MORTALITY AMONG PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

HOSPITALIZED WITH SEPSIS: HIGH VARIATION AMONG U.S. HOSPITALS

Maria G. Tektonidou, Abhijit Dasgupta, and Michael M. Ward

Maria G. Tektonidou, MD, First Department of Propaedeutic Internal Medicine, Joint Academic Rheumatology Program, Medical School, National and Kapodistrian University of Athens Athens, Greece

Abhijit Dasgupta, PhD, Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

Michael M. Ward, MD, MPH, Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

Address for correspondence: Michael M. Ward, MD, NIAMS/NIH, Building 10 CRC, Room 4-1339, 10 Center Drive, Bethesda, MD 20892. Telephone (301) 496-7263; Facsimile (301) 480-2714; electronic mail [wardm1@mail.nih.gov](mailto:wardm1@mail.nih.gov).

Running title: Hospital variation in sepsis mortality in SLE

The authors have no financial or commercial conflicts of interest related to this work.

ABSTRACT

Infections account for 13% to 37% of hospitalizations among patients with systemic lupus erythematosus (SLE), and are major determinants of in-hospital mortality [1-3]. Although respiratory infections are the most common causes of infection-related hospitalizations, bacteremia and sepsis are the most frequent causes of infection-related mortality [4]. Hospitalization rates for sepsis in SLE in the U.S. increased 3.6-fold between 2002 and 2011 [5]. In-hospital mortality among patients admitted with sepsis was 11.4% among young and middle-aged adults with SLE [5].

In the general population, in-hospital mortality among patients admitted with sepsis varies widely among hospitals [6]. For example, among 188 U.S. academic-affiliated hospitals, in-hospital mortality ranged from 0.9% to 18.2% [7]. Importantly, this variation persisted after adjustment for differences in the severity of illness and comorbidities among patients at different hospitals. This variation suggests that differences in the use of key interventions and processes of care may contribute to differences in mortality. Processes of care may, in turn, be associated with particular hospital characteristics. Some evidence suggests that urban hospitals, academic hospitals and those that treat higher volumes of patients with sepsis have better outcomes [7, 8]. It is not known if sepsis-related mortality among patients with SLE also varies among hospitals. High variation would suggest that there may be clinical practices that hospitals with good outcomes could share with other hospitals to improve outcomes for more patients.

The aim of this study was to examine the degree of variation in in-hospital mortality among adults with SLE and sepsis among a nationally representative sample of U.S. hospitals. We compared sepsis-related mortality in patients with SLE to that of patients without SLE within hospitals to identify hospitals that had better or worse SLE-specific outcomes, while accounting for the differences in the nature of patients seen at different hospitals. We also sought to identify hospital characteristics associated with lower SLE-specific mortality. We hypothesized that mortality among patients with SLE and sepsis would vary widely among hospitals, and would be associated with a hospital’s experience in treating patients with SLE.

METHODS

Data source. We used the Nationwide Inpatient Sample (NIS), which is the largest all-payer inpatient database in the U.S. NIS contains data from approximately 8 million hospitalizations from over 1,000 hospitals sampled annually to approximate 20% of all discharges from U.S. community hospitals, excluding rehabilitation and long-term hospitals [9]. NIS includes discharge abstracts of all hospitalizations in the selected hospitals, and uses International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) codes to record discharge diagnoses and procedures. The NIS database also includes information on patient demographic characteristics, health insurance, length of stay, discharge disposition, and selected hospital characteristics. Data are provided for each hospitalization, but NIS does not include unique patient identifiers, precluding tracking of patients over time. A comprehensive synopsis on NIS data is available at http://www.hcup-us.ahrq.gov.

We included data from 2002 to 2011, after which the sampling scheme of NIS changed. Data were provided through a data use agreement. This study was exempted from human subjects review by the National Institutes of Health Office of Human Subjects Research Protection.

Study population and variables. Using data from all study years, we identified all hospitalizations of adults age 18 to 64 for which sepsis was the primary discharge diagnosis, based on ICD-9 codes 038 and 790.7. We excluded hospitalizations of patients age 65 or older to focus on sepsis that may be more associated with SLE and its treatment than with comorbidities. Among this group, we identified hospitalizations for adults with SLE using ICD-9 code 710.0 listed as any secondary discharge diagnosis. We have previously validated this approach to identification of patients with SLE [5]. We excluded hospitalizations of patients with SLE if these also included discharge codes for other connective tissue diseases.

