with very good performance and added significant prognostic information to SOFA score.

1. Introduction

Sepsis remains an ongoing challenge in intensive care medicine largely because of the high mortality rate despite the provision of optimal care [1]. Initial Sequential Organ Failure Assessment (SOFA) score is one of the scoring systems used for predicting mortality in septic patients [2]. However, this approach has been criticised for its lack of capacity to discriminate outcome [3]. The use of serum biomarkers has significantly improved the clinician's ability to diagnose and predict the outcome of sepsis [4,5].

In everyday clinical practice, the leukocytes count has been the most widely used biomarker to guide the prognosis of septic patients in addition to other clinical parameters [6]. Over the last two decades, procalcitonin (PCT) and interleukin-6 (IL-6) have emerged as biomarkers for the prediction of sepsis outcome [7-12]. Recent studies suggested the possible role of decreased PON-1 activity in septic patients [13,14]. PON-1 is an enzyme that is synthesised primarily in the liver, which neutralizes lipopolysaccharides and inhibits the synthesis of some pro-inflammatory cytokines. PON-1 can be evaluated according to its different activities, such as its paraoxonase (PON) activity and arylesterase (ARE) activity. Few studies have revealed the potential prognostic value of PON-1 activity in septic patients [15-17].

Because of the complex pathophysiology of sepsis, it is unlikely that a single biomarker would be able to reflect the various host responses to infection. Combining several biomarkers into a single classification rule should help to improve their accuracy and hence, their usefulness. The purpose of the present study was to derive a prediction equation using combination of leukocytes count, PCT, IL-6, and PON and ARE activities of PON-1 to predict 30-day mortality in septic patients, which we call the sepsis mortality score. We then sought to compare the performance of this prediction equation to that of the SOFA score in their ability to predict mortality in sepsis.

2. Methodology

2.1. Study design and participants

This prospective observational study was performed from July 2011 to June 2014 in a 12-bed intensive care unit (ICU) in a major tertiary hospital in Pahang, Malaysia. The protocol used in this study was approved by the local medical research and ethics committee and registered under the National Medical Research Register (NMRR-13-879-15223). Written informed consent was obtained from either the patients or their legally

* Corresponding author.
E-mail address: m.basri@iium.edu.my (M.B. Mat-Nor).

http://dx.doi.org/10.1016/j.jcrc.2017.09.009
0883-9441/

acceptable representative prior to recruitment. Consecutive adult patients with suspected or documented infection who fulfilled the criteria for Systemic Inflammatory Response Syndrome were recruited. Patients who had received antimicrobial treatment for >24 h before the baseline blood samples were drawn for use in the biomarker analysis were excluded. One hundred and sixty-four patients were initially recruited. However, because the definition of sepsis was revised in early 2016, the patients were re-categorised according to the new Sepsis-3 definition [3]. Five patients could not be included in the new sepsis category; thus, 159 patients participated in the study. This number of patients fulfilled the sample size calculation that at least 142 patients were required to achieve the relevant anticipated area under the receiver operating characteristic curve (AUROC) of 0.65 at a significance level of 5%, power of 90% and a dropout rate of 20%.

For the remaining 159 patients, relevant demographic and clinical data were collected, including age, sex, admission category, initial SOFA score, comorbidities as assessed by Charlson Comorbidity Index, primary sites of infection and presence of bacteraemia. Patients were followed-up until day 30 of study enrolment to assess for 30-day mortality. There was no lost to follow-up. The characteristics of the study population are summarized in Table 1. The 30-day mortality was noted in 46 (28.9%) of the patients.

