OBSERVATIONAL STUDY

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Mortality and Sequential Organ Failure Assessment Score in Patients With Suspected Sepsis: The Impact of Acute and Preexisting Organ Failures and Infection Likelihood

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IMPORTANCE: The Sequential Organ Failure Assessment (SOFA) was chosen in the definition of sepsis due to superior validity in predicting mortality. However, few studies have assessed the contributions of acute versus chronic organ failures to SOFA for mortality prediction.

OBJECTIVES: The main objective in this study was to assess the relative importance of chronic and acute organ failures in mortality prediction in patients with suspected sepsis at hospital admission. We also evaluated how the presence of infection influenced the ability of SOFA to predict 30-day mortality.

DESIGN, SETTING, AND PARTICIPANTS: Single-center prospective cohort study including 1,313 adult patients with suspected sepsis in rapid response teams in the emergency department.

MAIN OUTCOMES AND MEASURES: The main outcome was 30-day mortality. We measured the maximum total SOFA score during admission (SOFATotal), whereas preexisting chronic organ failure SOFA (SOFAChronic) score was assessed by chart review, allowing calculation of the corresponding acute SOFA (SOFAAcute) score. Likelihood of infection was determined post hoc as "No infection" or "Infection."

RESULTS: SOFAAcute and SOFAChronic were both associated with 30-day mortality, adjusted for age and sex (adjusted odds ratios [AORs], 1.3; 95% CI, 1.3–14 and 1.3; 1.2–1.7), respectively. Presence of infection was associated with lower 30-day mortality (AOR, 0.4; 95% CI, 0.2–0.6), even when corrected for SOFA. In "No infection" patients, SOFAAcute was not associated with mortality (AOR, 1.1; 95% CI, 1.0–1.2), and in this subgroup, neither SOFAAcute greater than or equal to 2 (relative risk [RR], 1.1; 95% CI, 0.6–1.8) nor SOFATotal greater than or equal to 2 (RR, 3.6; 95% CI, 0.9–14.1) was associated with higher mortality.

CONCLUSIONS AND RELEVANCE: Chronic and acute organ failures were equally associated with 30-day mortality in suspected sepsis. A substantial part of the total SOFA score was due to chronic organ failure, calling for caution when using total SOFA in defining sepsis and as an outcome in intervention studies. SOFA's mortality prediction ability was highly dependent on actual presence of infection.

KEY WORDS: critical care; mortality; sepsis, emergency medicine; Sequential Organ Failure Assessment

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The general principles of sepsis management have remained unchanged for decades, despite great scientific effort (1). Presumably, the sepsis syndrome is too heterogenous for a "one-size-fits-all" approach to provide optimal care to most septic patients (1). Demarcation of sepsis from other

KEY POINTS

Question: What are the relative contributions of preexisting (chronic) and acute organ failures to mortality prediction by Sequential Organ Failure Assessment (SOFA) in patients with suspected sepsis in the emergency department (ED), and how does infection affect mortality prediction?

Findings: A substantial part of the SOFA score was present before the acute illness (chronic organ failures). SOFA due to chronic and acute organ failures contributed overall equally to mortality. A considerable number of patients with suspected sepsis in the ED did not have infection. SOFA was only predictive for mortality in patients with infection.

Meaning: Total SOFA best predicted sepsis mortality, with equal contribution from chronic and acute organ failure. However, since chronic organ failures make up a substantial part of the total SOFA score and sepsis intervention cannot be expected to improve chronic organ failures, we suggest the use of acute SOFA as outcome in interventional studies.

conditions was deemed necessary, and in 2016 sepsis was defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" (2). This was clinically operationalized and defined as an increase in the Sequential Organ Failure Assessment (SOFA) score greater than or equal to 2 attributable to a dysregulated host response to infection (2). The increase was estimated from the baseline preinfection SOFA, assumed to be zero if no chronic organ dysfunctions were known (2). SOFA was chosen due to its superior predictive validity for in-hospital mortality, assessed by Seymour et al (2, 3). Importantly, however, Seymour et al (3) could not distinguish chronic from acute organ failures, although a post hoc subanalysis was performed on SOFA increase from 48 hours prior to 24 hours after onset of infection. The latter post hoc analysis, however, poorly encapsulates chronic organ failures, as acute organ failures may precede infection diagnosis. The relationship between mortality and organ failure in sepsis has been extensively described (3, 4). However, little is known about the relative impact of chronic and acute organ failures. The sole study addressing this question found that acute organ failures causing SOFA greater than or equal to 2 were in fact not associated with increased mortality, in contrast to the corresponding total SOFA score (5). However, this study was performed in a cohort of hospitalized patients with low mortality and thus probably less relevant for patients admitted to the emergency department (ED) with suspected sepsis (5).

Information on how to emphasize chronic versus acute organ failures in the risk assessment of patients with suspected infection would be useful; both for bedside evaluation of patients with suspected sepsis and also in trial interventions that aim to modify dysregulated host responses (6), which can only be expected to amend acute organ failures. Thus, when evaluating new therapies using the SOFA score as a proxy for increased mortality, discriminating acute and chronic organ failures should be relevant.