We extracted data on patient age, gender, insurance status (Medicare, Medicaid, private or other), and all discharge diagnoses. Data on ethnicity were not consistently available, because some states prohibited its reporting. We used the Elixhauser Comorbidity score as the measure of severity of illness [10]. This measure is a weighted sum of 30 conditions recorded as present among the discharge diagnoses (possible range -19 to 89, with higher scores indicating more serious comorbidity). It has been extensively validated for in-hospital mortality risk adjustment [11]. We also included the use of mechanical ventilation, identified by the ICD-9 procedure code 967, as a marker of sepsis severity. Whether the patient was treated in an intensive care unit was not recorded in the database.

NIS included unique hospital identifiers, but hospitals are anonymous. Hospital characteristics included in NIS were hospital size (based on number of beds), geographic region (Northeast, Midwest, South, West), and teaching status. Hospital size was reported as small, medium or large, criteria for which varied depending on the region, location, and year. Hospital location and teaching status were reported as urban teaching hospital, urban non-teaching hospital, and rural hospital. Additionally, we defined SLE-high volume hospitals as those with 50 or more hospitalizations of patients with SLE per year.

The outcome was in-hospital mortality, defined as death from any cause during the index hospitalization.

Statistical analysis. The unit of analysis was the hospital. We limited the analyses to hospitals that had five or more sepsis-related hospitalizations among patients with SLE. This number represented a balance between including a large number of hospitals while also not characterizing hospitals based on the outcomes of very few patients.

We computed absolute mortality frequency among patients with SLE for each hospital. We also compared the observed mortality risks among patients with SLE relative to their expected mortality risk, based on the outcomes of patients without SLE treated for sepsis in the same hospital. The latter measure provided an assessment of whether patients with SLE had higher, lower, or similar mortality risks to those of other patients at a given hospital. We first modeled the risk of death among the patients with sepsis but without SLE, conditional on the admission hospital and using patient-level data on age, gender, type of health insurance, Elixhauser score, and ventilator use as covariates (modeling details are provided below). We then used this model to predict the risk (or probability) of death for each patient with SLE and sepsis using the observed covariates for that patient. This gives the risk of death for each patient with SLE under the assumption that they had the same conditional risk of death as patients without SLE but with the same age, gender, insurance, Elixhauser score, and ventilator use. Adding these predicted probabilities for patients in a given hospital gives the expected number of deaths (E) among patients with SLE. We then compared the observed number of deaths (O) among patients with SLE at each hospital with the expected number of deaths. The O/E ratio is therefore akin to a standardized mortality ratio.

We used machine learning methods to compute the expected number of deaths per hospital among patients with SLE. To flexibly model the conditional risk of death, we use the XGBoost algorithm [12]. This modern form of gradient boosted regression trees uses gradient descent to optimize a loss function (here, the logistic loss function), and boosting helps reduce the bias that weak learners exhibit while maintaining the low variance characteristics of the weak learners. This method has been shown to produce low bias, low variance predictors on a wide variety of data sets, provided it is trained well. Boosted decision trees have been found to work very well in lower-dimensional problems like this one, doing better than a random forest model [ref]. To train the XGBoost model, we used the R package xgboost, (R version 3.4) [13,14]. We trained this model on patients without SLE, with 5-fold cross-validation (using the R package caret) [15] to find optimal tuning parameters of our model using a grid search as implemented in the package. Our optimal trained model achieved a cross-validated average area under the curve of 0.86, indicating excellent discrimination. Predicted mortality, based on the model, fit the observed data well (Supplement). We then use this trained model to score each patient to get their predicted probability of death. Within hospitals, we then added these predicted probabilities to obtain the expected number of deaths. Finally, we compared the observed number of deaths per hospital with the expected number of deaths (O/E ratio) under the model. The expected conditional probabilities of death use information across all hospitals and patients through the XGBoost model. An O/E ratio of 1.0 indicates that the observed mortality among patients with SLE and sepsis was the same as that predicted for patients with the same covariate set, given the outcomes of patients without SLE. We chose an O/E ratio of 2.0 (i.e. twice the predicted mortality) to indicate hospitals that had excess mortality among patients with SLE admitted with sepsis. Because our analysis was conditional on the hospital, we did not use NIS sampling weights in our modeling.