2.2. Sample collection and processing

Ten millilitres of whole blood were collected by venous puncture upon ICU presentation but no longer than 24 h after antimicrobial administration. Two millilitres of the sample were sent on the same day to the haematology laboratory for the routine measurement of leukocytes count. The remaining samples were transferred into a serum separator tube and centrifuged at 3000 rotations per minute for 10 min. The serum collected was divided into small aliquots to avoid repeated freezing and thawing, and then stored at −80 °C until the day of assay. The frozen samples were thawed at room temperature and gently mixed just before the biomarkers were measured. The serum PCT concentrations were measured in batches every three months during the study period. The serum IL-6 concentrations were measured in one batch after completion of the study enrolment in June 2014. Laboratory analyses of serum PON-1 activities were performed over a span of four months from March to June 2015. In caring for the patients, the treating ICU physicians were blinded to the level of all biomarkers except the leukocytes count.

Table 1
Baseline demographics and clinical characteristics.

Variables	All (n = 159)	Survivors (n = 113)	Non-survivors (n = 46)	*p*
Demographic				
Age (years)	47 ± 16	45 ± 16	54 ± 16	0.002
Sex (male)	109 (68.6)	73 (64.6)	36 (78.3)	0.093
Clinical				
Admission category				
Medical	117 (73.6)	85 (75.2)	32 (69.6)	0.463
Surgical	42 (26.4)	28 (24.8)	14 (30.4)	0.463
Severity of illness				
SAPS II	43 [33–56]	40 [30–51]	53 [41–63]	<0.001
SOFA	9 [6–12]	7 [5–10]	12 [9–16]	<0.001
Septic shock	37 (23.3)	18 (15.9)	19 (41.3)	0.001
Charlson Comorbidity Index	1.8 ± 2.2	1.4 ± 1.7	2.6 ± 3.1	0.019
Primary sites of infection				
Lungs	90 (56.6)	65 (57.5)	25 (54.3)	0.714
Abdomen	15 (9.4)	10 (8.8)	5 (10.9)	0.693
Soft tissue	13 (8.2)	11 (9.7)	2 (4.3)	0.261
Urinary tract	9 (5.7)	7 (6.2)	2 (4.3)	0.648
Nervous system	8 (5.1)	8 (7.1)	0 (0)	0.064
Bacteraemia	27 (16.9)	16 (14.2)	11 (23.9)	0.137
Length of stay				
ICU	7.1 [3.2–13.1]	7.1 [3.5–13]	7.7 [1.9–15.5]	0.742
Hospital	12.7 [7.5–22.5]	14.1 [8.6–30.2]	8.8 [2.8–17.2]	<0.001
30-day mortality	46 (28.9)	–	–	–

Note. Data are expressed as mean ± standard deviation, frequencies (percentage) or median [interquartile range]. The results of the comparison between the two groups was analysed by independent *t*-test, the Mann-Whitney test for continuous variables or the chi-squared test for categorical variables. SAPS II = Simplified Acute Physiological Score II, SOFA = Sequential Organ Failure Assessment, ICU = intensive care unit.

2.3. Biomarker assays

2.3.1. Leukocytes count

The leukocytes count was performed in the Haematology Laboratory using the Sysmex XE-2100 haematology analyser (Kobe, Japan) as part of the automated full blood count.

2.3.2. Procalcitonin (PCT)

Serum PCT concentrations were measured using the BRAHMS Kryptor compact assay (Henningsdorf, Germany). This measurement principle is based on time-resolved amplified cryptate emission technology at reference intervals of <0.05 ng/mL. The assay has a measuring range of 0.02 to 5000 ng/mL, a functional sensitivity of 0.06 ng/mL and an analytical sensitivity of 0.02 ng/mL. The manufacturer's intra-assay and inter-assay coefficients of variation (CV) for PCT were ≤5% and ≤6%, respectively.

2.3.3. Interleukin-6 (IL-6)

Serum IL-6 concentrations were measured using the Quantikine enzyme-linked immunosorbent assay kit from R&D Systems (Minnesota, USA). This assay uses the quantitative sandwich enzyme immunoassay technique at reference intervals of <9.7 ρg/mL. All samples were assayed in duplicate. The assay has a functional sensitivity of 0.7 ρg/mL and an assay range of 31–300 ρg/mL. The manufacturer's intra-assay and inter-assay CV for IL-6 were 1.7–4.4% and 2–3.7%, respectively.