Infection is required for the sepsis diagnosis but can be remarkably difficult to verify (7). Several studies define "suspected infection" as antibiotic treatment and culture acquisition (3). Suspected infection, however, corresponds poorly with the presence of infection after post hoc evaluation (7). In fact, the actual presence of infection has been shown to be negatively associated with mortality (7) and even the type of pathogen (e.g., bacterial, viral, fungal) influences prognosis among septic patients (8–11). Taken together, this calls for caution when predicting mortality and defining sepsis based on suspected infection alone.

Hypothesizing that acute organ failures predict 30-day mortality to a greater extent than chronic organ failures, we performed a study that included 1,313 patients in the ED with suspected sepsis. SOFA scores were disaggregated by chronic and acute organ failures, and infection was adjudicated post hoc as either likely ("Infection") or not likely ("No infection"). The main objective in this study was to assess the relative importance of chronic and acute organ failures for 30-day mortality prediction in patients with suspected sepsis at hospital admission. We also wanted to evaluate how actual presence of infection influenced the ability of the SOFA score to predict 30-day mortality.

MATERIALS AND METHODS

Study Design, Setting, and Participants

This prospective, observational study was conducted at Oslo University Hospital Ullevål (OUH), a tertiary care

referral hospital, from May 2017 to October 2020. Patients were recruited from Sepsis or Medical Rapid Response Teams (RRTs) in the ED. RRTs were applied if severe disease was suspected (criterion details in **Supplementary Table S1**, http://links.lww.com/CCX/B141) (12–14). Patients were included if infection was suspected: defined as blood cultures drawn and nonprophylactic antibiotic administered in the ED (**Fig. 1**) (3, 15, 16). The project was temporarily approved by the hospital Institutional Review Board (IRB) (OUH Information Security and Privacy Office/Data Protection Official) on March 27, 2017, with reference number 2017/5382 and received permanent approval on December 14, 2018, with reference number 17/19067 with the study title "Sepsis register." The IRB waived the need for informed consent and approval from an external ethics committee and informed consent due to the strictly observational nature of the study. This trial was registered at ClinicalTrials.gov as NCT03956043. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies (17) and conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Routine blood samples were collected within 15 minutes of admission, in which creatinine, leukocytes, bilirubin, and platelets were analyzed as previously described (18). Pao_2 was analyzed in arterial blood on a Roche Cobas b221 instrument (Roche Diagnostics, Indianapolis, IN). Vital parameters (temperature, heart rate, blood pressure, Glasgow Coma Scale, oxygen saturation [Spo_2], and Fio_2) during the first hour of observation in the ED were registered. In addition to SOFA, quick SOFA (qSOFA) (3), Systemic Inflammatory Response Syndrome criteria, and National Early Warning Score were calculated (19). Icteric index was used to estimate bilirubin levels if the latter was missing (20). If not available, Pao_2 was estimated from Spo_2 and Fio_2 was estimated from any oxygen delivery device using the conversion tables from the Extended Prevalence of Infection in Intensive Care II study (21). Urine output was not registered. If patients deteriorated in-hospital, vital signs and blood analyses were recorded at the time point of the highest SOFA score. Comorbidities were registered and Charlson Comorbidity Index was calculated (22). Data were entered into a local database (MedInsight Version 2.17.8.0 [Oslo, Norway]). Date of death was collected from the Norwegian National Population Register.

Diagnostic Assessments and Definitions

The maximum total SOFA score during hospitalization was calculated ($SOFA_{Total}$) (23–25). Acute organ failure ($SOFA_{Acute}$) was defined as:

$$SOFA_{Acute} = SOFA_{Total}\ SOFA_{Chronic}$$

Chronic SOFA ($SOFA_{Chronic}$) was estimated by retrospective chart review: prior hospitalizations or visits at outpatient clinics with stable chronic disease (no acute organ