We used classification and regression trees to identify the characteristics of hospital subsets with poor relative SLE mortality (O/E ≥ 2.0). Candidate characteristics were hospital location/teaching status, size, region, and SLE volume.

RESULTS

We analyzed data from 423 hospitals that included 4001 hospitalizations of patients with SLE and sepsis and 202,888 hospitalizations of patients with sepsis without SLE. The number of SLE patients per hospital ranged from 5 to 66. Patient characteristics are shown in Table 1. Across all hospitals, 11.5% of patients with SLE and 13.1% of patients without SLE died during the hospitalization. The main predictors of mortality were ventilator use and high Elixhauser score (Figure 1).

Hospital-specific crude mortality among patients with SLE and sepsis ranged from 0% (at 163 hospitals) to 60%, with a median of 11.11%. The O/E ratio of relative SLE mortality ranged from 0 to 10.5, with a median of 0.94 (Figure 2). In the hospital performing at the mid-range of all hospitals, patients with SLE were 47% more likely to die compared to patients without SLE when admitted with sepsis. Seventy-seven hospitals (18%) had an O/E ratio ≥ 2.0, with mortality among patients with SLE at least two times more likely than mortality among those without SLE.

The most important hospital-level predictor of an O/E ratio ≥ 2.0 was SLE volume. Twenty-seven percent of low volume hospitals had an O/E ratio ≥ 2.0, compared to only 15% of high volume hospitals (Figure 3). Among high volume hospitals, those in the Northeast comprised a larger proportion of hospitals with a high O/E than those in other regions. Bedsize and location/teaching status were not discriminative.

DISCUSSION

In this national population-based study, we found a large variation in in-hospital mortality among patients with SLE and sepsis. Observed to expected ratios for mortality ranged from 0 to X compared to other hospital’s experience with sepsis in SLE, and ranged from 0 to X compared to the outcomes of patients without SLE. More favorable mortality outcomes were present in hospitals that admitted larger numbers of patients with SLE for any reason.

Our approach to compare mortality experiences among hospitals is novel in several respects. First, we examined hospitals relative to one another using O/E ratios, with the expected number based on risk-adjusted estimates of mortality among hospitals. Second, we used boosted classification trees to model predicted mortality, with highly accurate prediction. Third, we assessed hospitals both on the outcomes of other patients with SLE, and relative to the outcomes of patients without SLE. The former measures variation in the outcomes of patients with SLE that may similarly affect patients without SLE at these hospitals, while the latter measures differences in outcomes specific to patients with SLE.

Our findings of hospital variation in sepsis-related mortality of patients with SLE are consistent with the results of a few studies examining this variation in the general population. High variation among 188 US academic medical units was found in observed mortality (median = 8.6%; range = 0.9%-18.2% [7]). A retrospective multicenter study of 4,605 patients from 28 intensive care units from the Dutch National Intensive Care Evaluation registry showed that the risk-adjusted mortality rates for patients with severe sepsis ranged from 14.3% to 47.9% [16].

Variations among hospitals indicate . . . Lit on hospital features assoc with better/worse survival

Variation in mortality rates can be attributed to heterogeneous patient case-mix and differences in organizational structure and processes of care ( ). In our study, the variation in mortality among hospitals was not associated with differences in patient characteristics. Possible relations between in-hospital mortality related to sepsis and patient characteristics have been previously examined in the general population. Analysis of severe sepsis discharges from all community hospitals in California between 2005 and 2010 showed that in-hospital mortality increased with increasing age and was higher among males, whites, Asian/Pacific Islanders, non-Hispanics, and those with Medicare coverage ( ). A large study using data from all nonfederal hospitals in seven U.S. states showed that in addition to age, differences in mortality were explained by differences in underlying comorbidity and the site of infection( ). Comorbidities in our study…..

Substantial variation may exist in the processes of care between various hospitals which can explain the differences in mortality rates. Outcomes of sepsis are significantly impacted by the performance of time-sensitive and resource-dependent measures, such as fluid resuscitation, interhospital transfer, subspecialist referral, and intensive care. Earlier studies showed a significant reduction in sepsis mortality with early goal-directed therapy ( ), which led to the development of evidence-based guidelines on sepsis control and management ( ). Implementation of a severe sepsis bundle, such as the Surviving Sepsis Campaign guidelines, has resulted to significant in-hospital mortality reduction ( ). A recent systematic review and meta-analysis of fifty observational studies showed that performance improvement programs were associated with increased compliance to management sepsis bundles and with a reduction in sepsis-related mortality (OR = 0.66, N = 434,447)( ).