2.3.4. Paraoxonase-1 (PON-1)

The serum PON and ARE activities of PON-1 were determined spectrophotometrically using a Perkin Elmer Lambda 35 UV/VIS spectrophotometer according to the method described by Eckerson et al. [18]. The substrates paraoxon and phenylacetate were purchased from Sigma-Aldrich (Missouri, USA). The intra-assay and inter-assay CV for PON activity and ARE activity, as determined in our laboratory, were 3.98% and 5.2% and 4.75% and 3.9%, respectively.

2.4. Statistical analysis

Data are presented as mean ± standard deviation for normally distributed variables or median [interquartile range] for non-normally distributed variables. Shapiro-Wilk test was used to assess for normality of the data. Univariate comparisons of variables between the two groups was analysed using the independent *t*-test for normally distributed variables and the Mann-Whitney test for non-normally distributed variables. Categorical variables were presented as frequencies (percentages) and were compared using a chi-squared test; $p < 0.05$ was considered statistically significant.

Our sepsis mortality score represents the predicted probability of 30-day mortality. To derive this score, we used logistic regression by including all biomarkers with univariate significance of $p < 0.1$ as covariates and 30-day mortality as the dependent variable, employing the backward elimination method. The generated coefficients for each biomarker in the final step of the logistic regression were used to create the

equation to predict a logit transformation of the probability of 30-day mortality:

$$\text{Logit (p)} = \beta 0\ (\text{intercept}) + \beta 1\ (\text{leukocytes count}) + \beta 2\ (\text{PCT}) + \beta 3\ (\text{IL-6}) + \beta 4\ (\text{PON}) + \beta 5\ (\text{ARE})$$

To determine the probability of 30-day mortality, logit (p) was converted to a probability of the outcome using the following conversion:

$$\text{Probability of 30-day mortality (sepsis mortality score)} = [e^{\text{logit(p)}}/(1 + e^{(\text{logit(p)})}] \times 100$$

Multicollinearity was detected using tolerance and variation inflation factor (VIF); where tolerance <0.10 and VIF exceeding 10 warrant further investigation.

The model calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test. The AUROC (95% confidence interval [CI]) of the sepsis mortality score in predicting 30-day mortality was calculated. The differences in the AUROCs were tested for significance using the test proposed by DeLong et al. [19]. All 159 patients were then grouped according to the optimal cut-off value of the sepsis mortality score, and the groups were compared according to the 30-day mortality using Kaplan-Meier survival curves. A log rank test was performed to compare the survival curves of the groups. To determine the independent predictive ability of the sepsis mortality score, we used its log transformation as a covariate in another multivariate logistic regression in order to control for confounders. The independent value of the sepsis mortality score was expressed as an odds ratio (OR) with 95% CI.

All statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA) except the DeLong tests, which were determined using MedCalc for Windows, version 17.5.5 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Biomarker profiles

The medians and interquartile ranges are shown for each of the five biomarkers for the population as a whole, as well as stratified by the outcome of 30-day mortality (Table 2). As a summary measure of predictive accuracy, we determined the AUROC and the ideal cut-off values for the ability of each biomarker to classify patients with 30-day mortality (Table 2).

3.2. Development of sepsis mortality score

We used multivariate logistic regression to model the ability of biomarkers to identify patients who have the outcome of 30-day mortality. The regression model was first constructed using all five biomarkers as covariates. By employing backward elimination method, the covariate with the highest *p*-value was eliminated and the model was refit to the remaining four biomarkers. This process was repeated until only biomarkers which were statistically significant remained in the model.