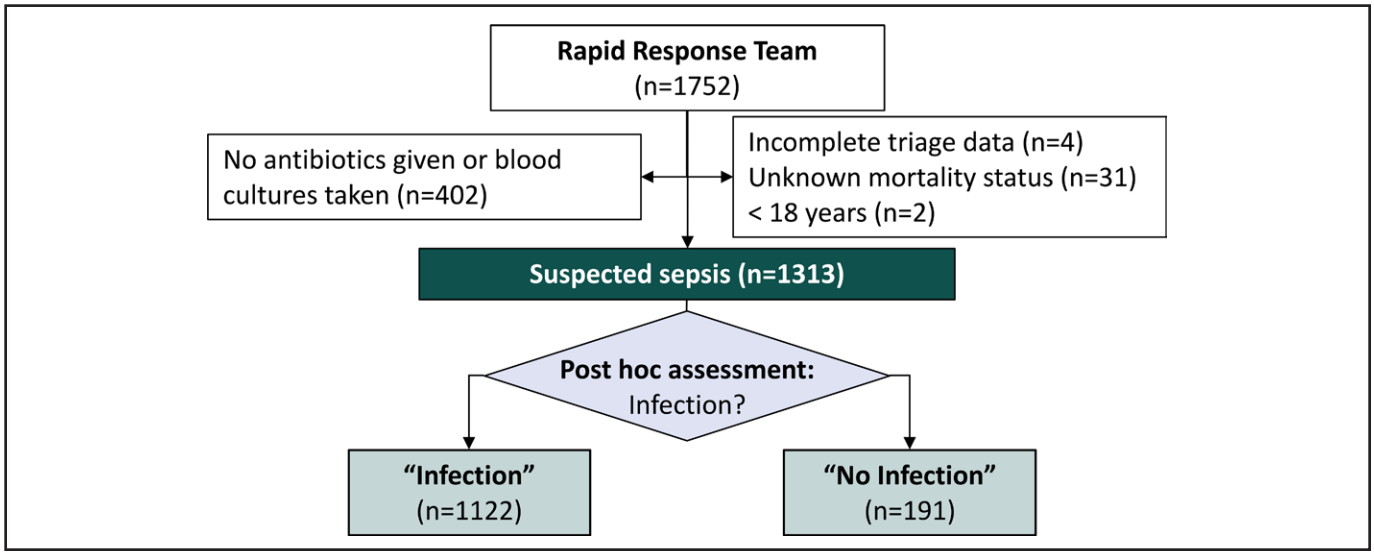

Figure 1. Flow chart depicting inclusion of patients in the emergency department.

dysfunction or deterioration of chronic organ dysfunction), following strict instructions (**Supplementary Table S2**, http://links.lww.com/CCX/B141). If normal function of an organ system was registered at any point during or after the hospitalization, $SOFA_{Chronic}$ was assumed to be zero for that organ system. If, however, no information was available, the value was set to missing. Missing values were valued as zero (2). A sensitivity analysis excluding patients with missing $SOFA_{Chronic}$ values was performed to evaluate the potential bias of this decision.

The diagnosis of sepsis also requires the presence of infection. Likelihood of infection was determined post hoc by internal medicine and infectious disease specialists after medical record review (7, 26). The patients' discharge summaries, admission and progress notes, radiology, microbiology and other laboratory test and pathology and autopsy records were evaluated. The Infection likelihood was classified as not likely ("No infection") or likely ("Infection") (14): "No infection" when the post hoc evaluation and discharging clinician considered noninfectious causes to be more likely; "Infection" when the discharging clinician and the post hoc evaluation considered infection to be the most likely cause of hospitalization and/or infection was microbiologically confirmed (14). Patients were assessed for potential viral, bacterial, fungal, or parasitic infections. Detected pathogens were registered and assessed as causative if detected in normally sterile body tissues (blood, cerebrospinal fluid, bile, pleural fluid, biopsies, etc., but not urine or airways sample), abscesses, or established strict/obligate pathogens from other tissues or fluids. The finding of common contaminants with opportunistic potential (like coagulase-negative *Staphylococci*) were registered only if thought to be causative of the infection. Etiology was classified as bacterial, viral or other. The latter included fungal, parasitic, and mixed (bacterial/viral) infections.

As a quality control measure for the infection likelihood assessment, a second, independent assessment was performed on consecutive patients that also were included in a 2020 trial (14): By case-by-case chart review, two study doctors (blinded for the original assessment and each other) classified patients according to infection likelihood, using established infection criteria (27). To settle diverging cases, a third study doctor made the final decision. Inter-rater variability between the original assessment and the quality control was evaluated.

Statistical Analysis

Statistical analysis was performed with SPSS statistical software (Macintosh version 26.0; IBM, Armonk, NY). An a priori decision was made to exclude patients with missing information incapacitating SOFA score calculation or with unknown mortality status. Only the patients' first encounter during the study period was included in the study. Pearson chi-square, Wilcoxon signed-rank, and Student *t* tests were used to compare variables between patients classified as "No infection" and "Infection." Infection likelihood inter-rater variability was assessed using Cohen's κ. The Jonckheere-Terpstra Trend test (JTT) was used to assess the association between Charlson Comorbidity Index, $SOFA_{Acute}$, and $SOFA_{Chronic}$. We assessed the importance of several covariates for predicting mortality simultaneously by logistic regression adding one variable to the model in a step-wise manner. The baseline model (model A) included age and sex; $SOFA_{Acute}$ was added in model B, $SOFA_{Chronic}$ in model C, and infection likelihood in model D. Etiologic group (bacterial, viral, other) was added to model E, which was only applied to "Infection" patients. Sensitivity analyses excluding patients with any missing $SOFA_{Chronic}$ component was performed. Last, the baseline model was extended with Charlson Comorbidity Index for comparison. If any two covariates exhibited significant interaction effects on mortality, the associated interaction term was included in the final prediction model. To assess the regression model's overall mortality prediction performance, the area under the receiver operating characteristic curve (AUC) was estimated for all regression models. AUCs were compared using the DeLong method. A higher AUC indicates better ability to discriminate surviving from nonsurviving patients. Relative risk for 30-day mortality was calculated for $SOFA_{Total}$ greater than or equal to 2 versus less than 2 and $SOFA_{Acute}$ greater than or equal to 2 versus less than 2. Sensitivity, specificity, and positive and negative predictive values were calculated for the same cutoffs. Figures were made using Graphpad Prism Version 9 (GraphPad Software, San Diego, CA).

