Aggregate Evaluable Organ Dysfunction Predicts In-Hospital Mortality from Sepsis in Uganda

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Abstract. We evaluated the association between severity of sepsis and in-hospital mortality in 150 patients with non-surgical sepsis at a regional referral hospital in Uganda. In-hospital mortality occurred in 5 of 52 (9.6%) patients with sepsis, 24 of 71 (33.8%) patients with severe sepsis, and 16 of 27 (59.3%) patients with septic shock. In the multivariate analysis, the identification of severe sepsis (adjusted hazard ratio [AHR] = 2.9, 95% confidence interval [CI] = 1.0–8.2, P = 0.04), septic shock (AHR = 5.7, 95% CI = 1.6–20.3, P = 0.007), and dysfunction of three or more organs (AHR = 2.9, 95% CI = 1.1–7.3, P = 0.03) increased the risk of in-hospital mortality. Adding aggregate organ dysfunction to the multivariate equation that included the sepsis category statistically significantly improved the model, but the opposite did not. Predictors of mortality were easily measurable and could be used to risk stratify critically ill patients in resource-constrained settings.

INTRODUCTION

The high burden of infection in sub-Saharan Africa (SSA) has led to an increased awareness of the importance of sepsis as a cause of death in this region.1,2 However, most studies of critical illnesses in SSA are disease-specific and do not address sepsis as a syndrome. Despite heightened concern about critical illness, the natural history of sepsis and sepsis-related organ dysfunction in SSA is not fully described.3,4 Where resources are limited, a better understanding of septic patients in SSA may improve triage decisions, allocation of treatment, and ultimately, outcomes.

Definitions and scoring systems that describe the severity of sepsis and predict outcomes have not been validated in septic patients in SSA.4,5 Many such scoring systems rely on frequent and diverse laboratory testing that are not often available in resource-limited settings. Compared with patients in most sepsis studies, critically ill patients in SSA are often younger with a higher prevalence of human immunodeficiency virus (HIV) infection.6 Additionally, there are microbiological differences in the etiology of bacteremia which differ by regions.7 For example, Salmonella is a leading cause of bacteremia in SSA. These epidemiological and microbiological differences may translate into differences in sepsis severity and mortality rates for patients in SSA compared with other populations.

We prospectively studied septic patients admitted to the adult medical ward of a government regional referral hospital in southwestern Uganda. The objective of this study was to determine in-hospital mortality caused by sepsis according to severity of illness.

MATERIALS AND METHODS

Site descriptions. Mbarara Regional Referral Hospital (MRRH) is located in Uganda in Mbarara municipality and is 286 km southwest of Kampala. It is a 400-bed hospital that serves a population of approximately 1.2–2.5 million people from surrounding districts in southwestern Uganda. It also doubles as a teaching hospital for the Faculty of Medicine at the Mbarara University of Science and Technology.

Site resource capacity. Patients considered for medical admission are initially evaluated in one of two admission rooms for the 54 bed medical ward, which is divided into male and female sections. Surgical and obstetric patients are evaluated and admitted elsewhere in the hospital. There are two functioning oxygen tanks and two functional oxygen concentrators on the ward. Vasopressor and inotropic medications are scarce on the medical ward and are rarely administered to septic patients. There is a separate two-bed intensive care unit (ICU) which is primarily reserved for surgical and intoxicated patients requiring mechanical ventilation. Patients with sepsis are rarely admitted to the ICU.

The hospital has a radiology department with X-ray and ultrasound facilities but no capability for computed tomography. It also has a clinical laboratory in which basic investigations, including microbiology, can be performed. The laboratory is enrolled in the International Organisation for Standardisation, and it maintained satisfactory performance throughout the study period.

