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Development and validation of a parsimonious and pragmatic CHARM score to predict mortality in patients with suspected sepsis

Kuan-Fu Chen, MD, PhD [a,b,c], Su-Hsun Liu, MD, PhD [d,e,1], Chih-Huang Li, MD [f,1], Chin-Chieh Wu, PhD [a,1], Chung-Hsien Chaou, MD [f], I-Shiang Tzeng, PhD [f], Yu-Hsiang Hsieh, PhD [g], Gerald N. Blaney, MPH [a], Zhen-Ying Liu, MPH [a], Shih-Tsung Han, MD, PhD [f,*], Yi-Lin Chan, MD, PhD [f,*]

[a] Department of Emergency Medicine, Chang Gung Memorial Hospital, Keelung, Taiwan
[b] Clinical Informatics and Medical Statistics Research Center, Chang Gung University, Taoyuan, Taiwan
[c] Community Medicine Research Center, Chang Gung Memorial Hospital, Keelung, Taiwan
[d] Department of Family Medicine, Chang Gung Memorial Hospital, Linkou, Taiwan
[e] School of Medicine, Chang Gung University, Taoyuan, Taiwan
[f] Department of Emergency Medicine, Chang Gung Memorial Hospital, Linkou, Taiwan
[g] Department of Emergency Medicine, Johns Hopkins University, Baltimore, MD, USA

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ABSTRACT

Background: We aimed to derive and validate a parsimonious and pragmatic clinical prediction rule using the concepts of Predisposition, Infection, Response, and Organ Dysfunction to predict in-hospital mortality; and to compare it with other prediction rules, as well as with conventional biomarkers for evaluating the mortality risk of patients with suspected sepsis in the emergency department (ED).

Methods: We conducted a pragmatic cohort study with consecutive ED patients aged 18 or older with documented diagnostic codes of infection and two sets of blood culture ordered by physicians between 2010 and 2012 in a tertiary teaching hospital.

Results: 7011 and 12,110 patients were included in the derivation cohort and the validation cohort for the final analysis. There were 479 deaths (7%) in the derivation cohort and 1145 deaths (9%) in the validation cohort. Independent predictors of death were absence of Chills (odds ratio: 2.28, 95% confidence interval: 1.75–2.97), Hypothermia (2.12, 1.57–2.85), Anemia (2.45, 1.97–3.04), wide Red cell Distribution Width (RDW) (3.27, 2.63–4.05) and history of Malignancy (2.00, 1.63–2.46). This novel clinical prediction rule (CHARM) performed well for stratifying patients into mortality risk groups (sensitivity: 99.4%, negative predictive value 99.7%, receiver operating characteristic area 0.77). The CHARM score also outperformed the other scores or biomarkers such as PIRO, SIRS, MEDS, CURB-65, C-reactive protein, procalcitonin and lactate (all $p < .05$).

Conclusions: In patients with suspected sepsis, this parsimonious and pragmatic model could be utilized to stratify the mortality risk of patients in the early stage of sepsis.

1. Introduction

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1,2]. Most clinical trials utilize lactatemia or refractory hypotension as indicators of septic shock [3,4], which may not be sufficiently sensitive or specific for timely therapy [5,6]. Early identification of patients who might develop septic shock or severe sepsis and who are likely to benefit from timely therapy is therefore critical and deserves to be better researched.

Many clinical prediction rules have been developed to stratify the mortality risk for sepsis in different clinical settings. The Mortality in Emergency Department Sepsis (MEDS) score uses 9 predictors, but some predictors require subjective judgment that can generate inaccuracy (e.g., status of terminal illness) [7]. More recently, the concept of predisposition, infection/insult, response and organ dysfunction (PIRO) was introduced to categorize septic patients into different stages [8]. However, most prediction rules that adapt the PIRO principle include more than a dozen of predictors [9,10], making them less useful. An exception is the simple Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure and age 65 score (CURB-65), which was originally

* Corresponding authors at: 5 Fu-shin Street, Gueishan district, Taoyuan 333, Taiwan .
E-mail addresses: drkfchen@gmail.com (K.-F. Chen), shliu41@mail.cgu.edu.tw (S.-H. Liu), chhli2002@gmail.com (C.-H. Li), wujinja@gmail.com (C.-C. Wu), m7088@adm.cgmh.org.tw (C.-H. Chaou), istzeng@gmail.com (I.-S. Tzeng), yhsieh1@jhmi.edu (Y.-H. Hsieh), gblaney3@gmail.com (G.N. Blaney), zhenyingtw@gmail.com (Z.-Y. Liu), adrianhst@gmail.com (S.-T. Han), chan.yiling@gmail.com (Y.-L. Chan).
[1] Contributed equally.