RESULTS

Patient Characteristics, Infection Likelihood Assessment, and Inter-Rater Variability

A total of 1,752 unique patients were assessed by RRTs throughout the inclusion period. Infection likelihood assessment inter-rater reliability was satisfactory

(inter-rater concordance 232/247 [94%], Cohen's κ 0.870). One-thousand three-hundred thirteen met the inclusion criteria and thus were initially labeled "Suspected sepsis" in the ED (Fig. 1). Pao_2 was missing in 194 patients and had to be estimated from Spo_2. One-hundred ninety-one patients (15%) were classified after discharge or death as "No infection," while 1,122 patients (85%) were classified as "Infection" (Fig. 1). Patient characteristics are summarized in **Table 1**. The "No infection" and "Infection" groups were comparable with regards to age, gender, comorbidities, and degree of acute and chronic organ failure. However, the "No infection" group were more often admitted to the ICU and had higher mortality. Noninfectious diagnoses are listed in **Supplementary Table S3** (http://links.lww.com/CCX/B141), with heart failure, noninfectious exacerbation of chronic obstructive pulmonary disease and malignant disease as the most common. The presence of infection remained negatively associated with 30-day mortality also after adjusting for age and sex (adjusted odds ratio [OR], 0.4; 95% CI, 0.2–0.6; $p < 0.001$). Furthermore, confirmed viral infections were more lethal than confirmed bacterial infections (overall mortality 20% vs 10%; χ^2 9.76; $p = 0.002$). The two major viral pathogens were influenza (20% 30-d mortality, $n = 55$) and severe acute respiratory syndrome coronavirus 2 (36% 30-d mortality, $n = 11$) (full list of pathogen distribution available in **Supplementary Table S4**, http://links.lww.com/CCX/B141).

SOFA Score: Acute and Chronic Organ Failures and 30-Day Mortality

A negative association was found between SOFA scores due to chronic and acute organ failures (JTT

TABLE 1.
Patient Characteristics

Characteristic	Suspected Sepsis (Total)	No Infection	Infection	*p*
Number	1,313	191	1,122	Not tested
Age, yr, mean (SD)	68 (19)	67 (20)	68.0 (19.0)	0.543[b]
Gender, male (%)	735 (56)	101 (53)	634 (57)	0.351[c]
Admitted from nursing homes, *n* (%)	232 (18)	32 (17)	200 (18)	0.720[c]
Charlson comorbidity index, median (IQR)	2 (1–4)	2 (1–4)	2 (1–4)	0.082[a]
Scoring systems				
Quick SOFA, median (IQR)	2 (1–2)	2 (1–2)	1 (1–2)	0.697[a]
Systemic Inflammatory Response Syndrome, median (IQR)	3 (2–4)	3 ((2–3)	3 ((2–4)	0.004[a]
National Early Warning Score, median (IQR)	9 (6–11)	10 (7–12)	9 (6–11)	0.008[a]
Acute SOFA, median (IQR)	2 (1–4)	3 (1–5)	2 (1–4)	0.424[a]
Chronic SOFA, median (IQR)	0 (0–1)	1 (1–4)	0 (1–4)	0.473[a]
Total SOFA , median (IQR)	3 (2–5)	4 (2–6)	3 (2–5)	0.268[a]
Outcomes				
Hospital stay(days), median (IQR)	6 (3–10)	6 (2–10)	6 (4–10)	0.975[a]
Admitted to ICU, *n* (%)	420 (32)	88 (46)	332 (30)	< 0.001[c]
Mechanical ventilation, *n* (%)	86 (7)	15 (8)	71 (6)	0.430[c]
In-hospital mortality, *n* (%)	146 (11)	33 (17)	113 (10)	0.003[c]
30-d mortality, *n* (%)	200 (15)	46 (24)	154 (14)	< 0.001[c]
90-d mortality, *n* (%)	270 (21)	60 (31)	210 (19)	< 0.001[c]

IQR = interquartile range, SOFA = Sequential Organ Failure Assessment.

[a]Stratified by infection likelihood. *p* values comparing "No infection" and "Infection" groups computed using Wilcoxon signed-rank test.

[b]Stratified by infection likelihood. *p* values comparing "No infection" and "Infection" groups computed using Student *t* test.

[c]Stratified by infection likelihood. *p* values comparing "No infection" and "Infection" groups computed using Pearson χ^2 test.

test; $p < 0.001$; **Fig. 2*A***). $SOFA_{Chronic}$ and Charlson Comorbidity Index showed a positive association (JTT test; $p < 0.001$). Mortality increased with both higher $SOFA_{Chronic}$ and $SOFA_{Acute}$ scores (**Table 2** and **Fig. 2**, ***B*** and ***C***). The AUC of $SOFA_{Total}$ isolated (0.750; 0.715–0.786) was significantly higher (p = 0.01) than that of $SOFA_{Acute}$ isolated (0.728; 95% CI, 0.689–0.767).