Patient recruitment. From February 2009 to July 2009, patients were consecutively enrolled on week days during daytime hours from the two medical admission rooms. Patients were included if they were ≥ 18 years of age, admitted to the medical ward, and had a suspected infection and more than or equal to two of the systemic inflammatory response syndrome (SIRS) criteria (temperature > 38°C or < 36°C, heart rate > 90 beats/minute, or respiratory rate > 20 breaths/minute).4 The white blood cell (WBC) component of the SIRS criteria was not used for inclusion, because complete blood count results were not immediately available at the time of recruitment. Patients were excluded if they required triage to a surgical or obstetrics and gynecology ward, had received any treatment or intravenous fluids on the ward before recruitment, or had a suspected acute cerebrovascular accident or gastrointestinal hemorrhage.

Data collection and definitions. At the time of enrollment, consent was obtained from the patient or a surrogate (an accompanying family member or friend) if the patient could not provide consent. The study team observed patients until discharge or death, but the admitting medical team was responsible for clinical management. We retrieved the following data for each patient: demographics, history of presenting symptoms, examination findings, including vital signs, laboratory results, microbiology results, treatment, complications, and outcomes. We used the Sequential Organ Failure Assessment (SOFA) score6 to classify organ dysfunction as none, mild, moderate, or severe. We determined severity of sepsis using the criteria of the Surviving Sepsis Campaign.8

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signs and Glasgow Coma Scale (GCS), HIV serology status, and in-hospital mortality.

Laboratory investigations were obtained for each patient at the time of enrollment, including complete blood cell count (Beckman Coulter, Villepinte France), random blood glucose (Accu-Chek portable glucose analyzer; Roche Diagnostics, Mannheim, Germany), and whole-blood lactate (Accutrend Portable Lactate Analyzer; Roche Diagnostics, Mannheim, Germany). Blood cultures were obtained through aseptic inoculation of 10 mL blood into two aerobic blood culture bottles before antibiotic administration. Sub-culturing and species identification were performed using standard methods. Bacteremia was defined as bacterial isolation from one or more blood culture bottles. Cultures growing coagulase-negative staphylococci were considered contaminated and not included in the final analyses. Evaluation of malaria was performed through Field’s staining as previously described. All clinical and laboratory data were provided to the attending medical team as soon as they were available.

Enrolled patients without evidence of organ dysfunction were diagnosed with sepsis, and patients with organ dysfunction were diagnosed with severe sepsis. The criteria for organ dysfunction included acute encephalopathy (GCS < 15), a platelet count < 100,000/mm$^3$, whole-blood lactate concentration > 4 mmol/L, or systolic blood pressure (SBP) < 90 mmHg. Because of resource constraints, renal and liver functions were not assessed through laboratory testing. Urine output was not measured on the ward and could not act as a marker of renal dysfunction. Similarly, the lack of routine chest X-rays and pulse oximetry monitoring of the patients did not allow objective evaluation of pulmonary dysfunction. Lactate monitoring served as an objective marker of cardiovascular dysfunction rather than subjective evaluation of mottled skin or decreased capillary refill time.

Patients were diagnosed with septic shock if they had an initial SBP < 90 mmHg or mean arterial pressure (MAP) < 60 mmHg that was refractory to resuscitation with a 2-L bolus of normal saline given over 2 hours. The initial bolus of 2 L was followed by 500-mL boluses every 30 minutes when necessary as indicated by an SBP < 90 mmHg and no signs or symptoms of fluid overload. The primary outcome measured was in-hospital mortality.

