Second-day Sequential Organ Failure Assessment (SOFA) Score as Predictor in 30–Day Hospital Mortality among Filipino Adult Patients who Presented with Sepsis at the Emergency Department

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Abstract

Introduction: The Third International Consensus Definitions for Sepsis and Septic Shock in 2016 promoted the new definition and prognostication scheme among patients with sepsis using the Sequential Organ Failure Assessment (SOFA) scoring system. This study determined the discriminative power of the second-day SOFA scoring system in predicting 30-day hospital mortality among adult Filipino patients who presented with sepsis in a tertiary government hospital in the urban setting in the Philippines.

Methods: We evaluated 107 adult with sepsis presenting at the emergency department from June 1, 2017 to August 31, 2017 in a 300 bed capacity tertiary hospital. Receiving operating characteristic curves were generated to determine optimal cut off scores of the SOFA scoring system in predicting 30-day mortality. Binary logistic regression was performed to determine the association of the SOFA derivatives with hospital mortality. STATA 15 was used for data analysis.

Results: Second-day SOFA scores had excellent predictive ability for 30-day mortality at a cutoff point of 5, with sensitivity and specificity at 84.21% and 84.81%, respectively as compared with other SOFA derivatives at a given point in time.

Conclusion: The utility of second-day SOFA Score at a lower cut off score of five, has s a good discriminative power in predicting the all cause mortality among adult septic patients. This lower cut off score indicated a lower threshold trigger in identifying patients needing more intensive monitoring given the association of higher mortality risk in comparison with other studies done abroad.

Keywords: sequential organ failure assessment, SOFA, sepsis. mortality, philippines

Introduction

The Third International Consensus Definitions for Sepsis and Septic Shock or Sepsis has recently released a guideline on the definition and prognostication of sepsis and septic shock.[1] It promotes the utilization of Sequential Organ Failure Assessment (SOFA) scoring system as an objective measure of organ dysfunction among patients with sepsis.[2] Organ dysfunction can be identified by an acute change in SOFA (ΔSOFA) score of ≥2 points consequent to the infection. Higher SOFA scores were associated with increasing mortality rates. However, most studies on the utilization of SOFA were extracted from US databases[2] and yet applicability to Asians, especially Filipinos could be questionable given the differences in the genetic, ethnic, epidemiological, economic and environmental variables.

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The SOFA scoring system was created in a consensus meeting of the European Society of Intensive Care Medicine in 1994 and was developed to quantify the severity of patients' illness, based on the degree of organ dysfunction data on six organ failures and scored on a scale of 0–4. One failure plus a respiratory failure indicated the lowest mortality while all the other combinations yield mortality between 65% and 74%.[3] A prospective study in 2013 showed that both the mean and highest SOFA scores are particularly useful predictors of outcome. Independent of the initial score and an increase in SOFA score at 48th hour of presentation predicts a mortality rate of at least 50%.[1] When the SOFA score was <7, the mortality was 56%. The mean SOFA score at 48 hours was 6.96 in patients who died and 2.5 in those who improved. Hence, the predictive value for mortality of SOFA score was better at 48 hourss than at initial presentation.[4] In another study in 2001 regardless of the initial score, an increase in SOFA score during the first 48 hours in the ICU predicts a mortality rate of at least 50%.[5] Both the mean and highest SOFA scores are particularly useful predictors of outcome.

Early prognostication of sepsis using a standardized system would guide physicians in starting a more appropriate

treatment strategy and more aggressive monitoring. This study elaborated an actual overview of sepsis cases in an urban setting in a tertiary government hospital in the Philippines. The data can be a potential aid in the improvement of health care policy making in the country. Furthermore, conferring with an international guideline warrants re-assessment for applicability in local settings. This study determined the suitability of SOFA scoring in the Philippine health care set up, suggested possible adjustment of SOFA applicability in a resource limited hospital and most importantly, to help objectively prognosticate Filipino patients who presented with sepsis at the emergency department.

