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The impact of acute organ dysfunction on long-term survival among sepsis survivors

Alejandro Schuler, MS¹, David A Wulf, BS², Yun Lu, MD, MPH², Theodore J Iwashyna, MD, PhD³, Gabriel J Escobar, MD², Nigam H Shah, MBBS, PhD¹, and Vincent X Liu, MD, MS²

¹Biomedical Informatics Research, Department of Medicine, Stanford University; Stanford, CA

²Division of Research, Kaiser Permanente Northern California; Oakland, CA

³Department of Medicine and Institute for Social Research, University of Michigan and VA Center for Clinical Management Research, VA Ann Arbor Health Healthcare System; Ann Arbor, MI

Abstract

Objective—To estimate the impact of each of six types of acute organ dysfunction (hepatic, renal, coagulation, neurologic, cardiac, and respiratory) on long-term mortality after surviving sepsis hospitalization.

Design—Multicenter, retrospective study.

Setting—21 hospitals within an integrated healthcare delivery system in Northern California.

Patients—30,163 sepsis patients admitted through the emergency department between 2010 and 2013, with mortality follow-up through April 2015.

Interventions—None

Measurements and Main Results—Acute organ dysfunction was quantified using modified Sequential Organ Failure Assessment scores. The main outcome was long-term mortality among sepsis patients who survived hospitalization. The estimates of the impact of each type of acute organ dysfunction on long-term mortality were based on adjusted Cox proportional hazards models. Sensitivity analyses were conducted based on propensity score-matching and adjusted logistic regression. Hospital mortality was 9.4% and mortality was 31.7% at one year. Median follow-up time among sepsis survivors was 797 days (interquartile range, 384 to 1,219 days). Acute neurologic (odds ratio [OR]: 1.86; $p < 0.001$), respiratory (OR: 1.43; $p < 0.001$), and cardiac (OR: 1.31; $p < 0.001$) dysfunction were most strongly associated with short-term hospital mortality, compared with sepsis patients without these organ dysfunctions. Evaluating only patients surviving their sepsis hospitalization, acute neurologic dysfunction was also most strongly associated with long-term mortality (OR: 1.52, $p < 0.001$) corresponding to a marginal increase in predicted one-year mortality of 6.0% for the presence of any neurologic dysfunction ($p < 0.001$).

Corresponding Author: Vincent Liu, MD, MS, Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612, Vincent.x.liu@kp.org, (510) 891-6933.

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Liver dysfunction (OR: 1.15, $p=0<0.01$) was also associated with long-term mortality in all models, while the association for other organ dysfunction subtypes were inconsistent between models.

Conclusions—Acute sepsis-related neurologic dysfunction was the organ dysfunction most strongly associated with short- and long-term mortality and represents a key mediator of long-term adverse outcomes following sepsis.

Keywords

sepsis; organ dysfunction; long-term mortality; brain dysfunction; outcomes research

Introduction

Sepsis is defined by life-threatening organ dysfunction resulting from a dysregulated host response to infection.(1–4) While short-term mortality has declined due to improved hospital care, sepsis exacts a considerable toll on post-hospital morbidity and mortality. (5–12) Yet sepsis is a heterogeneous syndrome and patients manifest widely variable types of organ dysfunction with variable short-term mortality.(13) The specific impact that each type of acute sepsis-related organ dysfunction plays in long-term mortality is unknown, but this knowledge is critical to personalize post-discharge prognosis as well as uncover potential mechanisms through which sepsis affects long-term survival.(14, 15)

Traditional approaches for estimating the association between acute organ dysfunction and long-term mortality typically fail to account for patients' baseline predisposition for organ dysfunction.(14) For example, patients with chronic kidney disease are much more likely to experience acute kidney injury,(16, 17) while patients with underlying neurocognitive disorders are much more likely to experience acute brain dysfunction.(18, 19) Failure to adequately account for these predisposing risk factors could result in biased estimates of the independent effects of acute, rather than chronic, organ dysfunction.(14, 19) However, there are limited existing data that can be used to quantify the risk of sepsis-related organ dysfunction based on pre-sepsis patient characteristics.

In this study, we assessed the association between acute organ dysfunction for each of six organ systems in a large, unselected cohort from a community-based healthcare system with rich data on both their acute organ dysfunction and their longitudinal pre-sepsis medical history. To adjust for pre-sepsis characteristics we applied organ-specific propensity score matched cohorts to estimate the independent effects of each organ dysfunction on long-term mortality among those who survived hospitalization.