**Statistical analysis.** Data were entered into an access database, FoxPro for windows (version 2.6; Microsoft), and SPSS software, version 18.0 (SPSS Inc.) was used for all statistical analyses. Patient characteristics were reported as frequency with percentage for categorical variables, mean with standard deviation (SD) for normally distributed continuous variables, and median with interquartile range (IQR) for continuous variables that were not normally distributed. Cox regression was used to calculate hazard ratios (HRs) for univariate and adjusted hazard ratios (AHRs) for multivariate analyses. Markers of severity of illness (i.e., SIRS criteria, sepsis category, and aggregate organ dysfunction) and covariates with a conservatively set $P$ value ≤ 0.30 were included in the multivariate Cox regression model. Only markers of severity of illness and those variables with a final two-sided $P$ value < 0.05 were considered independently associated with in-hospital mortality and retained in the final multivariate Cox regression model. Kaplan–Meier estimates were used to graphically present in-hospital mortality as a function of aggregate organ dysfunction. The area under the receiver-operating characteristic (AUROC) curve provided predictive use of sepsis category and aggregate organ dysfunction for in-hospital mortality. A $P$ value < 0.05 was considered statistically significant. Based on a sample size of 150 with 80% power and a two-sided $\alpha < 0.05$, the statistical power was adequate to detect a medium-sized effect of aggregate organ dysfunction on mortality (W of 0.27).

**Ethics statement.** Approval was obtained from the institutional review board of Mbarara University of Science and Technology as well as the Mbarara Faculty Research and Ethics committee.

**RESULTS**

We screened 186 patients for inclusion from February 2009 to July 2009. Of these patients, 22 had two or more SIRS parameters but no suspicion of infection, 8 had received treatment on the ward before recruitment to the study, 4 had suspected upper gastrointestinal bleeding, and 2 had a suspected cerebrovascular accident. The remaining 150 patients were consented, and their data were analyzed.

**Background and admission characteristics.** The patients were predominantly young HIV-infected men of Nkole ethnicity who lived in Mbarara and its surrounding districts. The mean (±SD) age was 35 ± 14 years (Table 1). A majority of the HIV-infected patients, 68 of 94 (72%), were receiving *Pneumocystis*
jirouei prophylaxis with trimethoprim and sulfamethoxazole, but only 21 of 94 (22%) were receiving antiretroviral therapy. Outpatient antibiotics had been taken by 81 of 148 (55%) patients before admission to the medical ward. An abnormal temperature was found in 133 of 150 (89%) patients, and 95 of 150 (63%) patients were found to have a respiratory focus of infection.

**Microbiology.** Bacteremia was detected in 39 of 150 (26%) patients, and *Staphylococcus aureus*, in 24 of 39 (61%) patients, was the predominant isolate followed by *Streptococcus pneumonia* in 7 of 39 (18%) patients. Other bacteria isolated included non-Typhi Salmonella (3 of 39; 8%), *Escherichia coli* (2 of 39; 5%), Salmonella Typhi (1 of 39; 3%), *Enterobacter cloacae* (1 of 39; 3%), and *Haemophilus influenza* (1 of 39; 3%). The malaria smear was positive in a minority of patients (7 of 150; 5%).

**Severity of illness.** A majority of patients, 120 of 148 (81%), met three or four SIRS criteria. Of the four SIRS criteria, the elevated heart rate criterion was most frequently noted (143 of 150; 95%). Sepsis, severe sepsis, and septic shock were diagnosed in 52 (35%), 71 (47%), and 27 (18%) of 150 patients, respectively. Of the 98 patients with end-organ dysfunction, 47 (31%) had single-organ dysfunction, 36 (24%) had two-organ dysfunction, and 15 (10%) had three- or four-organ dysfunction (Table 1).

**Mortality.** In-hospital mortality occurred in 45 of 150 (30%) enrolled patients (Table 2). The background rate of in-hospital mortality at MRRH was approximately 13%. Death occurred on the first day of admission for 18 of 45 (40%) patients that died in hospital. The median time from admission until death was 3 days (IQR = 1–5). For patients that survived to discharge, the median length of stay was 6 days (IQR = 4–9).

In-hospital mortality occurred in 5 of 52 (9.6%) patients with sepsis, 24 of 71 (33.8%) patients with severe sepsis, and 16 of 27 (59.3%) patients with septic shock. Within categories of sepsis, increasing organ dysfunction was associated with increased mortality (Figure 1).

