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Outcomes of ventilated patients with sepsis who undergo inter-hospital transfer: a nationwide linked analysis

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Abstract

Objectives—The outcomes of critically ill patients who undergo inter-hospital transfer (IHT) are not well understood. Physicians assume that patients who undergo IHT will receive more advanced care that may translate into decreased morbidity or mortality relative to a similar patient who is not transferred. However, there is little empirical evidence to support this assumption. We examined country-level U.S. data from the Nationwide Readmissions Database to examine whether, in mechanically ventilated (MV) patients with sepsis, IHT is associated with a mortality benefit.

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Design—Retrospective data analysis using complex survey design regression methods with propensity score matching.

Setting—The Nationwide Readmissions Database contains information about hospital admissions from 22 States, accounting for roughly half of U.S. hospitalizations; the database contains linkage numbers so that admissions and transfers for the same patient can be linked across one year of follow-up.

Patients—From the 2013 NRD Sample, 14,325,172 hospital admissions were analyzed. There were 61,493 patients with sepsis and on MV. Of these, 1630 (2.7%) patients were transferred during their hospitalization. A propensity-matched cohort of 1630 patients who did not undergo IHT was identified.

Interventions—None.

Measurements and Main Results—The exposure of interest was inter-hospital transfer to an acute care facility. The primary outcome was hospital mortality; the secondary outcome was hospital length of stay (LOS). The propensity score included age, gender, insurance coverage, do not resuscitate (DNR) status, use of renal replacement therapy, presence of shock and Elixhauser co-morbidities index. After propensity matching, IHT was not associated with a difference in in-hospital mortality (12.3% IHT vs 12.7% non-IHT, $p=0.74$). However, IHT was associated with a longer total hospital LOS (12.8 days IQR 7.7–21.6 for IHT vs 9.1 days IQR 5.1–17.0 for non-IHT, $p<0.01$).

Conclusions—Patients with sepsis requiring MV who underwent IHT did not have improved outcomes compared to a cohort with matched characteristics who were not transferred. The study raises questions about the risk-benefit profile of IHT as an intervention.

Keywords

inter-hospital transfer; outcomes; medical transport; sepsis; healthcare delivery

Introduction

Critically ill patients undergo inter-hospital transfer (IHT) to receive care from providers with more expertise, and to obtain consults and procedures unavailable at the sending hospital(1). Tele-medicine may provide access to intensivists with more extensive training and experience, but cannot fully replace the specialized care delivered by larger medical centers.

The assumption has been that IHT of critically ill patients will result in improved outcomes, and that the risks and costs of transportation are outweighed by the benefits (1–3). The risk-benefit ratio appears to strongly favor transfer for some conditions, such as acute coronary syndrome, stroke, and trauma (4–11), but the ratio is less clear (and often remains to be studied) for many others (12, 13). IHT has been shown to cause delays in administering timely treatments for sepsis, and there is recent concern that IHT could be a vector for nosocomial pathogens(14, 15). Medical errors and adverse events may also result from the care transitions and logistic challenges of IHT (1, 16–18).

The present literature generally compares transferred patients to those already in the receiving hospital's ICU, or with those admitted from the emergency department (ED) (19–21). However, few studies are available that compare outcomes in transferred patients to a comparable group who remained at the sending hospital and who, as closely as can be determined, had an equivalent likelihood of being transferred. Performing a randomized trial would raise serious ethical concerns; fortunately, similar information can be obtained using propensity-based methods.

We therefore performed a nationwide linked analysis examining the outcomes of mechanically ventilated patients with sepsis who underwent IHT. Our primary hypothesis was that, after adjustment for severity of illness (SOI) and other factors that affect the decision to transfer, patients who underwent IHT would not experience improved outcomes compared to those who were not transferred.

Materials and Methods

This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (22). A de-identified dataset was utilized for this analysis, for which a waiver of consent was obtained from the University of British Columbia Institutional Review Board. The primary outcome for this analysis was in-hospital mortality for patients with sepsis requiring mechanical ventilation.

The Nationwide Readmission Database (NRD) was used for this analysis. The NRD is a national dataset that allows for linkage of all hospital visits a patient has during a calendar year. It is created by the Agency for Healthcare Research and Quality (AHRQ) and gathers data from 22 states, covering approximately 50% of all US hospitalizations. The NRD was used for this analysis as it allows a patient's records from the sending and receiving hospitals (i.e. before and after transfer) to be linked. Thus, we were able to track the outcomes of patients after transfer, a unique feature of the NRD. The NRD employs a complex survey design, which allows for the calculation of national projections. Further information on the sampling frame and survey design of the NRD is available from the AHRQ (23).