In the context of better predictability of second-day SOFA score for mortality outcomes as with from previous Western studies, the primary objective of this study determined the discriminative power of the second-day SOFA scoring system as predictor 30-day hospital mortality among adult Filipino patients who presented with sepsis at the emergency department. Specifically this study detailed on determining the optimum cut-off score of the SOFA scoring system at the second-day of hospitalization as predictor of 30-day hospital mortality in comparison with SOFA taken on admission (baseline), other derivatives such as delta SOFA scores and total maximum SOFA scores.

Methods

Study design and setting

We performed an observational prospective cohort study that was conducted from June 1, 2017 to August 31, 2017 in a tertiary government hospital in an urban area with 300 bed capacity. The study started only after extensive review and approval of the hospital's Research Development and Innovations and the Institutional Review Board. Patients in the emergency room with suspected and / or documented sepsis referred and / or admitted under the Department of Internal Medicine were screened for eligibility in this study.

Participants

The inclusion criteria involved adult patients of ≥ 18 years old admitted for >24 hours and diagnosed of sepsis at time of admission and has a hospital course of more than 24 hours from time of admission, with clinically or microbiologically confirmed focus of infection plus two or more of the SIRS Criteria: (a) temperature >38°C or <36°C, (b) heart rate >90/min, (c) respiratory rate >20/min or PaCO2 <32 mm Hg and (d) white blood cell count >12 000/mm^3 or <4000/mm^3 or >10% immature bands. Exclusion criteria were: patients re-admitted for any infection in the last three months, patients who stayed in the hospital for less than 24 hours, either expired or transferred to another institution, those with known or suspected malignancy and any patient who underwent any surgical operation in past one month.

Variables and data collection methods

We recruited patients with suspected or documented sepsis seen at the emergency room and referred to an internal medicine resident doctor through convenience sampling. Patients who qualified the inclusion criteria and who agreed to give informed consent were enrolled in the study. Every patient was identified by their hospital number to provide confidentiality with a signed informed consent from patients themselves, and / or if patient is unstable, consent from a legally capable immediate relative at the time of admission.

Upon admission from the emergency department, we recorded the baseline demographic profiles of each patient including age, sex, comorbid illness and focus of infection. We also gathered the following laboratory and clinical variables: arterial blood gas (ABG), complete blood count (CBC) with platelet count, total bilirubin, creatinine, blood pressure (mean arterial pressure), the use of any inotropic support, urine output in 24 hours (reported in mL per day) and Glasgow coma Scale (GCS). Furthermore, we obtained two peripheral blood cultures as well as culture of other specimens when necessary based on the suspected source of sepsis. All clinical specimens were collected by the duty laboratory personnel and were discarded after release of official results.

We recorded the worst values for each parameter in the 24-hour period for each clinical and laboratory parameters included in the SOFA and used them to compute for the baseline SOFA (SOFABASELINE). We also collected the same data variables that comprised SOFA on the second-day of hospitalization and were used to compute for the SOFA Score. (SOFA2). We followed up admitted patients until the 30th hospital day where repeat SOFA Score (SOFA30) were again be measured. The 30 day observation period was based on the study of Alejandria, et.al. in 2000 that described that among their patients seen at the ER, there was 17 days mean length of hospital stay.[11] In this study though, we extended the observation period up to 30 days to better discern patients who initially presented as severe sepsis and septic shock that were expected to have longer hospital stay. Among patients who were discharged before the 30th hospital day, we measured the SOFA score on the day of discharge and values were equated to the SOFA score to be measured on the 30th hospital day (SOFA30) among patients who stayed longer.

We used the SOFA scores obtained in different points in time (SOFABASELINE, SOFA2 and SOFA30) to calculate for the total maximum SOFA score (SOFATMAX) and Delta SOFA. The total maximum SOFA score (SOFATMAX) is the SOFA score acquired from the sum of the highest values obtained from each individual organ score in a period of 30 days observation. Delta SOFA Score, on the other hand, is the difference between SOFA2 and SOFABASELINE.

We recorded outcome measures 30 days from the time of admission based on mortality classified as "Alive" and "Expired". Alive included subjects who were improved and discharged while expired included subjects who died during the hospital stay for any reason. Patients who were discharged "Alive" were followed up at out patient clinic on Day 30 from admission.