In the univariate analysis, the clinical correlates associated with in-hospital mortality included GCS < 15 (HR = 2.4, 95% CI = 1.3–4.4, \( P = 0.005 \)), SBP < 90 mmHg (HR = 2.2, 95% CI = 1.2–3.9, \( P = 0.01 \)), and MAP < 60 mmHg (HR = 2.4, 95% CI = 1.2–4.6, \( P = 0.01 \)). Laboratory findings associated with in-hospital mortality included thrombocytopenia (HR = 2.1, 95% CI = 1.1–3.7, \( P = 0.01 \)), lactate > 4.0 mmol/L (HR = 3.0, 95% CI = 1.8–5.0, \( P = 0.001 \)), urea > 4.0 mmol/L (HR = 2.5, 95% CI = 1.4–4.5, \( P = 0.001 \)), and Cr > 110 μmol/L (HR = 2.9, 95% CI = 1.7–5.0, \( P = 0.001 \)).
CI = 1.6–5.3, \( P < 0.001 \), and hypoglycemia (HR = 2.8, 95% CI = 1.3–6.0, \( P = 0.008 \)).

Factors related to severity of illness were also evaluated in the univariate analysis. Compared with patients with sepsis, there was a higher risk of in-hospital mortality for patients with severe sepsis (HR = 3.4, 95% CI = 1.3–8.9, \( P = 0.01 \)) or septic shock (HR = 7.2, 95% CI = 2.6–19.7, \( P < 0.001 \)). Similarly, compared with patients with no organ failure (i.e., patients with sepsis), there was a higher risk of in-hospital mortality with increasing organ dysfunction (two dysfunctional organs: HR = 3.8, 95% CI = 1.4–10.7, \( P = 0.01 \); more than or equal to three dysfunctional organs: HR = 15.1, 95% CI = 4.9–46.8, \( P < 0.001 \)) (Figure 2).

In the multivariate analysis, severe sepsis (AHR = 2.9, 95% CI = 1.0–8.2, \( P = 0.04 \)), septic shock (AHR = 5.7, 95% CI = 1.6–20.3, \( P = 0.007 \)), and three or more three dysfunctional organs (AHR = 2.9, 95% CI = 1.1–7.3, \( P = 0.03 \)) increased the risk of in-hospital mortality. The presence of three SIRS criteria was associated with improved in-hospital survival (AHR = 0.4, 95% CI = 0.2–0.9, \( P = 0.04 \)). ROC curve analysis revealed AUROCs of 0.7 (95% CI = 0.6–0.8, \( P < 0.001 \)) and 0.8 (95% CI = 0.7–0.9, \( P < 0.001 \)) for sepsis category and aggregate organ failure, respectively (Figure 3). In addition, a stepwise Cox regression analysis using overall model coefficients was used to specifically determine whether organ failure significantly increased predictive accuracy over that of sepsis category. Adding aggregate organ dysfunction to the multivariate equation that included the sepsis category statistically significantly improved the model (change from previous step, \( \chi^2 = 9.7, P = 0.008 \)) but the opposite did not (change from previous step, \( \chi^2 = 5.4, P = 0.07 \)).

**DISCUSSION**

A delay in the initiation of antimicrobial therapy and fluid resuscitation increases mortality in patients with severe sepsis. Therefore, it is imperative to quickly identify severely ill patients who are most in need of life-saving therapy. Here, we have shown that the severity of illness in septic patients with a medical illness in rural Uganda is easily measurable and identifies patients with a high likelihood of in-hospital mortality. Specifically, knowing aggregate organ dysfunction provided additional predictive value for in-hospital mortality compared with knowing sepsis category alone.
Assessment of critically ill patients in SSA often occurs in the setting of limited clinical laboratory infrastructure. Accordingly, scoring systems that are routinely used in resource-rich settings are unlikely to be applicable in this region. Our ability to determine the severity of illness in septic patients was based on a limited array of clinical and laboratory tests that, with the exception of the platelet count, were performed at the bedside. These tests included whole-blood lactate testing, which was performed with a validated handheld monitor that is increasingly being used in SSA.