In the final step of the logistic regression model, leukocytes count, PCT, IL-6 and ARE remained statistically significant. Using the resulting regression equation, we converted the log of probability to the probability of 30-day mortality, which represents our final "sepsis mortality score". The score was derived as follows:

$$\text{Logit (p)} = 0.74 + (0.004 \times \text{PCT}) + (0.001 \times \text{IL-6}) - (0.025 \times \text{ARE}) - (0.059 \times \text{leukocytes count}) \quad (1)$$

$$\text{Sepsis mortality score} = \text{probability of 30-day mortality} = [e^{(\text{logit(p)}}/(1 + e^{(\text{logit(p)})}] \times 100 \quad (2)$$

The tolerance of all biomarkers was >0.10, and the VIFs were <10, which suggested that multicollinearity was not an issue.

3.3. Predictive performance of sepsis mortality score

The Hosmer and Lemeshow chi-squared test was 13.27 ($p > 0.05$, 8° of freedom), indicating the good calibration of the model. The AUROC of the sepsis mortality score and each of its constituent individual biomarkers for the prediction of 30-day mortality are shown in Fig. 1. We found that the AUROC of the model was 0.814 (95% CI 0.736–0.892, $p < 0.001$), which suggested very good model discrimination. The optimal cut-off value of the score was 30.4. At this cut-off value, the sensitivity was 78%, and the specificity was 72.9%. The positive predictive value was 52.5%, and the negative predictive value was 89.7%. The sepsis mortality score outperformed its constituent individual biomarkers in predicting 30-day mortality; these biomarkers showed only moderate to good performance when they were used alone. The differences in the AUROC of the sepsis mortality score and each of its constituent individual biomarkers are statistically significant from the DeLong tests ($p < 0.005$).

In another ROC curve analysis (Fig. 2), the AUROC of the sepsis mortality score was higher than the SOFA score [0.814 (95% CI 0.736–0.892) vs. 0.767 (95% CI 0.677–0.857)], but the difference is not statistically significant ($p = 0.377$). When the sepsis mortality score was added to the SOFA score, prediction of 30-day mortality improved compared to the SOFA score used alone [0.845 (0.777–0.899)]. The increase in the AUROC provided by the sepsis mortality is statistically significant ($p = 0.022$).

In the Kaplan-Meier analysis, mortality was significantly higher in the patients with increased sepsis mortality score (log rank test, $p < 0.001$) (Fig. 3). The 30-day mortality rates for patients with sepsis mortality score greater than and <30.4 were 52.5% (n = 32) vs. 10.3% (n = 9), respectively.

When included in multivariate models with clinical variables, the sepsis mortality score remained the most significant predictor of 30-day mortality with adjusted OR of 15.696 (95% CI 3.766–65.416, $p < 0.001$). The SOFA, although remained significant, had a less independent value with adjusted OR of 0.187 (95% CI 1.075–1.353, $p = 0.001$).

Table 2
Leukocytes count, PCT, IL-6, PON and ARE in survivors and non-survivors and their predictive performance for 30-day mortality.

Biomarkers	All (n = 159)	Survivors (n = 113)	Non-survivors (n = 46)	*p*	AUROC (95% CI)	Cut-off
Leukocytes count ($\times 10^9$/L)	15.99 [12.18–21.99]	17.21 [12.81–23.70]	13.46 [6.92–20.80]	0.004	0.654 (0.553–0.755)	14.2
PCT (ng/mL)	10.49 [1.03–43.07]	8.35 [0.95–22.70]	22.56 [1.62–104.23]	0.009	0.645 (0.531–0.733)	14.6
IL-6 (pg/mL)	329.52 [87.98–628.89]	154.66 [70.67–573.49]	491.97 [305.63–772.63]	<0.001	0.715 (0.645–0.802)	431.9
PON (U/mL)	138.92 [85.84–205.44]	149.26 [88.57–230.82]	110.85 [78.25–174.96]	0.032	0.609 (0.515–0.702)	125.7
ARE (U/mL)	70.42 [48.58–91.89]	79.29 [53.73–97.69]	59.33 [37.05–79.52]	0.002	0.697 (0.607–0.787)	68.9

Note. Data are expressed as medians [interquartile range]. Comparison of the two groups was conducted using the Mann-Whitney test. AUROC = area under the receiver operating characteristic curve, CI = confidence interval, ARE = arylesterase, IL-6 = interleukin-6, PCT = procalcitonin, PON = paraoxonase.