We used a standard collection tool at the emergency room on admission and ward and/or ICU among patients enrolled in this study. We carefully identified each patients' data with their hospital number and recorded necessary data in the standard collection tool. Records were analyzed and kept in a sealed envelope by the researcher. We limited the access to patients' data only to the researchers, adviser and statistician.

Study size and statistical methods

In this study, desired computed sample size was 123. It was computed based at a level of significance of 5% and a power of 80% with an assumed 1.417 effect size of SOFA score on survivor and non-survivor patients as noted from reference article by Jones, et al[6] using the Cohen's d formula.

Receiving operating characteristic curves were generated to determine optimal cutoff scores of the SOFA scoring system at different points in time and their derivatives (SOFABASELINE, SOFA2, SOFATMAX and Delta SOFA) in predicting 30-day mortality. We performed binary logistic regression to determine the association of the SOFA Scores with all cause hospital mortality. Crude and adjusted odds ratios were reported with 95% confidence intervals.

We included all valid data in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05 α-level of significance. STATA 15 was used for data analysis.

Results

A total number of 128 patients were screened with 21 subjects excluded. Among the exclusion, 15 were subsequently diagnosed of unlikely sepsis, five were dropped out from the study (four transferred to other hospital and one was discharged against medical advise) and one was excluded since the patient was confined beyond 30 days. A total of 107 patients were included in the study analysis with an average age of 58±20 years and a male to female ratio of about 3:2. The all cause mortality for patients with sepsis in this study was 34% (27 out of 107 patients). The top diagnoses were pneumonia (35%), UTI (14%), and cellulitis (10%). The most common comorbid diseases were diabetes (25%) and hypertension (21%). Gram negative bacteria were identified in 10%, while the majority of cultures did not show growth of any organism (88%). The median length of stay for patients was eight (range 1-41) days. Those who expired (n=27) were older by an average of 15 years compared to the patients who improved (n=80). Length of hospital stay was not significantly different according to patient outcomes (*P*=0.190) (Table I).

Both baseline and second-day SOFA scores had good predictive ability for 30-day mortality (Table II). At a cutoff point of five, day 2 SOFA (SOFA2) the sensitivity and specificity were 84.21% and 84.81%, respectively. Its area under the curve (AUC) of 0.904 (95% CI 0.84-0.97) was better than the AUC of either baseline score (SOFABASELINE: 0.811 (95% CI 0.72-0.90)) or highest score (SOFATMAX:0.860 (95% CI 0.78-0.94)) (Figure 1). In the determination of Delta SOFA score (SOFA2 minus SOFABASELINE), it revealed excellent specificity scores at various cutoff points however with poor sensitivities. (Table II).

Overall, patients who had a baseline SOFA score >5 were 3.837 times more likely to die during the hospital admission, within 30 days (95% CI 1.6 to 9.18, *p*=0.003). Age and sex were not found to be statistically significant predictors of in-hospital mortality in this study (Figure 2, Table III).

Discussion

Since most studies for SOFA Scoring System as predictor of mortality among cases of sepsis were executed among patients in the Western race and / or American based institutions, this study aimed to describe the utility of SOFA among Filipino adults with sepsis admitted in a tertiary government urban based hospital. Ferreira, et.al., in 2001 on which subjects were from 31-bed medico surgical ICU at a university hospital in Belgium described that at cut off score of >7, the sensitivity to predict mortality was around 65% (AUC of 0.84 at 95% CI 0.78-0.88).[1] However, in this study done among Filipino patients, SOFA Score at a lower cut off score of five exhibited a higher level of sensitivity of 84.21% (AUC of 0.904 at 95% CI 0.84-0.97) as predictor of hospital mortality. This is also comparable to those seen among Indian patients on which the SOFA score taken on the second hospital day that had an associated 56% mortality risk but also at a higher cut off value of seven.[7] The importance of these differences on the obtained cut off score could probably be racial dependent on the expected mortality outcome of sepsis in relation to the SOFA Score. Mayr, et.al., in 2010 described that racial differences in severe sepsis existed between whites and blacks.[8] This risk of sepsis to the latter was explained by higher infection rate and a higher risk of acute organ dysfunction.[8] However, other possible factors that could probably affect the differences on the cut off score will include the differences in standards of care in a particular setting given the limitations of some resources, the variabilities in antimicrobial susceptibility in a specific geography and selection pressure of microorganisms in a different country. Interestingly, this lower cut off SOFA score obtained on the second hospital day as predictor of mortality observed among Filipino septic patients may have an impact on health policy making setting. This suggests a