Cohort Selection

The entire NRD dataset was used to select patients. All patients ≥ 18 years of age who had sepsis as defined by the methodology developed by Angus and colleagues were included in the analysis (24). The Angus code-based definition for sepsis has been prospectively validated to have a sensitivity of 50.4% and a specificity of 96.3% (24). A patient selection algorithm is displayed in Figure 1.

Covariates

The following patient level variables were obtained from the NRD: age, gender, length of stay, inter-hospital transfer status (yes vs no), and 24 Elixhauser co-morbidity index values. We also captured the use of hemodialysis (ICD-9 code 39.95), cardiopulmonary resuscitation (99.60) the presence of Do Not Resuscitate (DNR) status (V4986). We obtained insurance coverage status (yes vs no), total hospital charges, and patient zip-code median income as a surrogate of socioeconomic status. In addition, we obtained whether initial hospital admission occurred on a weekend versus a weekday (Sat, Sun). We unfortunately were unable to determine the day of the week of ICU admission if patients decompensated on the weekend but were originally admitted to hospital on a weekday.

Severity of Illness

In order to adjust for the severity of illness, we modelled our analysis on the work of Ford et al, who developed and validated a sepsis severity model using administrative data (25). Because the database does not include the care venue (e.g. floor or ICU) of individual patients, we selected patients who were on mechanical ventilation to ensure that the cohort included only patients in the ICU. The need for mechanical ventilation in the setting of sepsis also establishes both transferred and non-transferred patients as being at similarly high degrees of severity. Only 24 of the 29 Elixhauser co-morbidity indices were used in our analysis as these were the final ones included in the modelling by Ford et al. The Elixhauser co-morbidity indices are a widely utilized dichotomous set of variables which capture medical co-morbidities and are intended to correct for in-hospital mortality (26).

Transfer Status

Hospitalization records in the NRD contain detailed information on the transfer status of each admission. We first identified patients who were transferred between two acute care hospitals. These transfers were clearly differentiated from patients who were transported to another facility and back on the same day (for example, to receive a procedure not available at the sending hospital). Patients who were transferred to rehabilitation facilities were flagged with a different variable in the NRD and were not included as transfers in this analysis. The NRD does not have any information regarding timing of the transfer from the sending hospital to the receiving hospital.

Statistical Analysis

All analyses were completed using the appropriate complex survey procedures (PROC SURVEYMEANS, SURVEY FREQ, etc.) in SAS v9.4 (SAS Institute, Cary NC) while utilizing the weights specified by the AHRQ. A two-sided alpha level of 0.05 was used for all statistical testing. For univariate analysis, normally distributed data was compared using the independent t-test whereas non-normal data was compared using the Wilcoxon Rank-Sum test. Categorical data was compared using chi-squared analyses.

To better examine the association between IHT and outcomes in severe sepsis, a propensity score-matched analysis (matching based on likelihood of IHT) was performed. A logistic regression model predicting the outcome of IHT was created; the variables included in this model were chosen a priori and included: age, gender, insurance coverage (yes vs no), use of renal replacement therapy, “do not resuscitate” status, shock (identified by ICD9 code), and each of the 24 Elixhauser co-morbidities. The propensity for IHT was then assigned to each individual. The final c-statistic for the model was 0.73.

Cases of IHT were matched to controls (non-IHT) one-to-one by a greedy matching algorithm, with a minimum match caliper of 0.01. The success of the match was evaluated for each of the included match variables by a measure of association.

Results

From the 2013 NRD Sample, 14,325,172 hospital admissions were analyzed. There were 61,493 patients with sepsis who underwent invasive mechanical ventilation. Of these, 1630 (2.7%) were transferred during their hospitalization. The univariate analysis comparing the two cohorts is displayed in Table 1.

In the original unmatched cohort, there was no difference in the unadjusted in-hospital mortality between those who underwent IHT (12.3%) compared to those who did not (13.7%, p=0.10). Female patients were more likely to receive IHT (54.6% IHT vs 51.6% non-IHT, p=0.04). Insurance coverage was more prevalent amongst those who underwent IHT (93.1% vs 90.4%, p<0.01). There was no difference in age, DNR status, or hemodialysis use among those receiving IHT vs those who did not (Table 1). Similarly, there was no association between IHT and median household income and weekday hospital admission.