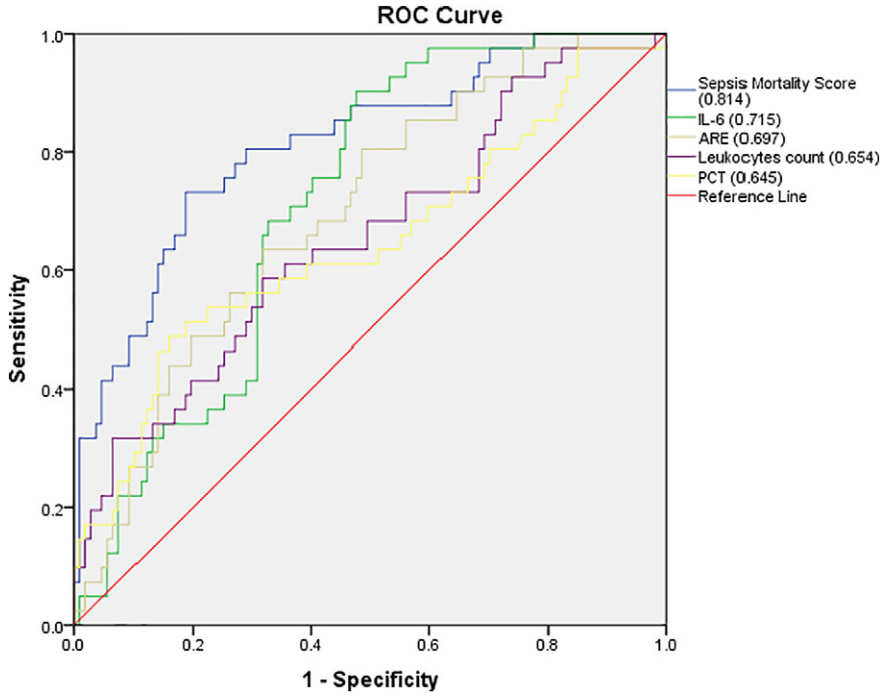

Fig. 1. Receiver operating characteristics curves of the sepsis mortality score compared to its constituent individual biomarkers for their mortality predictive performance. ARE = arylesterase, IL-6 = interleukin-6, PCT = procalcitonin.

4. Discussion

In this prospective study, we assembled a cohort of 159 patients with sepsis and studied five biomarkers on their ICU admission with the overall goal of creating a prediction equation, the "sepsis mortality score", that would allow discrimination of those who are at increased risk of 30-day mortality. A sepsis mortality score using baseline leukocytes count, PCT, IL-6 and ARE activities of PON-1 predicted 30-day mortality with a very good performance (AUROC 0.814) in our sepsis cohort. Of particular note, the sepsis mortality score added significant prognostic information, and is thus a valuable supplement to the SOFA score, one of the scoring methods commonly used to predict outcome in sepsis.