To assess the relative contributions to mortality prediction by $SOFA_{Acute}$ and $SOFA_{Chronic}$, as well as the importance of post hoc-assessed infection likelihood, we performed multiple logistic regression (Table 2). Baseline risk was calculated using age and sex. Analyzing all included patients, $SOFA_{Acute}$ and $SOFA_{Chronic}$ were both associated with mortality with comparable adjusted ORs per unit increase of the

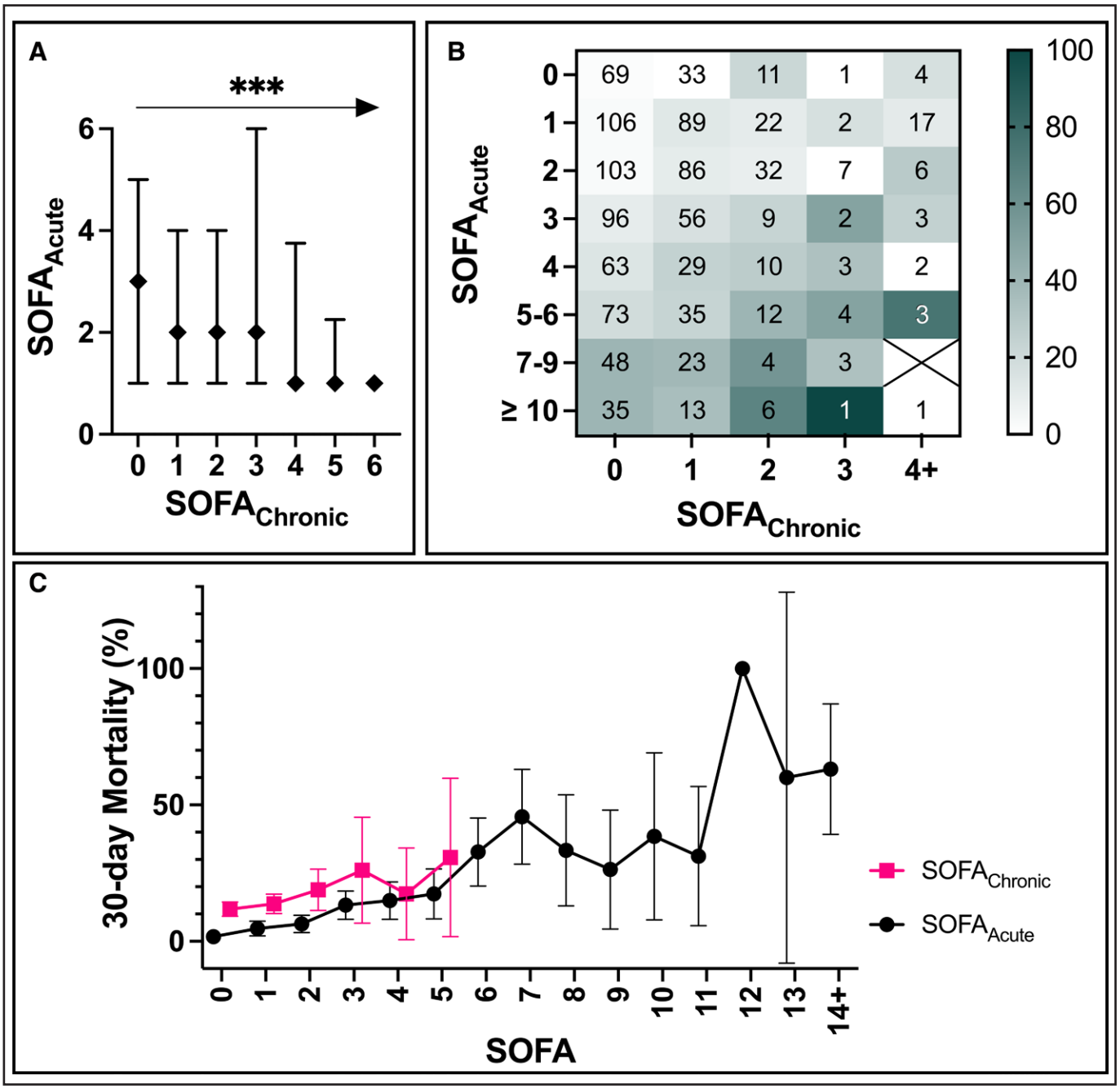

Figure 2. Relationship of chronic and acute organ failures and mortality. **A**, Association between chronic Sequential Organ Failure Assessment ($SOFA_{Chronic}$) and median acute Sequential Organ Failure Assessment ($SOFA_{Acute}$), *whiskers* indicate interquartile range. *Asterisks* indicates association, using Jonckheere-Terpstra Trend test: ***$p < 0.001$. **B**, Mean mortality across combinations of $SOFA_{Acute}$ and $SOFA_{Chronic}$, number of patients in each combination labeled in the cell. **C**, Associations between $SOFA_{Chronic}$, $SOFA_{Acute}$ and mortality: mean (*square/dot*) and 95% CI (*whiskers*) mortality at different levels of $SOFA_{Chronic}$ and $SOFA_{Acute}$.

TABLE 2.