After propensity score matching, there were 1630 non-transferred patients matched to 1630 transferred patients. The results of the matching and analysis are displayed in Table 2. After matching for propensity of transfer including comorbidities, we found no difference in in-hospital mortality between transferred and non-transferred patients (12.3% IHT vs 12.7% no IHT, p=0.74). The total hospital LOS was longer for those who underwent IHT (12.8 days IQR 7.7–21.6 days) compared to those who did not (9.1 days, IQR 5.1–17.0 days, p<0.01).

Discussion

In this nationwide linked analysis, we found that ventilated patients with sepsis who undergo IHT did not have better outcomes than a comparable group who were not transferred. Notably, IHT was associated with a longer total LOS; however, these findings need to be interpreted with caution given the lack of timestamp for ICU admission and initiation of mechanical ventilation. This is the first analysis that compares outcomes of transferred patients to a propensity-matched group who remained at the sending hospital.

Multiple explanations may account for our findings. First, the currently available therapies for sepsis that provide benefit – intravenous fluids, vasopressor medications, mechanical ventilation and broad-spectrum antibiotics – are equally available at community and academic centers. For patients optimally resuscitated with these therapies, there may be little that an academic center can add unless there is an uncontrolled source or unidentifiable type of infection that cannot be addressed by the community ICU. Second, in an effort to prepare a patient for transport, adequate resuscitation and treatment may be delayed or withheld (14). Third, there are risks related to transport that may diminish the benefit of transfer-these are discussed further discussed below (2, 16). Fourth, transfer creates a complex patient-care handoff that introduces an opportunity for miscommunication or information gaps regarding the patient's prior care (18).

Studying patients who have undergone IHT poses many challenges. Information is rarely available from both the sending and receiving hospital, and missing information (e.g., lack of records from the sending hospital) makes it difficult to study the risk-benefit ratio of transfer. Importantly, outcomes for this intervention appear to be condition-specific. The risk-benefit ratio appears to strongly favor transfer for some conditions, such as the acute coronary syndrome (ACS) and trauma; in these cases, specific interventions at the receiving hospital appear to have a benefit (4–9). However, the calculus is less clear (and often remains to be studied) for many others (12, 13, 27).

To understand the risks and benefits for a given condition, we would need to compare outcomes in transferred patients to similar patients who remain at the sending hospital. Most prior outcomes studies have not had access to records from the sending hospital, and so must compare transferred patients to those admitted from the emergency department (ED). Typically, these studies find that transferred patients have longer lengths-of-stay, higher mortality, and greater resource utilization than the comparator population (19–21, 28). This is unsurprising; one would expect the population of transferred patients to be sicker and more complex. However, the key question is not addressed by these studies: do transferred patients have better outcomes than similar patients who remain at the sending hospital? Our study addresses this question by performing a propensity-matched cohort analysis of patients transferred for sepsis of sufficient severity to require mechanical ventilation (presumably, among the sickest sepsis patients); we found that transfer did not provide a benefit in this instance.

It is understandable for physicians and families to think that transfer might benefit the patient, and such reasoning is borne out for ACS and trauma. However, those benefits do not necessarily extend to other medical conditions, and unanticipated obstacles may offset these benefits. There may be adverse events related to the transport itself; examples include mechanical issues such as dislodged tubes or catheters, deterioration en route, and occasional accidents en route. There are challenges once the patient reaches the receiving hospital; a recent multidisciplinary survey reported that that 77.2% of responding physicians felt that expectations of care were unrealistic for transferred patients (26). More notably, faulty communication is a key issue- the majority of patients arrived without a complete medical record.

Furthermore, there are many costs to the patient and his or her family that can be more difficult to capture in structured data sets. Receiving hospitals are often many hours' drive away from the patient's home so that family members incur transportation costs, lodging costs, and loss of income related to missed work. The patient's prior medical records may be difficult to obtain, unavailable, incomplete, or overwhelmingly extensive. Additionally, intensive care unit stays often require difficult discussions with patients and their families; when a patient is transferred, the physicians who have relationships with the patient and family members are unable to be involved in such conversations. Considering the potential for adverse events related to transfer and the costs to the patient and family, research to assess the utility of condition-specific IHT is badly needed; our finding that it appears to be unhelpful should further raise interest in this topic.

The results of this study should be interpreted in the context of its study design, and are subject to several limitations. First, the use of administrative databases allows for the possibility of selection and misclassification bias. Second, because there were only 1,630 patients in the NRD who met our inclusion criteria (sepsis, MV, and underwent IHT), the size of our study is relatively small. We recognize that our findings need to be investigated in a larger study, but given the near-complete absence of literature on this topic, small studies suggesting future pathways are relevant in the design of more definitive studies. Third, the NRD does not contain severity of illness (SOI) scores, such as SOFA, OASIS, or APACHE, and these scores could not be retrospectively calculated from the database. We are aware that the propensity score is only as good as the inputs, and note here that the small number of covariates may fail to address important differences in SOI not captured in administrative data. Additionally, while the obvious concern might be that the transferred patients are ‘sicker’ than the ones who remain, there may also be offsetting groups of patients who are not transferred because they are identified as ‘too sick to transfer or travel’.