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developed to predict mortality of community-acquired pneumonia patients. CURB-65 has been validated with moderate performance for septic patients [11,12].

We conducted this retrospective cohort study on patients with clinically suspected sepsis to derive and validate a parsimonious and pragmatic rule. We further compared this novel clinical prediction rule with conventional models and biomarkers for the ability to discriminate the mortality risk of patients with suspected sepsis in the emergency department (ED).

2. Methods

2.1. Study Design, Site and Patients

We retrospectively reviewed patients who visited the ED in a tertiary teaching hospital with 3700 beds and approximately 180,000 annual ED visits between 2010 and 2012. A two-step inclusion method was adopted to enroll the subjects: first, all adult patients aged 18 and older who visited the ED with a documented ICD-9-CM codes of infection in the ED (Supplementary Table 1), who also had at least two sets of blood cultures ordered at physician's discretion were selected; and second, patients transferred from other medical institutes, patients who had repeated visits, and patients with traumatic injuries were excluded. The institutional review board of the Chang Gung Memorial Hospital approved the study and waived requirement for informed consent.

2.2. Data Collection and Definition

All electronic medical records of ED visits and hospitalization were retrospectively retrieved from the Hospital Information System (HIS) from 2010 to 2012 via Structural Query Language (Microsoft Access, Redmond, WA) by the trained data abstractor, who was blinded to the study objectives and hypotheses. Variables were defined prior to data collection. We also verified collected data by different computer algorithms and by manual review on 5% of randomly selected medical records. All discrepant results were resolved by consensus meetings. Basic demographic data, underlying diseases, terminal illnesses, infectious focuses, symptoms and signs, initial vital signs, laboratory data were abstracted.

2.3. Definition of Endpoint

Our primary goal was to derive a novel rule to predict in-hospital mortality among patients with clinically suspected sepsis and evaluate its performance in the derivation and validation cohort. We then compared the performances between this novel rule, conventional biomarkers i.e., C-reactive protein (CRP), lactate, and other scores, including Systemic Inflammatory Response Syndrome (SIRS) criteria [13], MEDS, CURB-65 and PIRO.

2.4. Statistical Methods

Statistical analyses were performed with R (version 3.2.1; R Foundation for Statistical Computing, Vienna, Austria), ROCKIT (University of Chicago Medical Center, Chicago, IL) and Stata 13.0 (StataCorp, College Station, TX). The candidate predictors were selected according to the PIRO principle. Namely, variables of predisposition included age, gender, nursing residents, underlying diseases, and receiving hemodialysis or immunosuppressant medication. Variables of infection included the anatomical location of the infection. Variables of response included vital signs, white blood cell counts and differential counts, concentrations of serum electrolytes and CRP, and symptoms of subjective fever or chills. Variables of organ dysfunction included blood pressure, Glasgow coma scale, pulse oximeter oxygen saturation, result of arterial blood gas analysis, Red blood cell Distribution Width (the percentage of the standard deviation of red blood cell volume to the mean corpuscular volume, and RDW was measured in our institution with normal range between 11.5% and 14.5%), level of lactate, creatinine, liver function, bilirubin and hemoglobin, platelet count and coagulation profile. Variables with more than 5% of missing values were not considered as candidate predictors [14]. The cohort in year 2010 was utilized as the derivation set while the cohort in year 2011 and 2012 was utilized as the validation set. Continuous variables of candidate predictors were converted into categorical variables according to the results from the visualization, using locally weighted scatterplot smoothing, as well as guidelines from clinical practice, descriptions in other studies, or laboratory references.

2.5. Prediction Rule Development and Validation

Because of the relatively large sample size in our study, only categorical variables with $p < 0.05$ and beta coefficient > 0.1 were evaluated by multivariable logistic regression with Allen-Cady backward selection procedure, with priority determined by clinical relevance and an expert panel meeting. In order to generate a parsimonious rule, the final multivariable logistic regression model with the best capability to discriminate patients with the probability of developing mortality was chosen according to the Akaike information criterion (AIC). The Hosmer-Lemeshow Goodness-of-Fit statistics were used to verify the capability to calibrate with the observed mortality rates. After dividing through the smallest beta coefficient, we rounded the other beta coefficients obtained from the final model to the nearest integer to generate a simple scoring system. The score for each patient was calculated by summation of the points of each predictor. We further evaluated the performance of the rule by receiver-operating characteristic (ROC) curves. The discriminatory ability of the rule and the correlated clinical prediction rule and biomarkers were compared using the partial paired area under ROC curve (AUC). Furthermore, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated according to different scores of the prediction rule. The performance of the rule obtained from the year 2010 derivation cohort was further validated in the year 2011 and 2012 cohort.