Logistic Regression Predicting 30-Day Mortality in Patients With "Suspected Sepsis" (Model A–D, *n* = 1,313) and "Infection" (Model E, *n* = 1,122)

		Multivariate				
Variable	**Univariate**	**Model A**	**Model B**	**Model C**	**Model D**	**Model E**
Age, decennials	1.6 (1.4–1.7)[a]	1.6 (1.4–1.8)[a]	1.7 (1.5–1.9)[a]	1.7 (1.5–2.0)[a]	1.7 (1.5–2.0)[a]	1.8 (1.5–2.2)[a]
Male sex	1.4 (1.0–1.9)[c]	1.4 (1.0–1.9)	1.1 (0.8–1.6)	1.0 (0.7–1.4)	1.0 (0.7–1.5)	1.2 (0.8–1.8)
Acute SOFA	1.3 (1.2–1.3)[a]		1.3 (1.2–1.4)[a]	1.3 (1.3–1.4)[a]	1.4 (1.3–1.5)[a]	1.5 (1.4–1.6)[a]
Chronic SOFA	1.2 (1.1–1.4)[b]			1.4 (1.2–1.7)[a]	1.5 (1.2–1.7)[a]	1.6 (1.3–1.9)[a]
No infection	2.0 (1.4–2.9)[a]				1.8 (1.2–2.7)[b]	
Etiology						
Bacteria (*n* = 564)	(Reference)					(Reference)
Viral (*n* = 100)	2.4 (1.4–4.2)[b]					3.0 (1.5–5.9)[b]
Unknown (*n* = 437)	2.1 (1.5–3.1)[a]					3.1 (2.0–4.8)[a]
Other (*n* = 21)	0.4 (0.1–3.1)					0.3 (0.0–2.9)
Area under the receiver operating characteristic curve (95% CI)		0.69 (0.65–0.72)	0.79 (0.75–0.82)[e]	0.80 (0.77–0.83)[d]	0.81 (0.78–0.84)[not significant]	0.85 (0.82–0.88)[f]

SOFA = Sequential Organ Failure Assessment.

Significance marked:

[a]$p < 0.001$,

[b]$p < 0.01$,

[c]$p < 0.05$ for associations between the variables and mortality, and

[d]$p < 0.05$,

[e]$p < 0.001$ when comparing area under the receiver operating characteristic curves (AUCs) with the former model (comparing model B with A, C with B, D with C, and E with D),

[f] $p < 0.01$.

Other included mixed bacterial/viral (*n* = 16), fungal (*n* = 3), and parasitic (*n* = 2) infections.

Odds ratios and 95% CIs in all cells, except for AUCs.

TABLE 3.

Test Characteristics for Acute SOFA and Maximum Total SOFA Score During Admission (Which Includes Chronic Sequential Organ Failure Assessment) Cutoffs at Greater Than or Equal to 2 to Predict 30-Day Mortality

Group	Characteristic	Total SOFA ≥ 2	Acute SOFA ≥ 2
All patients (suspected sepsis, *n* = 1,313)	*n* (%)	1,082 (82)	894 (68)
	30-d mortality, *n* (%)	196 (18)	172 (19)
	Sensitivity, % (95% CI)	98 (95–99)	86 (80–90)
	Specificity, % (95% CI)	20 (18–23)	35 (32–38)
	PPV, % (95% CI)	18 (17–18)	19 (18–20)
	NPV, % (95% CI)	98 (96–99)	93 (91–95)
Infection (*n* = 1,122)	*n* (%)	918 (82)	768 (68)
	30-d mortality, *n* (%)	152 (17)	141 (18)
	Sensitivity, % (95% CI)	99 (95–100)	92 (86–95)
	Specificity, % (95% CI)	21 (18–24)	35 (32–38)
	PPV, % (95% CI)	18 (18–19)	20 (19–21)
	NPV, % (95% CI)	99 (96–100)	96 (93–98)
No infection (*n* = 191)	*n* (%)	164 (86)	126 (66)
	30-d mortality, *n* (%)	44 (27)	31 (25)
	Sensitivity, % (95% CI)	96 (85–99)	67 (52–80)
	Specificity, % (95% CI)	17 (11–24)	34 (27–43)
	PPV, % (95% CI)	17 (16–18)	15 (13–19)
	NPV, % (95% CI)	96 (85–99)	86 (79–91)

NPV = negative predictive value, PPV = positive predictive value, SOFA = Sequential Organ Failure Assessment.
Estimated for the total cohort ("Suspected sepsis") and for the infection likelihood groups "Infection" and "No infection."

scores: 1.4 (1.3–1.5) and 1.5 (1.2–1.7), respectively. Adding $SOFA_{Chronic}$ to the prediction model significantly improved the model's ability to predict 30-day mortality, as defined by a significant increase of AUC (Table 2).

When only "Infection" patients were included (model E; Table 2), the adjusted ORs for mortality were higher overall, whereas the relative importance of $SOFA_{Acute}$ and $SOFA_{Chronic}$ was similar, compared with the analysis of all included patients. Furthermore, viral infections remained more lethal than bacterial infections after adjusting for the degree of organ failure (Table 2).