Table I. Demographic and clinical profile of patients diagnosed with sepsis based on mortality outcome seen at Ospital ng Makati emergency room, June 1, 2017 to August 31, 2017 (n=107)

	All (n=107)	Alive (n=80)	Expired (n=27)	*P*-value
Age in years (mean ± SD)	58.37 ± 20.1	54.49 ± 20	69.89 ± 15.8	0.0004*
Sex [n(%)]				
Male	65 (60.75)	52 (65)	13 (48.15)	0.121§
Female	42 (39.25)	28 (35)	14 (51.85)	
BMI in kg/m^2 (mean ± SD)	22.53 ± 3.4	22.6 ± 3.5	22.31 ± 3.3	0.700*
Height in cm (mean ± SD)	160.93 ± 6.8	160.91 ± 6.4	161 ± 8.1	0.954*
Weight in kg (mean ± SD)	58.47 ± 10.2	58.68 ± 10.5	57.85 ± 9.5	0.720*
Diagnosis [n(%)]				
Pneumonia	38 (35.5)	25 (31.25)	13 (48.15)	0.104‡
UTI	15 (14.0)	14 (17.5)	1 (3.7)	
Cellulitis	11 (10.3)	6 (7.5)	5 (18.52)	
Leptospirosis	7 (6.5)	7 (8.75)	0	
CNS infection	4 (3.7)	3 (3.75)	1 (3.7)	
Infectious diarrhea	4 (3.7)	4 (5)	0	
Others*	28 (26.3)	21 (26.25)	7 (25.93)	
Comorbidities/risk factors [n(%)]				
Electrolyte imbalance	27 (25.23)	20 (25)	7 (25.93)	0.924§
Diabetes mellitus	27 (25.23)	19 (23.75)	8 (29.63)	0.543§
Hypertension	22 (20.56)	13 (16.25)	9 (33.3)	0.058§
Pulmonary tuberculosis	15 (14.02)	11 (13.75)	4 (14.81)	1.000‡
Chronic kidney disease	9 (8.41)	6 (7.5)	3 (11.1)	0.689‡
Post stroke	7 (6.54)	3 (3.75)	4 (14.81)	0.066‡
Anemia	5 (4.67)	2 (2.5)	3 (11.1)	0.101‡
Asthma	4 (3.74)	3 (3.75)	1 (3.7)	1.000‡
Coronary artery disease	2 (1.87)	1 (1.25)	1 (3.7)	0.443‡
Others	4 (3.74)	4 (5)	0	0.570‡
SIRS criteria fulfilled [n(%)]				
Two	52 (48.6)	39 (48.75)	13 (48.150	1.000‡
Three	52 (48.6)	39 (48.75)	13 (48.15)	
Four	3 (2.8)	2 (2.5)	1 (3.7)	
Hospital stay in days [median (range)]	8 (1-41)	8 (2-32)	6 (1-41)	0.190ᵊ
Culture growth [n(%)]				
Gram negative bacteria	11 (10.28)	7 (8.75)	4 (14.81)	0.703‡
Gram positive bacteria	1 (0.93)	1 (1.25)	0	
Bacterial and fungal	1 (0.93)	1 (1.25)	0	
None	94 (87.85)	71 (88.75)	23 (85.19)	
Organism (n=13) [n(%)]				
Klebsiella pneumoniae	[n=13]	[n=9]	[n=4]	0.413‡
E. coli ESBL positive	3 (23.08)	1 (11.1)	2 (50)	
E. coli ESBL negative	3 (23.08)	3 (33.3)	0	
Acinetobacter baumanii	2 (15.38)	2 (22.2)	0	
Non-candida albicans and S. epidermidis	2 (15.38)	1 (11.1)	1 (25)	
CoNS	1 (7.69)	1 (11.1)	0	
Enterococcus faecalis	1 (7.69)	0	1 (25)	

BMI, body mass index; CNS, central nervous system; CoNS, coagulase-negative staphylococci; ESBL, extended spectrum beta lactamase; UTI, urinary tract infection.
Statistical tests used: * - Independent sample t test; ᵊ - Mann Whitney U test; § - Chi square test; ‡ - Fisher's exact test.

