Predictors of Long-term Mortality After Severe Sepsis in the Elderly

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Abstract: *Background:* Mortality rates after severe sepsis are extremely high, and the main focus of most research is short-term mortality, which may not be associated with long-term outcomes. The purpose of this study was to examine long-term mortality after a severe sepsis and identify factors associated with this mortality. *Methods:* The authors performed a population-based study using Veterans' Affairs administrative data of patients aged 65 years and older. The outcome of interest was mortality > 90 days following hospitalization. Our primary analyses were Cox proportional hazard models to examine specific risk factors for long-term mortality. *Results:* There were 2,727 patients that met the inclusion criteria. Overall mortality was 55%, and 1- and 2-year mortality rates were 31% and 43%, respectively. Factors significantly associated with long-term mortality included congestive heart failure, peripheral vascular disease, dementia, diabetes with complications and use of mechanical ventilation. Smoking cessation and cardiac medications were associated with decreased long-term mortality rates. *Conclusions:* The authors identified several factors, including receipt of mechanical ventilation, which were significantly associated with increased long-term mortality for survivors of severe sepsis. This information will help clinicians discuss prognosis with patients and their families.

Key Indexing Terms: Sepsis; Mortality; Predictors; Comorbid conditions. **[Am J Med Sci 2014;347(4):282–288.]**

Sepsis is defined as a systemic inflammatory response that is secondary to an acute infection.[1] Over the past 30 years, the incidence of sepsis and sepsis-related mortality has increased,[2] and it is now the 10th leading cause of death in the United States.[3] Approximately 750,000 people are affected annually by severe sepsis and more than one half of the effected population is aged older than 65 years.[4] With an increasingly aging population in the United States, the incidence of sepsis is likely to increase in the future.

Past studies have focused on short-term outcomes after severe sepsis and have shown that 28-day mortality rates average 28%.[4] Martin et al[2] reported not only a decrease of in-hospital mortality rates from approximately 28% to 18% over the period of 1979 to 2000 but also an increase in the incidence of sepsis seen in the United States. There has been little research on the long-term mortality of severe sepsis but the few studies have postulated that mortality rates at 1 year are extremely high and that current therapies based on reducing short-term mortality may be insufficient to reduce this long-term mortality.[5] Weycker et al[6] reported a 1-year mortality rate of 51% and a 5-year mortality rate of 74% and showed a direct relationship between mortality rates and Charlson comorbidity scores, in addition to number of sites of organ dysfunction. Benjamim et al[5] reported 1-year mortality rates of about 26% after severe sepsis. Another study comparing trauma patients with sepsis patients showed a 2-year cumulative mortality rate of 67% in sepsis patients, which was significantly higher than the 43% mortality rate of patients who were hospitalized for trauma.[7] There is a need for more data in this area because the high rates of long-term mortality after severe sepsis indicate that there may need to be a change in the treatment of patients both initially and during follow-up. In addition, an additional examination of the relationship between long-term mortality and specific comorbid conditions may give clinicians a better idea of prognosis for those who survive at least until discharge.

Our aim is to use the extensive data available in the Department of Veterans Affairs (VA) health care system to examine long-term (>90 days) mortality rates of patients aged older than 65 years hospitalized with severe sepsis and to assess the relationship between mortality and different variables such as sociodemographic factors, previous comorbid conditions, severity of illness, organisms isolated at the time of infection, drug or alcohol abuse and outpatient medications taken.

METHODS

Our study used data from the administrative databases of the Department of VA health care systems. The data were a collection of clinical data from all of the VA hospitals and outpatient clinics. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved this study under expedited review. Waiver of informed consent was obtained for this study.

Inclusion and Exclusion Criteria

Patients included in this study:

a. were aged 65 years or older on the date of admission;
b. had at least 1 outpatient clinic visit in the year preceding the index admission so as to ensure that information on prior comorbid conditions is available;
c. received at least 1 active and filled outpatient medication within 90 days of admission;

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d. were hospitalized during the fiscal years 2002 to 2007 (October 2001-September 2007);
e. had a previously validated discharge diagnosis of sepsis[2,8]—primary or secondary code of 038-038.9 plus at least 1 code for acute organ dysfunction—518.8x, 786.09, 799.1, 96.7, 458.0, 785.5x, 458.x, 796.3, 584, 580, 585, 39.95, 570, 572.2-3, 286.2, 286.6, 286.9, 287.3-5, 276.2, 293, 348.1, 348.3, 780.01, 780.09, 89.14; and
f. received at least 1 dose of antimicrobial therapy within the first 48 hours of admission.