A total of 663 patients (50%) had at least one missing component of $SOFA_{Chronic}$, most commonly the respiratory component (48%). Missing values were less common in the other components of $SOFA_{Chronic}$, ranging from 1% to 3% (**Supplementary Table S5**, http://links.lww.com/CCX/B141). We performed the same regression analysis (models A–E) in two sensitivity analyses: 1) including Charlson Comorbidity Index and 2) excluding patients with at least one missing component of $SOFA_{Chronic}$. ORs for mortality prediction remained largely the same in both sensitivity analyses (**Supplementary Tables S6** and **S7**, http://links.lww.com/CCX/B141).

Mortality Related to Acute and Chronic Organ Failures in Patients With "No Infection"

Patients with suspected sepsis classified post hoc as "No infection" had higher mortality, even when corrected for the degree of organ failure (Table 2). In this subgroup, the AUC for predicting 30-day mortality was 0.619 (0.528–0.710) for $SOFA_{Total}$ and 0.588 (0.489–0.687) for $SOFA_{Acute}$, thus performing poorer

than applied to the total cohort. Regression analysis confirmed the inferior prognostic performance of SOFA in this subgroup, as $SOFA_{Acute}$ was not significantly associated with 30-day mortality after adjusting for age and sex (**Supplementary Table S8**, http://links.lww.com/CCX/B141).

SOFA Greater Than or Equal to 2 in Mortality Prediction Only Suitable in Patients With Infection

In clinical practice, SOFA greater than or equal to 2 defines sepsis and is associated with increased mortality. Mortality and test characteristics of SOFA greater than or equal to 2 due to acute and chronic organ failures is presented in **Table 3**. In the whole cohort (n = 1,313), mortality was comparable between the criteria $SOFA_{Acute}$ greater than or equal to 2 and $SOFA_{Total}$ greater than or equal to 2 (Table 3). However, sensitivity for 30-day mortality was higher for $SOFA_{Total}$ (Table 3), with a higher relative mortality risk when compared with patients with $SOFA_{Total}$ less than 2 (**Fig. 3**).

A similar pattern was observed in the "Infection" subgroup (n = 1,122). Mortality remained comparable between the criteria $SOFA_{Acute}$ greater than or equal to 2 and $SOFA_{Total}$ greater than or equal to 2 and sensitivity for 30-day mortality was again higher for $SOFA_{Total}$ greater than or equal to 2 than $SOFA_{Acute}$ (Table 3). Relative mortality risk for $SOFA_{Total}$ greater than or equal to 2 versus less than 2 was also higher compared with $SOFA_{Acute}$ (Fig. 3). Interestingly, however, "Infection" patients' relative mortality risks, sensitivities and specificities based on SOFA were generally higher than for the suspected sepsis group as a whole and especially "No infection" patients (Table 3 and Fig. 3). Thus, a cutoff greater than or equal to 2 was superior for "Infection" patients compared with "No infection" patients in our cohort.

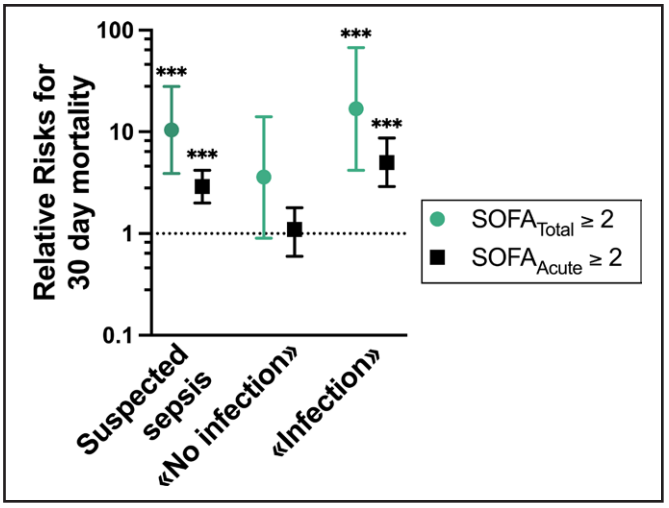

Figure 3. Relative risk for 30-d mortality across sepsis criteria. For the group "Suspected sepsis" and stratified based on the post hoc infection likelihood assessment. *Dot* illustrates mean, *error bars* 95% CI. *Asterisks* indicate significance, $^{***}p < 0.001$. $SOFA_{Total}$ = total Sequential Organ Failure Assessment score, $SOFA_{Acute}$ = acute Sequential Organ Failure Assessment.

DISCUSSION

We have here assessed SOFA scores disaggregated according to acute and chronic organ failure in patients with suspected sepsis in the ED and evaluated their relative importance in mortality prediction. We found that the degree of both chronic and acute organ failure predicts 30-day mortality and that subtracting chronic organ failures in SOFA calculations decreased the 30-day mortality prediction performance. Whereas the actual presence of infection was negatively associated with 30-day mortality, the SOFA score (independent of adjustment for chronic organ failures) was a stronger predictor of mortality in "Infection" compared with "No infection" patients.