Stark contrasts in population demographics between septic patients in SSA and Europe and North America may also diminish the validity of previously studied severity scoring systems when applied to critically ill patients in SSA. For example, many scoring systems use advanced age as a risk criterion, but the mean age in our study was an alarming 35 years of age compared with an average age of 61 years for septic patients in the United States. The prevalence of HIV infection was also much higher in our population than previously studied populations in Europe and North America. However, in our analysis, HIV seropositivity was not independently associated with mortality.

Previous studies of bacteremia in SSA have implicated non-Typhi Salmonella as the most frequent cause of bacteremia. In our study, *S. aureus* was the predominant cause of bacteremia. Perhaps because of the limited number of positive blood cultures, bacteremia was not a risk factor for in-hospital mortality in our study. However, clinicians in similar areas should be aware that *S. aureus* is an emerging cause of bacteremia that may not be adequately treated with commonly empirically prescribed antibiotics such as penicillin and chloramphenicol.

Despite these differences in our study population compared with others, our finding that aggregate organ dysfunction is an important predictor of sepsis mortality is similar to previous studies. Validated scoring systems for severe sepsis, including the Sequential Organ Failure Assessment (SOFA) and the Multiple Organ Dysfunction Score (MODS), use a graded scale to quantify the degree of organ dysfunction, which provides a refined prediction of mortality. These scoring systems are often applied repeatedly to measure the change in organ function over time. However, in the setting of a regional referral hospital in SSA, even if laboratory capability exists, it is often not possible to repeat laboratory testing. This limitation makes longitudinal evaluation of septic patients challenging.

Both SOFA and MODS incorporate non-laboratory assessments in their scoring systems. Despite clarion calls for the routine administration of supplemental oxygen for septic patients, it is rarely routinely available in our setting, and mechanical ventilation of septic patients occurs infrequently. Additionally, blood gas analysis is not performed; therefore, measurement of the PaO₂/FiO₂ ratio, a component of both SOFA and MODS scores, is not possible. Furthermore, SOFA scores require the determination of vasopressor use, but these medicines are rarely used for patients with septic shock in SSA.

In our setting, septic patients are infrequently admitted to the two-bed dedicated ICU, but selecting the most severely ill patients with a high chance of early mortality for treatment in the ICU may improve outcomes. This observation mirrors studies in regions outside of SSA that have suggested that there is a bias against admission of HIV-infected patients with severe sepsis to the ICU because of perceived futility. Beyond predicting severity of illness, some sepsis scoring systems are used to determine patient eligibility for certain therapies. For example, it is currently recommended that patients have an Autonomic Physiology and Chronic Health Evaluation (APACHE) II score of at least 25 for the administration of activated protein C (APC). Although expensive medications such as APC are not available in SSA, a rapid assessment of critically ill patients may similarly allow triage of patients to an ICU, where available, or a higher level of care and rapid administration of antimicrobials and fluid resuscitation.

Our study does have important limitations. Our primary outcome was in-hospital mortality. This focus may have underestimated the true mortality rate from sepsis in these patients, because death from sepsis is known to occur at 30 days and beyond. Additionally, because of limited resources, we were not able to measure organ dysfunction over time, which may provide a more accurate estimate of morbidity and mortality for septic patients. A battery of laboratory tests might also have revealed organ damage that was not noted with our limited assessment of each patient. Therefore, additional studies are required to determine if our findings can be generalized to similar settings with different or additional ability to test for organ dysfunction.

Despite these limitations, we have shown that septic patients admitted to a regional referral hospital in SSA can be stratified for risk of in-hospital death according to sepsis category and their cumulative organ dysfunction. Treatment algorithms for sepsis have been adopted that stipulate treatment based on severity of illness in areas outside of SSA. Sepsis severity assessment in SSA may ultimately allow adoption of a resource-appropriate sepsis algorithm that will decrease mortality from sepsis. Such an algorithm could be included in globally accessible guidelines such as the World Health Organization's Integrated Management of Adolescent and Adult Illness.