Differences among hospitals in processes of care may be associated with differences in structure and organizational hospital characteristics such as the type of hospital, hospital case volume and personnel staffing and workload. We found that SLE patients with sepsis admitted at ..urban/teaching hospitals ..and at high SLE-volume hospitals had lower in-hospital mortality. Large cohort or population-based studies for sepsis in the general population showed that hospitalizations in large, urban/teaching, and high volume hospitals have been associated with better outcomes ( ). A retrospective study using the NIS data from 646,988 patient discharges with severe sepsis from 3,487 hospitals between 2002 and 2011, demonstrated an association between a higher severe sepsis case volume and decreased mortality ( ). A recent meta-analysis provided also evidence for an inverse relationship between annualized case volume and mortality in patients with sepsis ( ). This likely is a result of increased provider expertise in association with higher adherence to best practice guidelines. For example, in a large cohort of U.S. patients with sepsis, select evidence-based processes of care were more likely implemented at high-volume hospitals ( ).

Our results showed lower adjusted risk for inpatient mortality among hospitals of high SLE volume. For many medical conditions and surgical procedures, patient outcomes are better when treatment is provided at hospitals that have greater experience treating patients with similar conditions ( ). Ward showed that in a sample of 9989 patients with SLE hospitalized in acute care hospitals in California from 1991 to 1994, patients hospitalized at hospitals that admitted large numbers of patients with SLE had a lower risk of in-hospital mortality than those admitted to less experienced hospitals ( ). These findings suggest that differences specifically in the management of SLE rather than differences in the general quality of medical care may attribute to better outcomes.

The significant variation among hospitals in in-hospital mortality suggests potential for quality improvement especially at low performing units. In addition, findings of the impact of specific hospital characteristics on inpatient mortality can be implemented to improve processes of care and outcomes. Policies such as selective referral may be suggested based on the relationship between [size/.. academic status?] and inpatient mortality risk. Based on the relationship between high SLE-volume hospitals and mortality rates, referral at highly experienced hospitals may also be suggested. However, caution must be used in translating these findings. Referral offers the possibility of expanding access to high-quality care, however, transfer of critically ill patients is not without risks and its impact on inpatient mortality risk in SLE patients is not known. Better understanding of the underlying mechanisms for hospital variation in sepsis-related mortality in SLE is crucial.

The strengths of this study include the large, nationally representative and population-based sample, and data covering many years. In an effort to provide reliable results, we included outcomes even at very low frequencies of hospitalization according to prior evidence. One limitation is the lack in the NIS of all the clinical and hospital characteristics or other aspects of quality of care such as processes of care that likely affect outcomes. However, we used rigorous statistical techniques and accounted for multiple relevant patient and hospital characteristics in order to have valid mortality estimates. Another limitation is that we used hospital discharge diagnoses which may be different from the diagnoses at admission, and therefore, causality of sepsis and mortality cannot be firmly established. Lastly, since the NIS contains only inpatient data, we didn’t capture deaths occurring after discharge.