We excluded any patient who died within 90 days of index admission so that we would be able to clearly examine factors associated with long-term mortality. If a patient was admitted more than once during the study period, only the first hospitalization was included.

Data Sources

We used demographic, utilization and comorbidity data from the National Patient Care Database, pharmacy data from the VA Decision Support System National Data Extracts and Pharmacy Benefits Management and vital status information from VA's Vital Status file, which incorporates data from veterans' death benefits claims, inpatient deaths, Medicare Vital Status files and the Social Security Administration death master file. Encrypted patient identifiers link the information across these databases.

We obtained demographic information (age, sex, race and marital status) from inpatient and outpatient data. Race categories included white, black, Hispanic and other/unknown. ICD-9 codes for tobacco use (305.1, V15.82), smoking cessation clinic use and/or use of medications for the treatment of nicotine dependence (Zyban, nicotine replacement or varenicline) were used to infer recent tobacco use. Priority status was used as a proxy for socioeconomic status. Priority groups include (a) at least 50% disabled by a military service-connected condition (priority group 1), (b) up to 40% service-connected disability or special wartime cohorts such as Operation Enduring Freedom/Operation Iraqi Freedom (priority groups 2–6) and (c) higher income patients with no service-connected injuries (priority groups 7–8).

We also obtained information on comorbid conditions from inpatient and outpatient administrative data. Alcohol abuse was defined by ICD-9 codes 291, 303, 305.0 and illicit drug use by ICD-9 codes 292, 304, 305 excluding 305.1. We used Charlson's comorbidity methodology to classify other pre-existing comorbid conditions.[9,10] Charlson's comorbidity system includes 19 comorbid conditions, which are classified using ICD-9 codes from prior outpatient and inpatient codes.[11]

Pharmacy data were obtained from the VA Decision Support System and Pharmacy Benefits Management databases. Subjects were considered a current user of a given medication if their last prescription had sufficient supply to overlap the date of hospitalization, assuming an 80% compliance rate. To control for potential confounding by medications, a count of unique drugs in each of the following classes per patient was calculated for drugs refilled/filled within 90 days of presentation: cardiac medications, respiratory medications and diabetic medications. A dichotomized variable was created for corticosteroid use. Previous research has demonstrated that using the count of these medication classes is preferable to adjusting for the individual medications.[12]

Outcomes

Mortality was determined using the VA Vital Status File, which has been demonstrated to be as accurate as the "gold standard" National Death Index.[13] We excluded those subjects who died within 90 days so as to better assess factors associated with long-term, rather than short-term, mortality. Mortality was assessed through October 1, 2007. To be able to include the maximum number of subjects and their follow-up information, we used Kaplan-Meier and Cox proportional hazard survival methods that not only allow censoring of information at the end

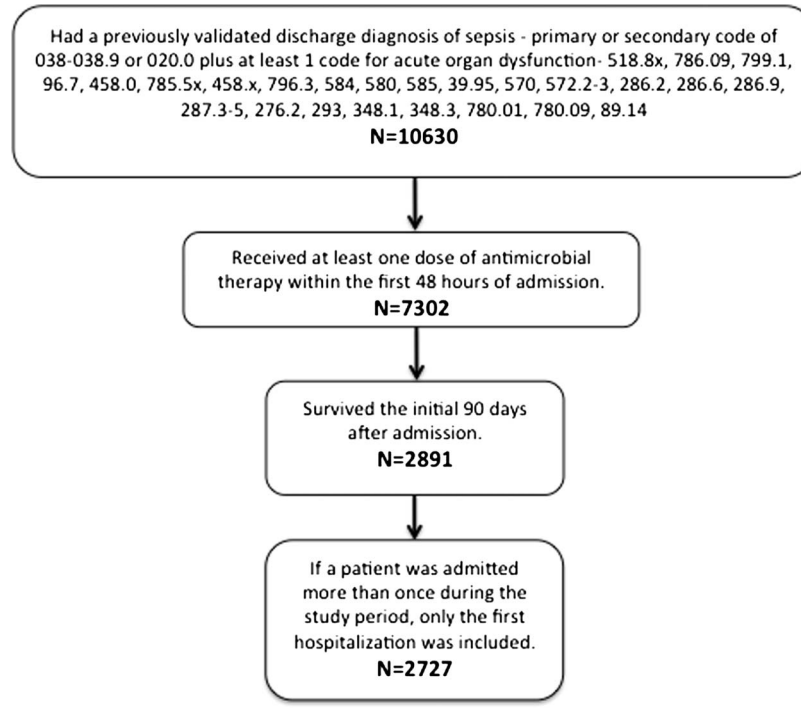

FIGURE 1. Cohort inclusion criteria.