2.6. Subgroup Analysis

Subgroup analysis was conducted a priori for patients with severe sepsis and laboratory confirmed bacteremia to evaluate the performance of the novel clinical prediction rule. Severe sepsis was defined as “sepsis-induced tissue hypoperfusion or organ dysfunction” [15,16].

2.7. Sample Size Consideration

In the multivariate logistic regression model, 10 subjects with outcomes would give statistical power over 80% with 5% type I error rate for one predictor [17]. In our previous experience in this institution, patients with clinically suspected sepsis in ED had 7% chance to develop in-hospital mortality [18]. Therefore, in order to achieve the statistical power, a cohort with 1429 subjects with suspected sepsis would power a multivariate logistic regression model with 10 predictor variables.

3. Results

Overall, there were 11,899 and 16,574 patients eligible in the derivation cohort in year 2010 and in the validation cohort in years 2011 and 2012, who visited the ED with a clinical diagnosis of sepsis, as indicated by diagnostic codes of infection and two sets of blood culture tests ordered by emergency physicians. After excluding transfers or repeat visits, 7011(59%) and 12,110 (73%) patients were included in the derivation and validation cohort, respectively (Fig. 1). The in-hospital

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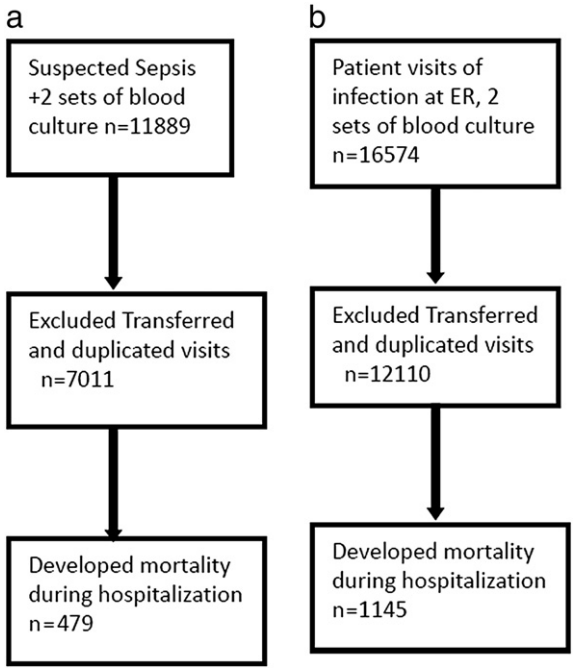

Fig. 1. Flow charts of enrollment in derivation and validation cohort.

mortality rates were similar to the derivation and validation cohort (7% and 9%, respectively, Supplementary Table 2).

Among 7011 patients in the derivation cohort, 20% had positive blood culture results, 54% were male and 49% were elderly (age ≥ 65 years, Table 1). The commonest comorbidity was diabetes mellitus (35%), followed by malignancy (24%). Mortality associated predisposition variables include age, diabetes mellitus, liver disease, malignancy, or immunosuppressive status, regular hemodialysis or chemotherapy (all $p < .05$, Table 1). Among variables of infection, unspecified infection focus and respiratory tract infection were associated with mortality. In variables of response, patients with higher white blood cell count, percent bands, level of CRP and procalcitonin (PCT), and presence of hypothermia and chills were associated with a higher mortality rate. In variables of organ dysfunction, wider RDW (>14.5%), prolonged prothrombin time/activated partial thromboplastin time, higher blood urea nitrogen, creatinine, aspartate aminotransferase, ammonia, bilirubin and lactate levels, and lower hemoglobin level, platelet and RBC counts were associated with a higher mortality rate.

A total of 34 out of 62 potential predictors were found in the univariate logistic regression. Five predictors found to be independently associated with mortality were included in the final multivariable logistic regression model: absence of Chills (OR: 2.28, 95% CI: 1.75–2.97), Hypothermia (<36 °C, OR 2.12, 95% CI: 1.57–2.85), Anemia (RBC counts < 4 million/μL, OR 2.45, 95% CI: 1.97–3.04), wide RDW (>14.5%, OR 3.27, 95% CI: 2.63–4.05) and history of Malignancy (OR 2.00, 95% CI: 1.63–2.46, Table 2). Since each of the five predictors had similar integers after rounding, we assigned equal weight to them for easy implementation.