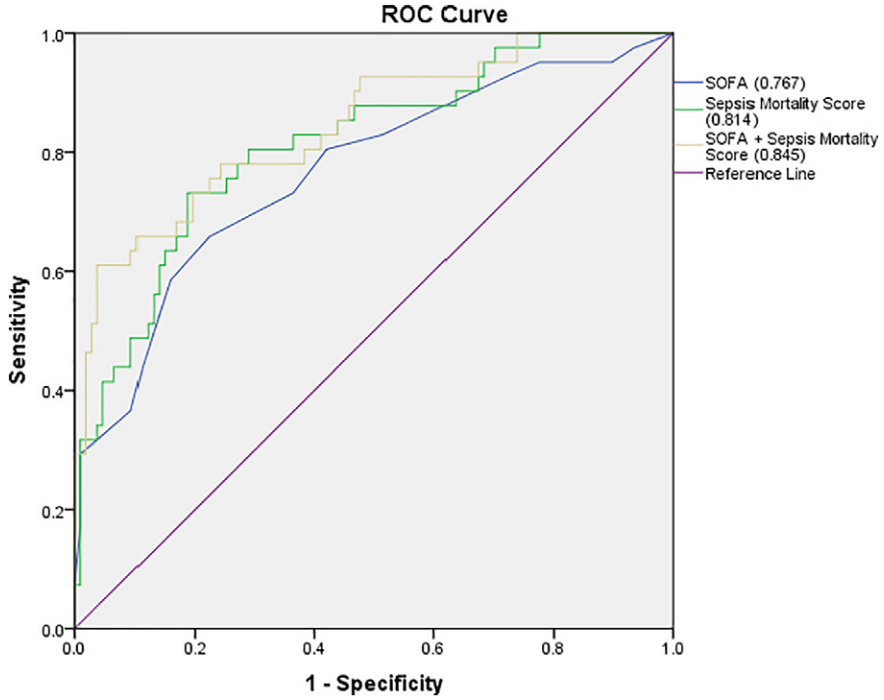

Fig. 2. Receiver operating characteristics curves of the SOFA score, sepsis mortality score and combination of the two scores for their mortality predictive performance. SOFA = Sequential Organ Failure Assessment.

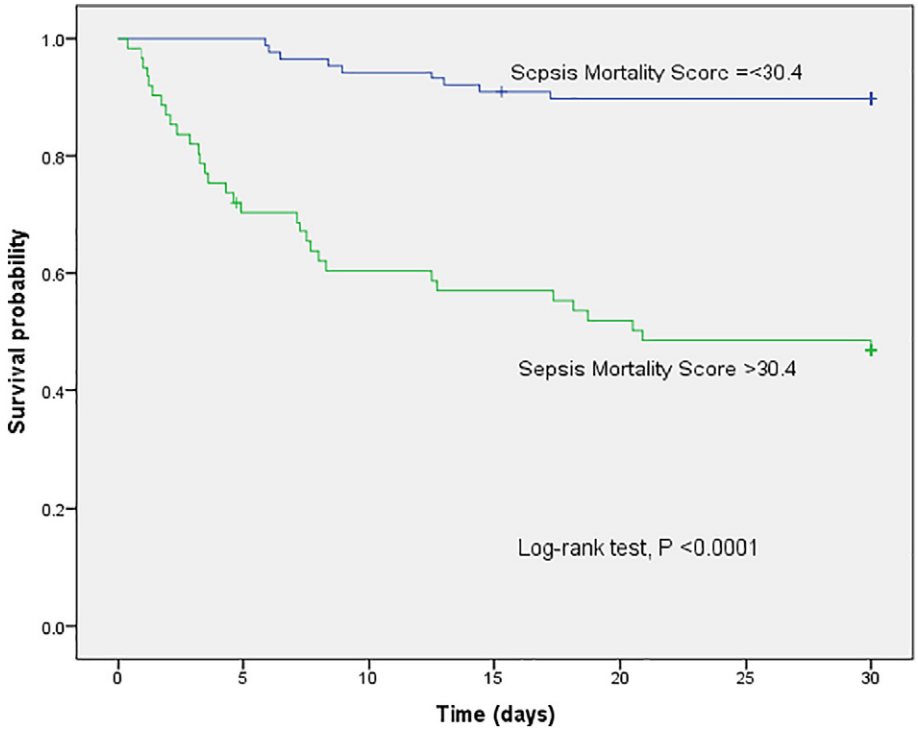

Fig. 3. Kaplan-Meier plot showing survival according to increased sepsis mortality score (>30.4) in the entire cohort.

