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Inter-hospital transfer is associated with increased mortality and costs in severe sepsis and septic shock: An instrumental variables approach☆,☆☆

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ABSTRACT

Purpose: The objective of this study was to evaluate the impact of regionalization on sepsis survival, to describe the role of inter-hospital transfer in rural sepsis care, and to measure the cost of inter-hospital transfer in a predominantly rural state.
Materials and methods: Observational case–control study using statewide administrative claims data from 2005 to 2014 in a predominantly rural Midwestern state. Mortality and marginal costs were estimated with multivariable generalized estimating equations models and with instrumental variables models.
Results: A total of 18 246 patients were included, of which 59% were transferred between hospitals. Transferred patients had higher mortality and longer hospital length-of-stay than non-transferred patients. Using a multivariable generalized estimating equations (GEE) model to adjust for potentially confounding factors, inter-hospital transfer was associated with increased mortality (aOR 1.7, 95% CI 1.5–1.9). Using an instrumental variables model, transfer was associated with a 9.2% increased risk of death. Transfer was associated with additional costs of $6897 (95% CI $5769–8024). Even when limiting to only those patients who received care in the largest hospitals, transfer was still associated with $5167 (95% CI $3696–6638) in additional cost.
Conclusions: The majority of rural sepsis patients are transferred, and these transferred patients have higher mortality and significantly increased cost of care.

1. Background

Sepsis is a life-threatening condition that has doubled in incidence over the past decade, now constituting 17% of US in-hospital deaths at a cost of almost $15 billion annually [1]. Severe sepsis and septic shock cases in the emergency department (ED) have increased as well, with an estimated 390 000 U.S. ED visits in 2009 [2]. Aggressive early ED care has been shown to decrease mortality [3,4]. Although no sepsis-specific therapies that target sepsis pathophysiology have been introduced, mortality has fallen by 25% over the past two decades [5], suggesting that systematic improvements in care processes are responsible for much of the survival increase [4]. The ED plays a pivotal role in sepsis survival, and quality improvement in the ED has been shown to decrease mortality [4]. Unfortunately, this outcome improvement has not completely extended to low-volume EDs, where sepsis mortality can be up to 38% higher than in high-volume EDs [6].

Strategies to improve outcomes in low-volume rural hospitals include improvement in local quality of care and regionalization. Regionalization is the practice of transferring patients to higher volume hospitals, and it has been shown to improve outcomes in trauma, myocardial infarction, and ischemic stroke [7-11]. Care in high-volume centers has been associated with increased survival in sepsis as well [6,12,13], so regionalization could narrow the sepsis survival gap between high-volume and low-volume centers by improving the delivery of life-saving interventions. However, the role of regionalization in changing sepsis survival for those who present to low-volume EDs is

Abbreviations: 2010$USD, US Dollars, indexed to 2010 values; 95% CI, 95% confidence interval; API, Application programming interface; aOR, Adjusted odds ratios; BIC, Bayesian information criteria; ED, Emergency department; GEE, Generalized estimating equations; *ICD-9-CM, International Classification of Diseases, 9th Edition, Clinical Modification*; RUCA, Rural Urban Commuting Areas; STEMI, ST-elevation myocardial infarction.

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less clear. Many transferred sepsis patients in rural states have low adherence with national sepsis resuscitation guidelines [14]. As sepsis survival depends in large part on time-sensitive interventions, the transfer process associated with regionalization could also *cause* harm to patients, driven by the administrative and time-consuming processes associated with inter-hospital transfer. Because both early resuscitation and later hospital care are important to improving patient outcomes, it is unclear what role inter-hospital transfer plays in improving sepsis survival.

The objective of this study was (1) to measure the association between inter-hospital transfer and survival for patients with severe sepsis or septic shock, (2) to describe the prevalence of inter-hospital transfer and factors contributing to its use for rural severe sepsis and septic shock patients, and (3) to estimate the increased health care costs and resource utilization associated with inter-hospital transfer. We also sought to explore the relative contribution of ED care and inpatient care on clinical outcomes.

2. Methods

2.1. Study design, setting, and selection of participants

This study is a cohort study of all adults (age ≥18 years) with severe sepsis or septic shock treated in Iowa EDs from January 1, 2005 to December 31, 2014. Participants were identified by claims data compiled in the Iowa Hospital Association Inpatient and Outpatient data sets. To identify transferred patients, a probabilistic linkage algorithm was used to link records across inter-hospital transfer, using date of birth, sex, patient zip code, county of residence, and date of visit through a sequential matching algorithm, using social security number to break non-matching linkages. A one-day time window between visits was permitted to account for patients whose transfer process spanned across a midnight (if discharge disposition from first visit was consistent with transfer). A sample of 10% of the records was manually verified to confirm appropriate linkages.