For patients without any CHARM predictors, mortality was only 0.4% (sensitivity: 99.4%, NPV: 99.7%, Fig. 2 and Supplementary Table 3). On the other hand, for patients with all CHARM predictors, the specificity and NPV were 99.6% and 93.3%, respectively. The AUROC curve of CHARM was 0.77 (95% CI: 0.75–0.79), which is slightly better than PIRO (AUROC 0.74, 95% CI: 0.72–0.77, $p = .05$, Supplementary Table 4), and much better than SIRS, MEDS, CURB-65, CRP, PCT and lactate (AUROC: 0.58, 0.67, 0.68, 0.60, 0.66, 0.69, respectively, all $p < .05$, Fig. 3a and b). The Goodness-of-Fit statistic and calibration curve indicated good calibration of CHARM (= .42, Fig. 4).

As for the performance of CHARM in the subgroups of severe sepsis and laboratory confirmed bacteremia, we found the model performed slightly better among patients without severe sepsis (AUC 0.78, 95% CI: 0.74–0.82) than those with severe sepsis group in the derivation cohort (AUC 0.72, 95% CI: 0.69–0.75, $p = .01$). However, for patients with and without laboratory confirmed bacteremia, the performance was similar (AUC 0.77, 95% CI 0.74–0.80 vs. AUC 0.76, 95% CI 0.74–0.79, respectively). Furthermore, using the updated definition of severe sepsis [16], CHARM performed much better among patients without severe sepsis in the derivation cohort (0.80, 95% CI: 0.77–0.84 vs. 0.71, 95% CI: 0.68–0.74, $p < .001$).

We next tested the performance of CHARM in the validation cohort. In terms of the predictor distribution of the derivation and validation cohort, there were fewer patients with hypothermia, bacteremia and severe sepsis in the validation cohort than the derivation cohort (all $p < .05$, Supplementary Table 4). The CHARM rule also successfully stratified patients into groups with different mortality rates (Fig. 2). For patients without any predictor of CHARM, the mortality was only 0.9% in the validation cohort; the AUROC curve of CHARM in the validation cohort was 0.76 (95% CI: 0.75–0.77).

4. Discussion

We have derived a clinical prediction rule, the CHARM score, which had good performance predicting in-hospital mortality for patients with clinically suspected sepsis. Patients with a zero CHARM score had less than 1% mortality rates in our study. The CHARM score demonstrated a comparative discriminative ability to PIRO, and a better discriminative ability than SIRS, MEDS, CURB-65, or blood CRP or PCT levels. This novel rule performed better among patients without severe sepsis.

In contrast to our results, the presence of chills has often been deemed a sign of active infection, or a 'toxic' sign. Chills has also been associated with higher circulating tumor necrosis factor-α and interleukin-10 levels [19,20] and the presence of bacteremia [21-23]. One explanation is that ED patients often remained in an early stage of sepsis, at which point not many patients developed chills as a presenting symptom. It may also be that patients who could express themselves better were more likely to complain about chills and consequently received more attention, leading to an earlier access to treatment and thus an improved outcome. Patients who were able to better describe their illness might have taken better self-care and could have sought medical attention earlier than others. Nevertheless, we think that further studies are merited to clarify the causal relationship between chills and sepsis mortality.

Hypothermia, one of the SIRS criteria, was associated with increased in-hospital mortality in our study as well as other studies [24,25]. Although the mechanism of hypothermia on physiological severity and outcome of sepsis is not well understood, many animal studies and clinical trials did find a negative effect of antipyretics induced hypothermic subjects [26,27]. Hypothermia might indicate the dysfunction of hypothalamus that causes a dysregulated alteration in the thermal setpoint, therefore some authors suggested hypothermia to be the manifestation of central nervous system dysfunction induced by sepsis [28]. Severely ill patients with hypothermia, instead of hyperthermia, might be unrecognized by clinicians, which may lead to delays in treatment and be a cause of worsened outcomes.

Lower RBC counts and wider RDW were associated with increased in-hospital mortality in our study. RDW is almost routinely obtainable for patients as part of the complete blood count report. Although the mechanism is not well understood, many researchers have reported that the inflammatory cytokines induced by the pathogen-associated molecular patterns [29] could subsequently induce direct red blood cell damage, interfere with iron homeostasis, cause myelosuppression, and down-regulate erythropoietin-receptor expression [28,30]. The association between RDW and severity of patients with infectious diseases

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Table 1
Patient characteristics in the derivation cohort.