Methods

This study was approved by the Kaiser Permanente Northern California (KPNC) Institutional Review Board for the Protection of Human Subjects.

Our starting sample included a total of 35,000 randomly selected inpatient admissions at 21 KPNC hospitals admitted for sepsis through the emergency department (ED) between 2010 and 2013.(20) For patients with multiple sepsis hospitalizations, we kept only their first

admission. We used International Classification of Disease, 9th Edition, Clinical Modification (ICD9) present on admission diagnosis codes to identify sepsis, including 0.38 and subtypes, 995.91, 995.92, and 785.52, because these were the prevalent codes in clinical and operational use at the time in an ongoing regional sepsis quality improvement program. (3, 7, 21)

Organ dysfunction scores

We quantified acute organ dysfunction with a modified Sepsis Organ Failure Assessment (SOFA) score(22) calculated in 6-hour increments starting from the time of ED arrival. Standard SOFA scores range from zero to a theoretical maximum of 24 and include six organ subscores (hepatic, renal, coagulation, neurologic, cardiac, and respiratory) which each range from zero to 4. For selected organ systems, we broadened the SOFA subscore criteria to include clinically relevant organ dysfunction variables (e.g., liver transaminase values >200 for hepatic dysfunction; clinical documentation of agitation or coma within nursing flowsheets for neurologic dysfunction; oxygen saturation-inspired oxygen ratios for respiratory dysfunction; Appendix Table 1).(23–26) We classified patients as having each type of acute organ dysfunction if they had a SOFA subscore ≥ 1 during the first 48 hours of hospitalization. We also recorded maximum SOFA subscores within the first 48 hours (theoretically identifying acute organ dysfunction resulting from present on admission sepsis) and over the entire hospitalization (theoretically attributable to either sepsis or secondary inpatient events). We were not able to assess pre-hospital SOFA scores to specifically differentiate pre-existing and acute organ dysfunction (e.g., patients with altered neurological status even prior to hospitalization).

Organ dysfunction and hospital mortality

To assess the association between each type of acute sepsis-related organ dysfunction and short-term mortality, we determined hospital mortality within each SOFA organ-specific subscore category. We also estimated the association between organ dysfunction and hospital mortality with multivariable logistic regression models adjusting for age, gender, predicted hospital mortality, acute severity of illness (Laboratory and Acute Physiology Score, version 2; LAPS2), composite comorbid disease burden (Comorbidity Point Score, version 2; COPS2), intensive care unit utilization, and full code status.(24, 25, 27–29) To reduce residual confounding, we also adjusted these models for covariates quantifying illness severity including the maximum SOFA subscore values for each organ besides the specific organ of interest during the entire hospitalization (since patients could have multiple types of organ dysfunction within the same hospitalization).

Long-term mortality analysis

Because we were primarily interested in long-term outcomes following sepsis among those who survived hospitalization, we then used organ-specific Cox proportional hazards models to assess the association of each organ dysfunction (as integer values ranging between zero and 4) with post-sepsis mortality including only patients discharged alive. We determined mortality based on electronic health records and state mortality data through April 2015.(24, 25, 27, 28) We also estimated the impact of organ dysfunction as a binary value (e.g., dysfunction present or absent) on long-term mortality using the same covariates.

Sensitivity analysis using propensity score model

We conducted several sensitivity analyses. Our primary sensitivity analysis utilized a propensity scoring method to adjust for patients' pre-sepsis risk factors for each specific organ dysfunction type. While traditional propensity scoring methods typically rely on a limited set of covariates in a logistic regression model as putative confounders, machine learning methods facilitate the development of propensity scores based on a much larger set of covariates.(30, 31) For each of the six organ dysfunction types, we developed a propensity score based on the unique counts of all possible ICD9 diagnosis and procedure codes in the year *prior to sepsis hospitalization* as covariates. We eliminated ICD9 codes if they were present in <15 sepsis patients, resulting in 3,265 ICD9 codes and demographic variables as features (i.e., covariates). We used gradient boosted trees, the 'one standard error' rule, and out-of-fold prediction to estimate each patient's organ-specific propensity score (see Appendix for full details).