**References**

1. Petri M, Genovese M. Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort. J Rheumatol. 1992;19:1559-65.
2. Goldblatt F, Chambers S, Rahman A, Isenberg DA. Serious infections in British patients with systemic lupus erythematosus: hospitalisations and mortality. Lupus. 2009;18:682–9.
3. Yang Y, Thumboo J, Earnest A, Yong SL, Fong KY. The effect of comorbidity on hospital mortality in patients with SLE from an Asian tertiary hospital. Lupus. 2014;23:714-20. doi: 10.1177/0961203314522340. Epub 2014 Feb 13.
4. Rúa-Figueroa Í, López-Longo J, Galindo-Izquierdo M, Calvo-Alén J, Del Campo V, Olivé-Marqués A, et al. Incidence, Associated Factors and Clinical Impact of Severe Infections in a Large, Multicentric Cohort of Patients With Systemic Lupus Erythematosus. Semin Arthritis Rheum. 2017 Jan 27. pii: S0049-0172(17)30075-6. doi: 10.1016/j.semarthrit.2017.01.010.
5. Tektonidou MG, Wang Z, Dasgupta A, Ward MM. Burden of Serious Infections in Adults With Systemic Lupus Erythematosus: A National Population-Based Study, 1996-2011. Arthritis Care Res (Hoboken). 2015;67:1078-85.
6. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals: estimating potentially avoidable deaths. JAMA. 2000;283:1159–66
7. Wang HE, Donnelly JP, Shapiro NI, Hohmann SF, Levitan EB. Hospital variations in severe sepsis mortality. Am J Med Qual. 2015;30:328-36.
8. Fawzy A, Walkey AJ. Association Between Hospital Case Volume of Sepsis, Adherence to Evidence-Based Processes of Care and Patient Outcomes. Crit Care Med. 2017;45:980-988.
9. Healthcare Cost and Utilization Project (HCUP). Overview of the Nationwide Inpatient Sample (NIS). 2013. URL: <http://www>. hcup-us.ahrq.gov/nisoverview.jsp.
10. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care 2009; 47:626-33.
11. Sharabiani MT, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. Med Care 2012; 50:1109-18.
12. Chen T, Guestrin C. Xgboost: A scalable tree boosting system. In: Proceedings of the 22nd ACM SIKDD international conference on knowledge discovery and data mining. ACM 2016; 785-94.
13. Chen T, He T, Benesty M, Khotilovich V, Tang Y. xgboost: Extreme Gradient Boosting (2017). R package version 0.6-4. https://CRAN.R-project.org/package=xgboost.
14. R Core Team. R: A language and environment for statistical computing (2017). R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org>.
15. Kuhn M, Wing J, Weston S , Williams A, Keefer C, Engelhardt A, et al. caret: Classification and Regression Training (2017). R package version 6.0-77. <https://CRAN.R-project.org/package=caret>.
16. Peelen L, de Keizer NF, Peek N, Scheffer GJ, van der Voort PH, de Jonge E. The influence of volume and intensive care unit organization on hospital mortality in patients admitted with severe sepsis: a retrospective multicentre cohort study. Critical Care 2007; 11:R40. doi.org/10.1186/cc5727.

* *Patient and hospital characteristics associated with inpatient severe sepsis mortality in California, 2005–2010. Crit Care Med 2012; 40:2960–6 (overall)*
* *Relation between volume and outcome for patients with severe sepsis in United Kingdom: Retrospective cohort study. BMJ 2012; 344:e3394*
* *The relationship between hospital volume and mortality in severe sepsis. Am J Respir Crit Care Med 2014; 190:665–74*
* Ward MM. Hospital experience and mortality in patients with systemic lupus erythematosus. Arthritis Rheum 1999;42:891-8
* Relationship between Annualized Case Volume and Mortality in Sepsis. A Dose–Response Meta-analysis. (Anesthesiology 2016; 125:168-79)

Table 1. Characteristics of patients with systemic lupus erythematosus (SLE) and without SLE who were hospitalized with sepsis in 2002 – 2013, by mortality status. Values in parentheses are standard errors.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | SLE | | Without SLE | |
|  | Alive | Dead | Alive | Dead |
| Mean age, years | 44.6 (0.26) | 48.0 (0.55) | 49.2 (0.08) | 52.7 (0.08) |
| Women, % | 88.7 (0.57) | 85.6 (1.69) | 49.4 (0.21) | 46.4 (0.36) |
| Medicare, % | 38.9 (1.03) | 42.5 (2.46) | 29.4 (0.35) | 30.1 (0.40) |
| Medicaid, % | 22.6 (0.90) | 19.7 (1.99) | 21.8 (0.50) | 24.2 (0.64) |
| Private insurance, % | 31.7 (1.08) | 27.8 (2.18) | 36.1 (0.75) | 32.6 (0.75) |
| Other insurance, % | 6.8 (0.51) | 10.0 (1.40) | 12.7 (0.40) | 13.1 (0.48) |
| Mean Elixhauser score | 7.44 (0.13) | 11.6 (0.38) | 8.2 (0.07) | 13.7 (0.12) |
| Ventilator use, % | 11.0 (0.59) | 70.0 (2.17) | 14.2 (0.31) | 66.4 (0.56) |