Fourth, detailed patient-level variables were not available; examples include vasopressor medication and dose, timing of mechanical ventilation, timing to antibiotic therapy, timing and volume of intravenous fluids, source of infection, and microbiologic culture results, as well as time-stamped physiologic variables and laboratory values (such as initial vital signs, ventilator settings, lactate measurement, partial pressure of arterial oxygen, fraction of inspired oxygen). This consideration is particularly relevant to our secondary outcome measures of hospital and ICU LOS; the timing of the onset of sepsis and initiation of mechanical ventilation is likely affect LOS. Additionally, patients who are stable at the time of transfer and then require ICU level care are known to have prolonged hospitalization (29). Matching patients based on timing of these events in future propensity studies would provide more accurate estimation of IHT’s effect on LOS.

Fifth, detailed information on the reason for transfer as well as timing of transfer were also unobtainable from the NRD. Illness severity, time-sensitive variables, and detailed information related to the transfer may be effect modifiers, and may have contributed to the outcomes of patients examined; due to limitations of the database, they could not be modelled, and should be investigated in future studies. The patient’s neurological status and intracranial haemorrhage as the reason for transfer, for example, have an effect on mortality but are not modeled here (11). Sixth, subgroup analysis would have been helpful to assess heterogeneity of treatment effect; however, relevant variables such as timing of the transfer and differences between the sending and receiving hospitals were not available in the database. Seventh, there is data to suggest that hospital volume may affect outcomes, both for sepsis and mechanical ventilation; but due to limitations of the database, we were unable to incorporate hospital volume into the analysis, and this should be addressed in future studies.

Eighth, the authors also recognize that the overall mortality rate in our population of around 12% is low, even compared to more recent studies suggesting that overall sepsis mortality is declining (30). Errors in coding in the database or unrecognized selection bias may have affected our results. The sickest patients with sepsis were perhaps too unstable for transfer, or transfer was not considered due to poor prognosis. By selecting patients who were transferred (and excluding those who were deemed too sick to be transferred), and then identifying a matched cohort based on the characteristics of the transferred patients for the analysis, we could have introduced a selection bias.

We recognize that the findings in these manuscripts are subject to residual confounding from variables not captured in the databases that we examined, and that our study results are constrained by issues such as incomplete SOI adjustment and the limitations of propensity matching. This study was not intended to provide the definitive answer to the question of whether patients with sepsis who are on mechanical ventilation benefit from being transferred from one ICU to another; our work is far from the final word on the value of IHT for critically ill patients. IHT is a complex, difficult-to-study phenomenon, and one for which randomized controlled trials would be extremely challenging or perhaps impossible to perform (31). Rather, with our undertaking to evaluate the usefulness of this understudied but common intervention in this paper, we hope to raise awareness and encourage more research into this increasingly important topic. Any contemporary study of such transfers is inherently limited in these (and other) respects, and our approach represents a valid first approximation that challenges the conventional wisdom that these kinds of ICU to ICU transfers are unquestionably beneficial. The intention of this analysis was not to definitively answer the question regarding the outcomes of patients in the ICU who undergo IHT, but rather to form a basis for hypothesis generation and to encourage future more rigorous research from the community.

Conclusion

In a propensity-matched cohort analysis of ventilated patients with sepsis, we found that patients who were transferred did not have better outcomes compared to those who were not transferred. The preliminary results should be considered hypothesis-generating, and must be validated with more detailed studies, including prospective trials. Nevertheless, these results highlight the fact that IHT should be regarded as a medical intervention with associated risks and benefits, and that benefit may not actually result from IHT for certain medical conditions.