We subjected propensity score models to a face-validity check by examining whether the most important predictors of each type of organ dysfunction (based on variable importance scores) were clinically relevant to that organ dysfunction.(32, 33). We then used the propensity scores (one per organ dysfunction per patient) to create matched cohorts of patients who did and did not have that acute organ dysfunction using standard 1:1 caliper matches with a caliper size of 0.005 without replacement. To evaluate covariate balance, we quantified the absolute standardized difference in means (ASDM) across all covariates in each matched cohort. We evaluated adjusted Cox regression models using the propensity-score matched cohorts. In addition, we conducted sensitivity analyses using an adjusted logistic regression model where the outcome was 1-year mortality as well as a Cox regression model including death starting from the time of sepsis hospital admission, thereby including both hospital and long-term mortality.

Data are reported as mean $\pm$ standard deviation, median (interquartile range, IQR), or number (percent). Analyses were conducted in R and STATA/SE 14.1.

Results

We evaluated 30,163 unique sepsis patients admitted through the emergency department with a median hospital length of stay of 3.7 days (Table 1). The majority of patients (60.8%) had total SOFA scores ≥ 2 points during the first 48 hours of hospitalization. Overall hospital mortality was 9.4%; mortality was 31.7% at one year, 44.0% at two years, and 59.7% at three years. Our median follow-up time among sepsis survivors was 797 days from hospital discharge with an interquartile range of 384 to 1,219 days.

The total maximum SOFA score, either within 48 hours or during the entire hospitalization, was strongly correlated with hospital mortality (Figure 1). For example, mortality was 1.7% among patients with ≤ 1 total SOFA points; it was 77.9% for patients with ≥ 15 points. The most prevalent organ dysfunction was cardiac (62.4% of patients), while the least common was liver (16.5%; Figure 2). Increasing organ specific SOFA subscores were also associated with increased hospital mortality (Appendix Table 2; p-value for trend <0.01 for each). The organ dysfunctions most strongly associated with hospital mortality included neurologic

(adjusted odds ratio [OR]: 1.86; $p < 0.001$ – Appendix Table 3), respiratory (OR: 1.43; $p < 0.001$), and cardiac (OR: 1.31; $p < 0.001$), compared to sepsis patients without these organ dysfunctions.

Evaluating only sepsis survivors, adjusted regression analyses demonstrated that acute neurologic dysfunction was most strongly associated with long-term mortality after living discharge with an adjusted hazard ratio for a 1-point increase in the SOFA subscore of 1.18 (95% CI: 1.15–1.20, $p < 0.001$; Table 2). Acute coagulation (1.12; 95% CI: 1.09–1.15; $p < 0.001$) and liver (1.08, 95% CI: 1.04–1.11; $p < 0.001$) dysfunction were also associated with increased hazards of long-term mortality in the primary analysis, albeit with smaller effect sizes.

In sensitivity analyses, the tree-based propensity score models identified the pre-sepsis conditions that had the greatest influence on acute organ dysfunction with good clinical face validity (Appendix Figure 2). For example, the variables of greatest importance in predicting sepsis-related neurologic dysfunction included age, a prior history of dementia and other neurological diseases, and a prior history of falls. For coagulation dysfunction, the most influential predictors included patients with a history of anticoagulation, thrombocytopenia, leukemia, and cirrhosis. In addition, even though the models were trained to predict binary outcomes (SOFA organ subscore = 1), each model showed good stratification according to the numerical SOFA scores (Appendix Figure 3). The tree-based propensity score model resulted in good covariate balance (Appendix Figure 4).

Sensitivity analyses using the matched and full cohorts as well as Cox and logistic regression supported the finding that the most robust increase in long-term mortality was attributable to neurological organ dysfunction (Table 2, Appendix Table 3, and Appendix Figure 4), while the effect sizes of other organ dysfunction categories were attenuated and, in several cases, not statistically significant. The marginal increase in predicted one-year mortality attributable to acute organ dysfunction was greatest for neurologic dysfunction (6.0%; 95% CI, 4.6%–7.4%; $p < 0.001$; Table 3).

Discussion

We evaluated a large multicenter sample of sepsis patients to determine which infection-related organ dysfunction portended the greatest risk to long-term mortality among those surviving hospitalization. We found that neurologic dysfunction within the first 48 hours of hospitalization had the greatest adverse impact on mortality after living hospital discharge adjusting for other concomitant organ dysfunction and severity of illness metrics.