SOFA score was developed 20 years ago to describe organ failures in sepsis, using six different sub-scores (ranging from 0 to 4) for each organ. In general, there was an increasing mortality rate with a greater SOFA score [20]. However, SOFA scoring systems had acknowledged limitations in terms of variables used and mortality discrimination [3]. Biomarkers, particularly combination of them, may present more reliable and objective guide for mortality prediction in sepsis. Two recent studies also demonstrated that combined biomarkers performed better than routinely used clinical score in predicting sepsis-related mortality [21,22].

Our results are novel with respect to the combined use of leukocytes count, PCT, IL-6 and PON-1 activity for mortality prediction. In probably the largest study using multi-marker approach in the critical care literature, Shapiro et al. acknowledged the limitation that biomarkers that were previously reported as promising, including PCT and IL-6, were not tested but also could have performed well [23]. Although others have also proposed a multi-marker approach to sepsis, they did not integrate their results into a tangible estimate of the risk of mortality for use by practicing clinicians [21,22,24].

Although our results are encouraging, our study has several pertinent limitations. The sepsis mortality score that we generated in this study predicted our single-centred data set, but whether it is generalizable to external populations is unknown. Patient outcome depends on patient management, which may vary among institutions; thus, the lack of standardisation may have confounded our outcomes. However, the mortality rate of 28.9% found in our study population is almost identical with that observed in United States [25]. Although we attempted to control for confounding by other clinical variables by modelling the sepsis mortality score in a logistic regression model, we may have failed to account for other unmeasured confounders or collinear effects. In addition, because this study used a convenience sample, selection bias may have led to a non-representative population. Furthermore, the performance of the sepsis mortality score for inpatients with suspected ICU-acquired sepsis was not assessed. Therefore, further research is warranted to validate the clinical utility of the sepsis mortality score in the prediction of mortality in sepsis.

5. Conclusion

The multi-marker approach using the baseline leukocytes count, PCT, IL-6 and ARE activity of PON-1 predicted 30-day mortality with a very good performance in our sepsis cohort. Although not superior to the SOFA score, our sepsis mortality score added significant prognostic information, and is thus a valuable supplement to the SOFA score in predicting mortality in sepsis. Further studies are warranted to validate these findings and to assess whether the sepsis mortality score derived from these biomarkers may be successfully integrated with physicians' clinical practice to improve prediction of mortality and clinical decision making at the patient's bedside.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding

This work was supported by the International Islamic University Malaysia Endowment B Research Grant (EDWB11-256-0734).

References

[1] Gupta RG, Hartigan SM, Kashiouris MG, Sessler CN, Bearman GML. Early goal-directed resuscitation of patients with septic shock: current evidence and future directions. Crit Care 2015;19:286. http://dx.doi.org/10.1186/s13054-015-1011-9.
[2] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10. http://dx.doi.org/10.1001/jama.2016.0287.
[3] Zygun DA, Laupland KB, Fick GH, Sandham JD, Doig CJ. Limited ability of SOFA and MOD scores to discriminate outcome: a prospective evaluation in 1,436 patients. Can J Anaesth 2005;52:302–8. http://dx.doi.org/10.1007/BF03016068.
[4] Reinhart K, Bauer M, Riedemann NC, Hartog CS. New approaches to sepsis: molecular diagnostics and biomarkers. Clin Microbiol Rev 2012;25:609–34. http://dx.doi.org/10.1128/CMR.00016-12.
[5] Biron BM, Ayala A, Lomas-Neira JL. Biomarkers for sepsis: what is and what might be? Biomark Insights 2015;10:7–17. http://dx.doi.org/10.4137/BMI.S29519.