Table II. Receiver operating curve (ROC) values of different SOFA scores and derivatives as predictor of the 30-day mortality among patients diagnosed with sepsis seen at Ospital ng Makati emergency room, June 1, 2017 to August 2017

SOFA score	AUC (95% CI)	Cutoff point	Sensitivity	Specificity	Correctly classified	LR+	LR-
Baseline	0.811 (0.72—0.90)	≥ 5	74.07%	71.25%	71.96%	2.5765	0.3639
2nd day (n=98)	0.904 (0.84—0.97)	≥ 5	84.21%	84.81%	84.69%	5.5439	0.1862
Delta	0.64 (0.47—0.81)	>2	42.11%	91.14%	81.63%	4.7519	0.6352
		>3	31.58%	94.94%	82.65%	6.2368	0.7207
		>4	21.05%	98.73%	83.67%	16.6316	0.7996
Maximum (on discharge, within 30 days, n =11)	0.860 (0.78—0.94)	≥ 5	92.59%	68.75%	74.77%	2.963	0.1077

Table III. Cox's proportional hazards ratio comparing probability of survival of patients with baseline SOFA score > 5 versus <5

	Adjusted hazard ratio	95% confidence interval	*P*-value
SOFA baseline score ≥ 5	3.837	1.6 to 9.18	0.003
Age	1.022	0.998 to 1.05	0.072
Female	1.503	0.68 to 3.32	0.314

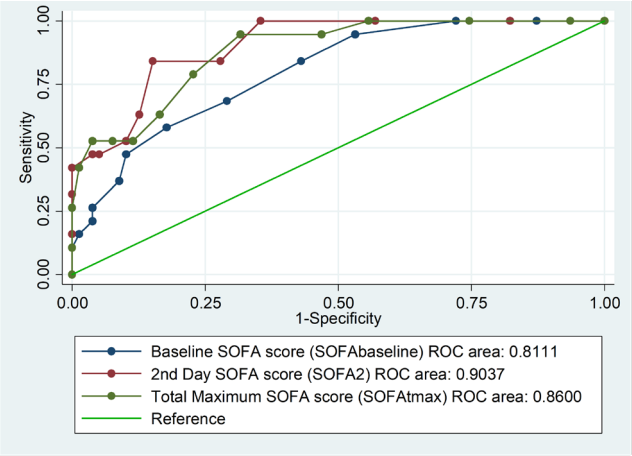

Figure 1. Receiver operating curves of SOFABASELINE, SOFA2 and SOFATMAX scores as predictor of the 30-day hospital mortality among patients diagnosed with sepsis seen at Ospital ng Makati emergency room, June 1, 2017 to August 31, 2017

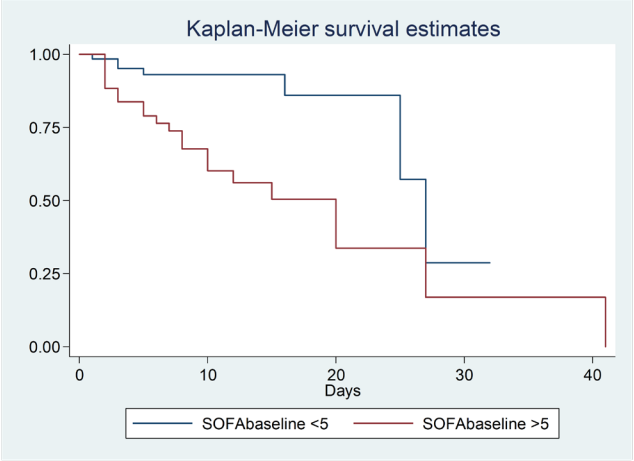

Figure 2. Kaplan meier survival estimates curve of baseline SOFA scores as predictor of 30-day hospital mortality among patients diagnosed of sepsis seen at Ospital ng Makati emergency room from June 1, 2017 to August 31, 2017

lower trigger score for a more intensive monitoring and more aggressive measures of those with second-day SOFA scores higher than five, given the higher mortality outcome.