Our findings are consistent with a large body of literature demonstrating that acute neurologic or brain dysfunction occurs commonly in sepsis patients and increases short- and long-term adverse outcomes.(14, 34) In 1990, Young and colleagues reported that encephalopathy was present in 71% of sepsis patients.(35) Similarly, in 1996, Eidelman and others found that at least half of sepsis patients had encephalopathy.(36) Several other studies have reported similar incidence rates.(37) In the current study, we also found that roughly half of our patients met criteria for neurological dysfunction based on a modified

SOFA subscore including both Glasgow Coma Score values as well as clinician documentation of mental status changes such as confusion or agitation.

Acute neurologic dysfunction in sepsis is strongly associated with adverse outcomes. The Sepsis-3 definitions incorporate altered mental status as one of three clinical factors comprising the qSOFA score which identifies patients with increased risk of mortality or critical illness.(1, 23) In the SAILS trial, 72% of patients exhibited delirium and, at 6 months, >35% of patients in each arm exhibited cognitive impairment.(38) The incidence of delirium and the rates of long-term cognitive impairment were remarkably similar to those reported in the BRAIN-ICU study of patients with respiratory dysfunction or shock treated in the intensive care unit.(39) Other landmark studies have similarly established the increased rates of cognitive impairment after sepsis.(6)

We were surprised to find that other types of organ dysfunction had a more modest effect on long-term mortality after living hospital discharge even while they were strongly associated with hospital mortality. For example, liver dysfunction was associated with an increased risk of long-term mortality in our primary analysis and in most of our sensitivity analyses. The rate of liver dysfunction in the current study was similar to the lower end of rates reported in various studies of organ dysfunction and sepsis epidemiology.(40–44) Liver dysfunction is strongly associated with worsened hospital mortality but relatively few studies have looked at its role in longer term outcomes. We found that increasing severity of respiratory and cardiac dysfunction was associated with increased hospital mortality but had favorable associations with long-term mortality among sepsis survivors. Further validation of these findings are needed.

In sensitivity analyses, we used a propensity score matching approach to adjust for the considerable baseline differences in health that could predispose patients to increased risks of specific organ dysfunctions. To account for the multitude of potential pre-existing conditions, we included >3,000 counts of diagnosis codes and were able to identify pre-sepsis clinical conditions that had clinical face validity. We also conducted additional sensitivity analyses which confirmed that our findings were robust to a variety modeling scenarios.

Our study has several other strengths. We included a large cohort of patients drawn from a contemporary multicenter sample with granular clinical data allowing us to characterize organ dysfunction both in the early phase of hospitalization as well as throughout the hospital stay. These data allowed us to adjust for concomitant organ dysfunction in patients who might be experiencing multi-organ dysfunction. We also had a median follow-up time of >2 years allowing us to confidently assess the role of organ dysfunction in longer-term outcomes after sepsis.

The study also has important limitations. First, we expanded our SOFA score variables in order to identify a larger spectrum of patients meeting clinical organ dysfunction criteria. For example, instead of only relying on Glasgow Coma Scale recordings, we also included patients with clinician documentation of confusion or agitation as having neurological dysfunction. While this hampers direct comparisons with other studies which rely

exclusively on SOFA criteria, we believe this enhances the clinical validity of our findings. Second, we were not able to assess pre-hospital SOFA scores and determine the incremental increase in SOFA scores resulting acutely from sepsis hospitalization, potentially resulting in our effect estimates including contributions of chronic organ dysfunction. However, accounting for organ-specific pre-hospital diagnosis data in our propensity score model resulted in largely consistent findings. Third, although we used a standard regression analysis and propensity scoring sensitivity analysis in order to establish the impact of specific organ dysfunctions on long-term mortality, there may be residual confounding that weakens the casual interpretability of our results. Finally, we were not able to ascertain the rates of residual neurocognitive impairment in our patients after hospitalization which may be a key pathway by which acute neurologic dysfunction impacts long-term mortality. We also were not able to identify long-term goals of care for patients which may differ for patients with significant neurological dysfunction after sepsis.