Severe sepsis and septic shock were identified using a previously validated definition based on diagnosis billing codes from the *International Classification of Diseases, 9th Edition, Clinical Modification* (*ICD-9-CM*) [15]. Inter-hospital transfer was defined as an ED visit with a discharge code (either ED or hospital inpatient) consistent with transfer to another acute care hospital, for which an inpatient visit could be linked. Sepsis patients were divided into two cohorts: (1) those transferred to another hospital and (2) those admitted locally without transfer. This study was approved by the local Institutional Review Board (IRB #01, protocol 201 409 761) under waiver of informed consent.

2.2. Methods and measurements

2.2.1. Definitions

Index ED was defined as the first ED to which a patient presented. *Sepsis capable hospital* was defined to be a hospital that presumably had resources to care for patients with severe sepsis or septic shock, and was estimated as any hospital with an intensive care unit that was not a federally-designated critical access hospital, and that had an annual ED volume above the 25th percentile in the data set. These values were selected to identify hospitals that may be able to provide sepsis care without transfer. A *top-decile sepsis-volume hospital* was a hospital in the top decile for inpatient severe sepsis or septic shock discharges. *Rurality* was defined using Rural Urban Commuting Area (RUCA) codes mapped to the zip code of the patient's residence [16], which is an accepted form of classifying census tracts by population density, urbanization, and daily commuting [17]. *Comorbidities* were defined using the Elixhauser methodology: a set of 30 comorbid conditions defined by *ICD-9-CM* codes that have been shown to predict mortality, hospitalization, and health care utilization in risk adjustment models [18-20]. *Source of infection* was defined from the *ICD-9-CM* codes from the discharge diagnoses [15].

2.2.2. Mapping and driving distances

Driving distances were estimated using the GoogleMaps Application Programming Interface (API) [21], using geocoded hospital locations from each hospital street address and the centroid of the zip code of residence, using public roads and highways.

2.2.3. Calculation of health care costs

Health care costs were estimated both from medical costs and family costs borne additionally by transferred patients. Medical costs were estimated from charges by using hospital-specific cost-to-charge ratios calculated from each hospital's annual financial statements, corrected for inflation (Consumer Price Index – Medical Costs), using methods similar to ratios published by the Health Care Utilization Project [22,23]. The objective of this correction was to account for imbalances in pricing similar care between different hospitals. Ambulance transfer costs were estimated from the 2010 Medicare ambulance reimbursement rate for an Advanced Life Support ambulance from the index hospital to the admitting hospital.

Family costs were estimated to be the sum of: (1) transportation (driving) to the admission hospital plus (2) either: (a) lodging near the admission hospital for the duration of admission or (b) daily commuting from home to the admission hospital (whichever was less expensive). Mileage costs were estimated from the Internal Revenue Service deduction rate for medical travel [24]. Lodging costs were estimated from a survey of hotel hospital rates near the 5 hospitals that accepted most inter-hospital transfers. All hotels on the hospital preferred hotel list were contacted and the hospital-preferred rate for the lowest cost double-occupancy room was elicited. The mean of the 3 lowest-cost hotels (tax included) was taken as the affordable hotel rate for each location. Since the mean rate for each of the 5 hospitals was very close, the mean of all 15 hotels was selected as the daily lodging rate ($70.85 2010$USD, with tax included). Additional costs, such as lost wages, were not included since those costs would likely apply equally to both transferred and non-transferred patients.

2.3. Outcomes

The primary outcome of the study was the association between inter-hospital transfer and hospital mortality. The secondary outcomes were to estimate the transfer rate for severe sepsis and septic shock patients, and to estimate the incremental cost of transfer among sepsis patients. Additionally, an analysis of clustering was conducted to determine the relative value of ED hospital vs inpatient hospital and clinical outcomes.

2.4. Availability of data and materials

Because this study was conducted with protected health information that could allow identification of study participants under waiver of informed consent, the data set upon which the conclusions were based is not publicly available.

2.5. Analysis

Univariate analysis was conducted using t-test, Wilcoxon rank-sum test, and the chi-squared test, as appropriate.

Variables for inclusion in multivariable models were selected based on both statistical and clinical criteria, screening statistically-significant variables ($P < .20$) for clinical relevance prior to inclusion (since statistical significance can be misleading with large samples). We included year of presentation in our models to capture changes in sepsis survival over time. Covariates were retained in the model according to Bayesian Information Criterion (BIC), and collinearity and statistical interactions were examined with each model.

No physiologic severity of illness measure was available in the data set, so severity of illness was estimated in two ways: (1) Elixhauser