Aside from the second-day SOFA, other SOFA scores at a particular point in time and their derivatives were also obtained on admission and prior to discharge. This study showed that SOFA score on the day of admission (SOFABASELINE) at cut off score of five had lower discriminative power with AUC of 0.811 at 95% CI 0.72-0.90 on the prediction of 30-day mortality as compared with second-day SOFA Score. The same finding was observed in the study of Ferreira, et.al. in 2001 showing that independent of the initial value of SOFA on admission, an increase in the SOFA score during the first 48 hours of admission predicts a mortality rate of at least 50%.[1]

Delta SOFA (Δ SOFA) defined as the difference of SOFA score from day two and Baseline (Day 0 on Admission), is another derivative of SOFA scores and was used by other randomized controlled trials as a better gauge to predict mortality. This study showed that delta SOFA at different cut off scores had excellent specificities (>2: 94.14%; >3 94.94% and >4: 98.73%), however with very low sensitivities in prediction of 30 day hospital mortality outcome. De Avezedo et al. (2014) described that Δ SOFA scores (difference between the SOFA score on the second or third day of evolution and the SOFA score on arrival) exhibited a correlation with mortality and revealed that any increase in Δ SOFA was associated with a 35% in hospital mortality rate, whereas any decrease in Δ SOFA was associated with 10% mortality.[9] It was further demonstrated by an older study by Jones et.al., in 2009 demonstrating that among patients with severe sepsis and septic shock, the Δ SOFA (initial – 72 hours) scores correlated strongly with mortality.[6] Grooth et al. (2017) also reiterated that delta fixed-day SOFA (similar to Δ SOFA as described initially) appeared to be most responsively and consistently associated with mortality.[10] Tmax SOFA was also obtained in this study, however most patients who were about to be discharged did not consent to do repeat SOFA score on the day of the discharge and /or on the 30th day of admission, hence only 11 subjects had their SOFA obtained at Day 30 and / or on discharge day. Given this small sample size available to compute for SOFATMAX (that will be based on the sum of all SOFA scores including the SOFA on discharge and / or 30th day), the analysis for SOFA TMAX on this study was not conclusive.

Conclusion

The second-day SOFA score has a strong discriminative power, at a cut off score of five, in predicting all-cause mortality in 30 days with a sensitivity of 84.21% and specificity of 84.81 among Filipino patients diagnosed of sepsis. This lower cut off score as compared from other international studies can help guide in the improvement in patient quality of care especially in terms of monitoring and more aggressive measures among those with SOFA score of five or more.

Furthermore, the use of second-day SOFA score has better sensitivity and specificity profile in predicting the all cause mortality as compared to baseline SOFA on admission, and delta SOFA scores. Though the classical recommendation for the utility of SOFA score as a predictor of mortality is for it to be done "sequentially" at different points in time, this study implies that SOFA Score taken at the

second-day of hospitalization alone can be a good gauge of mortality outcomes as compared to those obtained on admission and those done serially (delta SOFA). Serial SOFA scores at different points in time with its derivatives cannot be really cost effective while baseline SOFA is too early to more accurately predict the all cause mortality.

Recommendations

We recommend that same study be facilitated in a greater variety and larger patient population with a longer study duration across different institutions. This will give more power to the study and allow comparison of outcomes on different hospital settings. Correlation on the length of hospital stay, time for early weaning among intubated patients and SOFA scores at different points during admission is also suggested. Subgroup analysis for possible differences of cut off SOFA scores across different patient qualities (e.g. medical versus surgical causes of sepsis, organ system based causes of sepsis, special population such as HIV and Cancer patients) is also encouraged.

About the paper

- First Place on the 24th Annual Medicine Residents' Research Contest Ospital ng Makati 2017
- First Place on the Annual Research Development and Innovations Interdepartmental Research Contest Ospital ng Makati 2017
- First Place on the Philippine College of Physicians (PCP) Most Outstanding Research Analytical Prospective Category 2018
- First Place on the Philippine Society for Microbiology and Infectious Diseases (PSMID) Dr. Antonio J. Gonzaga Research Awards Analytical Category 2018

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