[6] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign. Crit Care Med 2013;41:580–637. http://dx.doi.org/10.1097/CCM.0b013e31827e83af.
[7] Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 2001;164:396–402. http://dx.doi.org/10.1164/ajrccm.164.3.2009052.
[8] Jekarl DW, Lee SY, Lee J, Park YJ, Kim Y, Park JH, et al. Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis. Diagn Microbiol Infect Dis 2013;75:342–7. http://dx.doi.org/10.1016/j.diagmicrobio.2012.12.011.
[9] Mat-Nor MB, Ralib A, Abdulah NZ, Pickering JW. The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality. J Crit Care 2016;33:245–51. http://dx.doi.org/10.1016/j.jcrc.2016.01.002.
[10] Mat-Nor MB, Ralib A. Procalcitonin clearance for early prediction of survival in critically ill patients with severe sepsis. Crit Care Res Pract 2014;2014.
[11] Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med 2006;34:2596–602. http://dx.doi.org/10.1097/01.CCM.0000239116.01855.61.
[12] Ruiz-Rodrigues J, Cabarello J, Ruiz-Sanmartin A, Ribas V, Perez M, Boveda J. Usefulness of procalcitonin clearance as a prognostic biomarker in septic shock. A prospective pilot study. Med Int 2012;36:475–80.
[13] Costa L, Furlong C. Paraoxonase (PON1) in health and disease: basic and clinical aspects. Prot. action HDL-associated PON1 against LDL Oxid. Kluwer Academic Publishers; 2002. p. 125–36.
[14] Novak F, Vavrova L, Kodydka J, Sr F, Hynkova M, Zak A. Decreased paraoxonase activity in critically ill patients with sepsis. Clin Exp Med 2010;10:21–5.
[15] Li Y, Zhai R, Li H, Mei X, Qiu G. Prognostic value of serum paraoxonase and arylesterase activity in patients with sepsis. J Int Med Res 2013;41:681–7.
[16] Bojic S, Kotur-Stevuljevic J, Kalezic N, Jelic-Ivanovic Z, Stefanovic A, Palibrk I, et al. Low paraoxonase 1 activity predicts mortality in surgical patients with sepsis. Dis Markers 2014;2014. http://dx.doi.org/10.1155/2014/427378.
[17] İnal V, Yamanel L, Taşkin G, Tapan S, Cömert B. Paraoxonase 1 activity and survival in sepsis patients. Balkan Med J 2015;32:183–8 (6 pp.) http://dx.doi.org/10.5152/balkanmedj.2015.15674.
[18] Eckerson HW, Wyte CM, La Du BN. The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet 1983;35:1126–38.
[19] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45. http://dx.doi.org/10.2307/2531595.
[20] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22:707–10. http://dx.doi.org/10.1007/s001340050156.
[21] Kim H, Hur M, Moon H-W, Yun Y-M, Di Somma S. Multi-marker approach using procalcitonin, presepsin, galectin-3, and soluble suppression of tumorigenicity 2 for the prediction of mortality in sepsis. Ann Intensive Care 2017;7:27. http://dx.doi.org/10.1186/s13613-017-0252-y.
[22] Dieplinger B, Egger M, Leitner I, Firlinger F, Poelz W, Lenz K, et al. Interleukin 6, galectin 3, growth differentiation factor 15, and soluble ST2 for mortality prediction in critically ill patients. J Crit Care 2016;34:38–45. http://dx.doi.org/10.1016/j.jcrc.2016.03.020.
[23] Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM, et al. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. Crit Care Med 2009;37:96–104. http://dx.doi.org/10.1097/CCM.0b013e318192fd9d.
[24] Wong HR, Lindsell CJ, Pettila V, Meyer NJ, Thair SA, Karlsson S, et al. A multibiomarker-based outcome risk stratification model for adult septic shock*. Crit Care Med 2014;42:781–9. http://dx.doi.org/10.1097/CCM.0000000000000106.
[25] Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840–51. http://dx.doi.org/10.1056/NEJMra1208623.