	Overall (N = 7011)		Mortality (n = 479)		Survivor (n = 6532)		OR	95% C.I.
	Median or N	(IQR or %)	Median or N	(IQR or %)	Median or N	(IQR or %)		
Predisposition								
Age	65	(49–78)	72	(56–81)	64	(49–77)	1.02***	(1.01,1.03)
>65 years	3422	48.8	293	61.2	3129	47.9	1.71***	(1.42,2.07)
Male	3795	54.1	276	57.6	3519	53.9	1.16*	(0.97,1.40)
Nursing home residents	207	3	21	4.4	186	2.8	1.56*	(0.99,2.48)
Comorbidity								
Diabetes	2475	35.3	226	47.2	2249	34.4	0.74***	(0.61,0.89)
Asthma	308	4.4	12	2.5	296	4.5	0.54*	(0.30,0.97)
COPD	784	11.2	39	8.1	745	11.4	0.86*	(0.55,1.35)
CHF	762	10.9	59	12.3	703	10.8	1.32*	(0.87,2.02)
CKD	495	7.1	42	8.8	453	6.9	1.29*	(0.93,1.79)
Hemodialysis	480	6.8	44	9.2	436	6.7	1.41*	(1.02,1.96)
CVA	910	13	71	14.8	839	12.8	1.18*	(0.91,1.53)
Chemotherapy	596	8.5	89	18.6	507	7.8	2.71***	(2.12,3.47)
Liver disease	792	11.3	66	13.8	726	11.1	1.73*	(1.33,2.25)
Malignancy	1665	23.7	228	47.6	1437	22	3.22***	(2.67,3.89)
Terminal illness	27	0.4	5	1	22	0.3	3.42*	(0.96,12.17)
Immunosuppressed	346	4.9	40	8.4	306	4.7	1.70***	(1.21,2.40)
Infection								
Respiratory	4056	57.9	318	66.4	3738	57.2	1.48***	(1.21,1.80)
Genitourinary	2678	38.2	140	29.2	2538	38.9	0.65***	(0.53,0.80)
Skin	1864	26.6	108	22.5	1756	26.9	0.79*	(0.63,0.99)
Abdominal	1619	23.1	93	19.4	1526	23.4	0.79*	(0.63,1.00)
CNS	155	2.2	11	2.3	144	2.2	1.04*	(0.56,1.94)
Unspecified	4994	71.2	407	85	4587	70.2	2.40***	(1.86,3.10)
Response								
Body temperature (°C)	37.7	(36.8–38.5)	37	(36.3–38.0)	37	(36.8–38.5)	0.68***	(0.63,0.73)
Fever	6548	93.4	428	89.4	6120	93.7	0.56**	(0.42,0.77)
Chill	2030	29	71	14.8	1959	30	0.41**	(0.31,0.53)
Heart rate (beat per minute)	104	(90–119)	108	(93–123)	108	(93–123)	1.00**	(1.00,1.01)
Respiratory rate	20	(18–22)	22	(19–25)	103	(90–118)	1.07***	(1.05,1.09)
WBC (10^3/μL)[b]	11.2	(7.8–15.1)	12.1	(7.7–16.6)	20	(18–22)	1.01**	(1.00,1.02)
Bandemia (%)	2	(1–5.5)	3	(1.5–9)	2	(1–5)	1.05***	(1.03,1.07)
CRP (mg/dL)[a]	67.86	(22.82–156.9)	113.14	(45.85–199.5)	66.04	(21.36–154.6)	1.00***	(1.00,1.00)
PCT (ng/mL)[a]	0.615	(0.09–3.965)	2.54	(0.445–23.4)	0.58	(0.09–2.56)	1.01**	(1.00,1.02)
Organ dysfunction								
Mean arterial pressure (mm/Hg)[b]	101.667	(87.66–115)	90.333	(73.33–107.3)	102	(89–115.3)	0.97***	(0.97,0.98)
RBC (million/μL)[b]	4.14	(3.56–4.62)	3.44	(2.96–4.06)	4.18	(3.63–4.65)	0.40***	(0.36,0.45)
Hematocrit (%)[b]	36.2	(31.4–40.6)	30.5	(26.7–35.9)	30.5	(26.7–35.9)	0.90***	(0.89,0.91)
Hemoglobin (mg/dL)[b]	12	(10.3–13.7)	10.1	(8.6–11.8)	36.6	(31.8–40.8)	0.74***	(0.71,0.77)
Platelet (10^3/μL)[b]	204	(149–270)	172	(97–268)	205	(152–271)	1.00***	(1.00,1.00)
RDW (%)[b]	13.9	(13–15.3)	15.7	(14.-17.6)	13.8	(13.-15.1)	1.28***	(1.24,1.32)
BUN (mg/dL)[a]	17.95	(11.3–32.5)	33.7	(18.6–65.2)	17.2	(11.1–30.05)	1.02***	(1.01,1.02)
Creatinine (mg/dL)[b]	0.95	(0.73–1.43)	1.18	(0.81–2.67)	0.94	(0.72–1.38)	1.12***	(1.08,1.16)
AST (U/L)[a]	35	(24–68)	62	(36.5–134)	34	(23–63)	1.00***	(1.00,1.00)
Total bilirubin (mg/dL)[a]	1	(0.6–2)	1.7	(0.8–4.1)	1	(0.6–1.8)	1.08***	(1.05,1.11)
APTT (sec)[a]	33	(28–39.6)	39.6	(31.7–55.8)	32.4	(27.8–38.1)	1.03***	(1.02,1.04)
PT (sec)[a]	13	(11.8–15.2)	15.7	(13.4–22.4)	12.8	(11.7–14.6)	1.05***	(1.03,1.06)
Lactate (mg/dL)	24.9	(15.2–46)	43.7	(22.3–86)	21.95	(14.1–37.7)	1.02***	(1.01,1.02)
Severity								
Triage level	2	(2–3)	2	(2–2)	2	(2–3)	0.28***	(0.24,0.33)
MEDS	6	(3–9)	8	(6–11)	6	(3–9)	1.19***	(1.16,1.22)
SIRS score	2	(1–3)	2	(2–3)	2	(1–3)	1.34***	(1.23,1.47)
SIRS criteria	4862	69.3	369	77	4493	68.8	1.52**	(1.22,1.90)
ICU admission	458	6.5	124	25.9	334	5.1	6.48***	(5.14,8.18)
Severe sepsis	2110	30.1	290	60.5	1820	27.9	3.97***	(3.28,4.81)
Severe sepsis (3.0)	3098	44.2	348	72.7	2750	42.1	3.65***	(2.97,4.49)
Bacteremia	1384	19.7	141	29.4	1243	19	1.77***	(1.44,2.18)