In summary, we studied a large community-based cohort of sepsis patients using granular clinical data to characterize acute organ dysfunction and its impact on long-term mortality following living hospital discharge. We found that acute neurologic dysfunction during sepsis hospitalization most strongly increased the risk of long-term mortality, while other types of organ dysfunction had a relatively modest impact on long-term outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Number of patients (left axis) and hospital mortality (right axis) stratified by the maximum total SOFA score within the first 48 hours of hospitalization (top) and maximum total SOFA score over the entire hospitalization (bottom).

Figure 2.

Distribution of unique combinations of organ dysfunction sorted by occurrence frequency. The single most common organ dysfunction was cardiac (displayed in the horizontal bar graph in the lower left panel) while the least frequent was liver. The main panel shows each unique combination of organ dysfunctions (as indicated by the corresponding pattern of dots) along with their occurrence frequency in the cohort (vertical bar graph above each unique combination).

Table 1

Characteristics and outcomes of patients.

Characteristic	Value
Year	
2010	4,750 (15.8)
2011	8,807 (29.2)
2012	8,390 (27.8)
2013	8,216 (27.2)
Age, years	69.8 ± 17.1
Male gender	14,500 (48.1)
Full code status	22,467 (74.5)
First hospital unit, if not ward	
Intensive care unit	6,201 (20.6)
Operating room	504 (1.7)
Maximum qSOFA, 48 hours	
0 points	2,750 (9.1)
1 points	10,279 (34.1)
2 points	10,762 (35.7)
3 points	6,372 (21.1)
Maximum SOFA, 48 hours	
<2 points	11,824 (39.2)
2 points	18,339 (60.8)
Length of stay, days	3.7 (2.4 – 6.2)
Mortality	
Hospital	2,847 (9.4)
One-year (n = 30,163)	9,549 (31.7)
Two-year (n = 26,616)	11,699 (44.0)
Three-year (n = 21,702)	12,954 (59.7)

Table 2

Adjusted hazard ratios based on multivariable Cox proportional hazards regression models of time-to-death and logistic regression models for 1-year mortality based on SOFA subscore points (top rows) or binary presence of organ dysfunction (bottom rows). Model covariates include maximum hospitalization SOFA subscore values for each organ system, age, predicted mortality, severity of illness (LAPS2 score), chronic comorbid burden (COPS2), intensive care unit utilization, and full code status.

Model	Organ dysfunction type					
	Liver	Nervous	Respiratory	Coagulation	Renal	Cardiac
Organ dysfunction, per point						
Cox regression model	1.08 ^{**} (1.04 – 1.11)	1.18 ^{**} (1.15 – 1.20)	0.99 (0.97 – 1.00)	1.12 ^{**} (1.09 – 1.15)	1.01 (0.99 – 1.03)	0.94 ^{**} (0.91 – 0.96)
Logistic regression model	1.16 ^{**} (1.10 – 1.22)	1.21 ^{**} (1.18 – 1.25)	0.97 [*] (0.94 – 0.99)	1.13 ^{**} (1.09 – 1.18)	0.98 (0.95 – 1.01)	0.89 ^{**} (0.85 – 0.92)
Organ dysfunction, binary						
Cox regression model	1.06 ^{**} (1.01 – 1.12)	1.43 ^{**} (1.36 – 1.49)	0.99 (0.94 – 1.04)	1.04 [*] (1.00 – 1.09)	0.97 (0.93 – 1.01)	0.96 (0.92 – 1.00)
Logistic regression model	1.15 ^{**} (1.05 – 1.26)	1.52 ^{**} (1.42 – 1.64)	0.92 [*] (0.85 – 0.99)	0.97 (0.91 – 1.04)	0.90 [*] (0.84 – 0.96)	0.90 [*] (0.84 – 0.96)

*
p<0.05;

**
p<0.001

Table 3

Marginal increases in the predicted probability of one-year mortality for the presence (versus absence) of any of the six acute organ dysfunctions based on adjusted logistic regression models.

Organ Dysfunction	Marginal increase in predicted probability of mortality	95% Confidence Interval	p-value
Liver	+2.0%	0.0% – 3.3%	0.002
Nervous	+6.0%	5.0% – 7.0%	<0.001
Respiratory	–1.2%	–2.3% – 0.1%	0.06
Coagulation	–0.4%	–1.3% – 0.5%	0.40
Renal	–0.6%	–2.0% – 1.0%	0.38
Cardiac	–1.0%	–2.0% – 0.1%	0.06