An increase in SOFA greater than or equal to 2 attributable to a dysregulated host response to infection was chosen by Seymour et al (3) to define sepsis, with no distinction between chronic and acute organ failure in the preceding assessment (2). SOFA was selected due to its superior prognostic validity for mortality, and the cutoff of greater than or equal to 2 was derived from a large epidemiological study in which chronic organ failures were not deducted from the SOFA score. Although acute organ failures contribute to the lethality of sepsis, so do chronic organ failures; the sensitivity of the SOFA score to identify lethal infections decreased when chronic organ failures were subtracted. By using SOFA not adjusted for chronic organ failures, the prognostic value of the sepsis definition may have been exaggerated in the large epidemiological studies where the differentiation between acute and chronic organ failures could not be made. In assessing mortality in patients with SOFA greater than or equal to 2 either due to total SOFA or acute SOFA only, Gadrey et al (5) found that only the prior was significantly associated with increased mortality. In our cohort, $SOFA_{Acute}$ greater than or equal to 2 also was associated with

increased mortality. Mortality was low in the cohort analyzed by Gadrey et al (5), that is, pretest probability was lower than in our cohort. Consequently, following Fagan's nomogram, the apparent performance of the SOFA score is worse, despite similar likelihood ratios. Taking the findings of Gadrey et al (5) and our own data into account, we argue that caution should be exercised when examining the SOFA score in low-risk cohorts.

Originally identified as a prognostic scoring tool, the use of the SOFA score has expanded since its invention beyond mortality prediction per se. In addition to the recognition and diagnosis of sepsis, SOFA is used as an endpoint in interventional studies (25). Based on our observations, we argue that the high sensitivity for mortality makes $SOFA_{Total}$ appropriate in identifying patients with sepsis. Nonetheless, we show that chronic organ failures make up a substantial part of $SOFA_{Total}$ and $SOFA_{Chronic}$ cannot be expected to be improved by any sepsis interventions. We thus argue that observational and interventional studies employing SOFA as an outcome ought to adjust for chronic organ failures to reduce underestimation of efficacy. However, discrepancies in SOFA score measurement lead to inter-study variability (25), and there is no consensus on how to adjust for chronic organ failures. Until such a consensus is reached, we suggest performing an individual chart review to estimate the preinfection SOFA score, as most electronic patient records contain some information on chronic organ failures. Difficulties arise, however, particularly in assessing preinfection respiratory dysfunction, which is the most common organ dysfunction in sepsis and is associated with lower mortality than other organ failures (24). In fact, studies have described habitual Pao_2 values under the SOFA cutoff for organ failure in elderly patients (28–30), long-term smokers (31), as well as individuals with obesity (32) and chronic heart failure (33). This suggests that respiratory failure may overestimate mortality relative to the other components of the SOFA score and arguably more when not adjusted for prior respiratory function. Finally, repeated failures of randomized trials in sepsis have been ascribed at least in part to sepsis heterogeneity (1). Variations across studies in how a defining feature of sepsis is calculated may further compound this problem.

Our study confirms that sepsis causes considerable mortality. Nevertheless, many patients with suspected sepsis in the ED die of other conditions; in our cohort, mortality was higher in patients with noninfectious conditions than patients with infections. This underscores the importance of establishing a correct diagnosis early during hospitalization. Furthermore, the efficacy of both antimicrobial and experimental treatments will be underestimated in trials if a substantial proportion of the treatment group has noninfectious causes of organ dysfunction and death. Of note, the SOFA score related to mortality in our cohort performed differently between infected and uninfected patients. This calls for thoroughness in assessing actual presence of infection when evaluating the SOFA scoring system (4, 7, 34).

This study has some limitations. First, this is a single-center study, and our findings have not been validated in a second, independent cohort. Due to the organization of the RRTs at the inclusion site, no gynecological and only a few patients with surgical or nosocomial sepsis were included. Second, we have used SOFA score throughout, although qSOFA was chosen to identify patients with sepsis in non-ICU encounters. However, SOFA AUC is largely comparable or even better than qSOFA in non-ICU encounters (3, 4). Third, as $SOFA_{Acute}$ may rise during the course of hospitalization as organ supportive measures such as vasopressors and mechanical ventilation were rarely initiated in the ED, we chose to assess the highest SOFA score during hospitalization. This departs from the Sepsis-3 task force's SOFA calculation, which used SOFA scores obtained near the time of infection suspicion (3). Fourth, as culture-negative sepsis is frequent, we argue that using a strict microbiological definition of infection is inferior to a clinical definition as presented here. However, although we evaluated the validity of our infection likelihood assessment in a subset of patients and found it satisfactory, we cannot exclude potential effects of subjective assessments. Last, $SOFA_{Chronic}$ was estimated following strict guidelines, and if there was insufficient information, the value was set as missing. Thus, the number of missing $SOFA_{Chronic}$ (especially the respiratory component) was high. Furthermore, in cases where information was available preadmission, the trajectory of the chronic illness and therefore also of $SOFA_{Chronic}$ immediately preceding infection onset is associated with uncertainty (35).

CONCLUSIONS

Both acute and chronic organ failures were associated with 30-day mortality in patients with suspected sepsis in the ED. Patients with infections had lower mortality, and their SOFA scores predicted mortality better than in patients where infection was unlikely. Finally, pre-infection chronic SOFA made up a substantial part of patients' total SOFA. Chronic organ failures cannot be expected to improve in any sepsis intervention, calling for caution when using total SOFA to evaluate effects in interventional studies.

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