OR: odds ratio, C.I.: confidence interval, IQR: interquartile range, N: number, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, CKD: chronic kidney disease, CVA: cerebrovascular accident, CNS: central nervous system, WBC: white blood cell, CRP: C-reactive protein, PCT: procalcitonin, RBC: red blood cell count, RDW: red blood cell distribution width, BUN: blood urea nitrogen, AST: aspartate aminotransferase, APTT: activated partial thromboplastin time, PT: prothrombin time, MEDS: Mortality of Emergency Department Sepsis score, SIRS: Systemic Inflammatory Response Syndrome, and ICU: intensive care unit.

[a] Missing > 1000: CRP (2463/7011), PCT (6767/7011), BUN (3405/7011), AST (4802/7011), total bilirubin (4779/7011), APTT (5893/7011), PT (5457/7011).

[b] Missing < 110: WBC (3/7011) or bandemia (5156/7011), mean arterial pressure (20/7011), RBC (38/7011), hematocrit (36/7011), hemoglobin (36/7011), platelet counts (38/7011), RDW (38/7011), creatinine (109/7011).

* p-Value < 0.05.

** p-Value < 0.01.

*** p-Value < 0.001.

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Table 2
Five predictors (CHARM) for mortality in multivariable logistic regression model.

Predictors	OR	95% C.I.	*p*-Value
No complaints of **chills**	2.28	(1.75–2.97)	<0.001
Hypothermia (<36°c)	2.12	(1.57–2.85)	<0.001
Anemia (RBC counts < 4 million/μL)	2.45	(1.97–3.04)	<0.001
RDW > 14.5%	3.27	(2.63–4.05)	<0.001
History of **malignancy**	2.00	(1.63–2.46)	<0.001

has been reported [31-34]. Also, anemia has been associated with longer Intensive Care Unit (ICU) stay and increased in-hospital mortality [35].

Our CHARM score is different from MEDS and PIRO in that first, we derived the score from a large number of heterogeneous patients with suspected sepsis, and second, we used only five independent predictors. Beside the concern of pragmatism, these rules may suffer from overfitting issue, i.e. from their smaller ratio of observations per predictor. This could lead to subsequent poorer performance in the validation cohorts [36]. In addition, the variation in performance of these scores in the validation cohorts may also originate from the study design, especially when other researchers validate them in different patient cohorts. While MEDS was originally validated in patients receiving blood culture within 3 h of ED admission, other researchers validated the score in patients with suspected or confirmed infection [37,38], patients with SIRS criteria [39] or patients with severe sepsis or septic shock [40]. As a result, the AUC from different studies vary from 0.61 to 0.88. These data should therefore be interpreted with caution, and researchers seeking to validate these scores should recruit a study population that is of similar characteristics to the original studies.

Aside from using the AUC curve, the performance of a clinical prediction rule should be further evaluated using in-depth methods. The CHARM score is simple and pragmatic, but also has a good sensitivity and negative predictive value that allows us to "rule out" patients with an elevated mortality risk. Physicians working at the front-line clinical settings could utilize the CHARM score to stratify the mortality risk of sepsis, and thus to better allocate the limited medical resources.

Our study has several limitations. First, in order to develop a pragmatic clinical prediction rule, we adapted the strategy of using blood culture ordered by physicians as one of the inclusion criteria. The criteria for ordering blood culture might be different among different physicians and institutions. We therefore caution readers to evaluate their own patient populations before validating or utilizing the CHARM rule. Second, as the nature of a retrospective observational study, information obtained from the HIS, especially the data extracted from the medical records, could be biased or inaccurate. Therefore, subsequent prospective studies to validate our findings are necessary. Lastly, as discussed by others [20,41-43], using overall in-hospital mortality as the primary outcome for performance evaluation might not be perfect, as in-hospital mortality may result from events other than the initial sepsis episode in the ED.

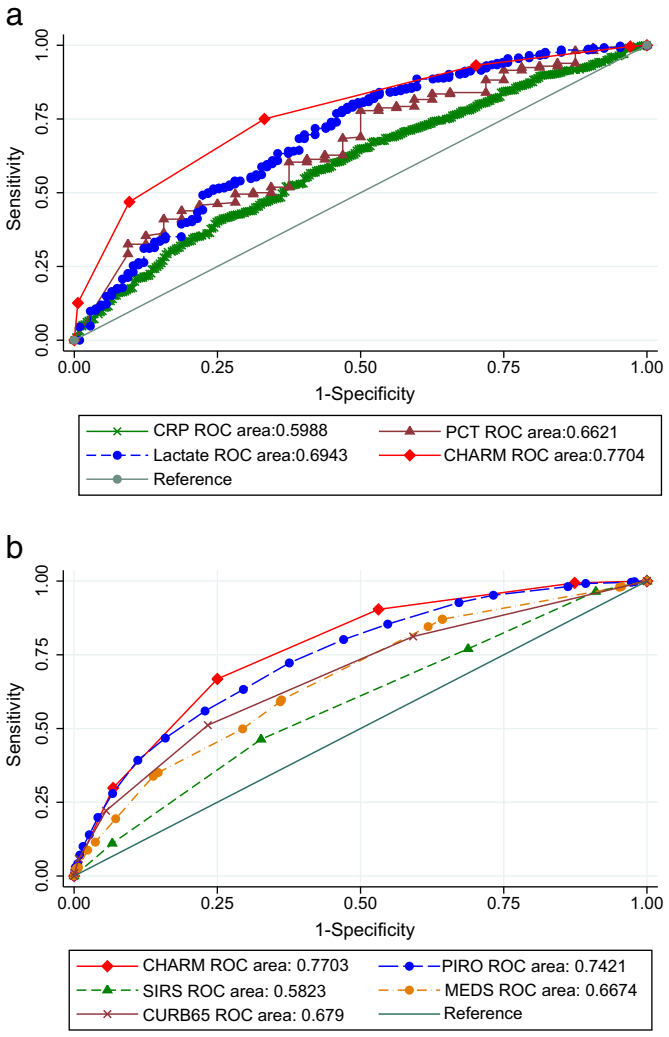

Fig. 3. a. Receiver operating characteristic curves comparing the CHARM score and other clinical prediction rules in predicting in-hospital mortality for patients with suspected sepsis. CHARM: absence of Chills, Hypothermia, Anemia, wide RDW and history of Malignancy; ROC: Receiver operating characteristic curves; PIRO: Predisposition, insult/infection, response and organ dysfunction; SIRS: Systemic Inflammatory Response Syndrome; MEDS: Mortality of Emergency Department Sepsis score, SIRS: Systemic Inflammatory Response Syndrome; and CURB-65: Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure and age 65 score. b. Receiver operating characteristic curves comparing the CHARM score and other biomarkers in predicting in-hospital mortality for patients with suspected sepsis. CHARM: absence of Chills, Hypothermia, Anemia, wide RDW and history of Malignancy; CRP: C-reactive protein, PCT: procalcitonin.

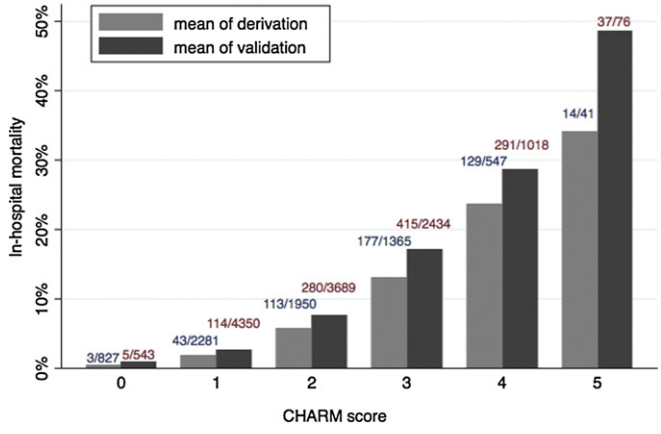

Fig. 2. The CHARM score - stratified mortality rates in derivation and validation cohort. CHARM: absence of Chills, Hypothermia, Anemia, wide RDW and history of Malignancy;

5. Conclusions

In conclusion, we derived and validated a pragmatic, parsimonious and novel clinical prediction rule with good performance; (CHARM: absence of chills, hypothermia, anemia, wide RDW and history of malignancy), to predict in-hospital morality of patients with suspected sepsis with good performance in a heterogeneous population. Utilizing this simple CHARM score could stratify the mortality risk of patients in the early stage of sepsis.

Supplementary data to this article can be found online at doi:10.1016/j.ajem.2016.10.075.

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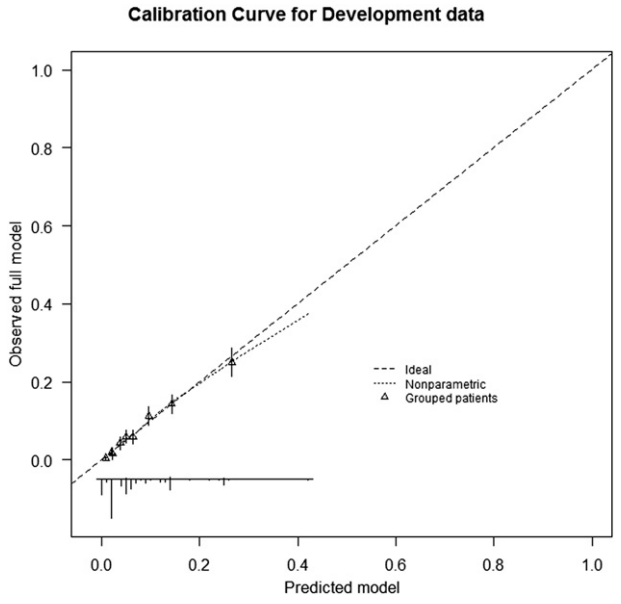

Fig. 4. Goodness-of-Fit statistic and calibration curve illustrate the calibration capacity of the CHARM score in predicting mortality.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Notation of Prior Abstract Publication/Presentation

This study has been presented in the international conference on emergency medicine in Dublin on June 29, 2012.

Abbreviation List

ED emergency department
CHARM score absence of Chills, Hypothermia, Anemia, wide RDW and history of Malignancy
MEDS score Mortality in Emergency Department Sepsis score
PIRO: predisposition, infection/insult, response and organ dysfunction
CURB-65 score Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure and age 65 score
HIS hospital information system
CRP C-reactive protein
SIRS Systemic Inflammatory Response Syndrome criteria
RDW red blood cell distribution width
AIC Akaike information criterion
ROC receiver-operating characteristic
AUC area under ROC curve
AST aspartate aminotransferase
PCT procalcitonin
BUN blood urea nitrogen
OR odds ratio

Availability of Data and Materials

The datasets analyzed during the current study available from the corresponding author on reasonable request.

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