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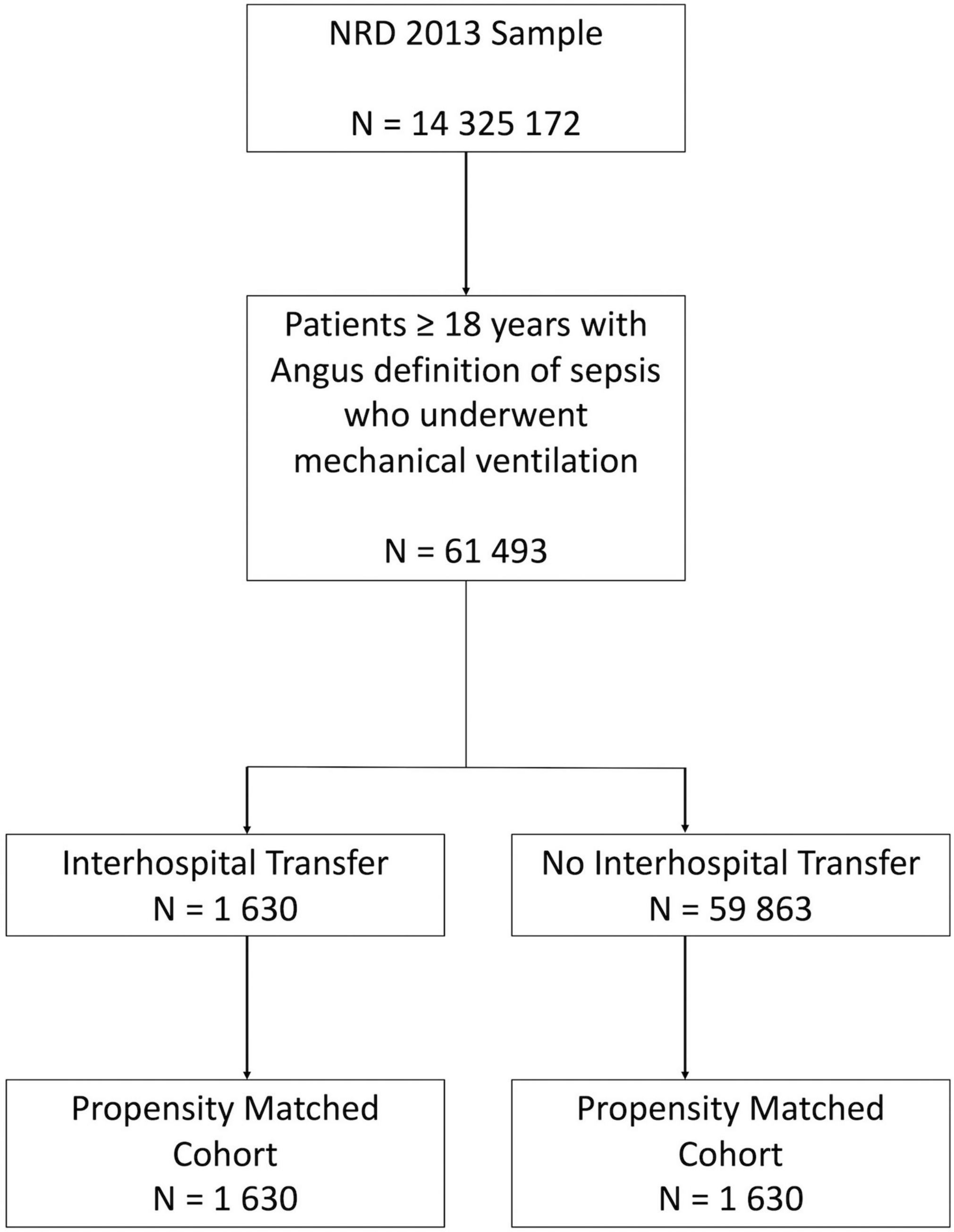

FIGURE 1.
Derivation of study population for propensity-matched study of mechanically ventilated patients with sepsis who underwent inter-hospital transfer.

TABLE 1

Univariate analysis showing basic sociodemographic variables of the two propensity-matched cohorts (transferred and non-transferred patients).

	Overall Cohort		
Variables	**IHT (n=1 630)**	**No IHT (n=59 863)**	**p**
Age in years, mean (SD)	61.3 (15.9)	61.7 (16.9)	0.45
In-hospital mortality, n(%)	192 (12.3)	8324 (13.7)	0.10
Female sex, n(%)	875 (54.6)	30941 (51.6)	0.04
Total Hospital Charges $, median (IQR)	132 342 (76 654–256 592)	94 307 (49 880–186 553)	<0.01
Insurance coverage, n(%)	1 528 (93.1)	54 169 (90.4)	<0.01
Weekend Admission, n(%)	420 (25.5)	15 549 (25.9)	0.79
Median Zip Code Income Quartile, n(%)			
1st	473 (31.3)	18 996 (33.4)	
2nd	441 (30.1)	15 975 (28.1)	
3rd	357 (21.6)	13 622 (22.5)	
4th	336 (17.0)	10 154 (15.9)	0.47
Total Length of stay, median (IQR)	12.8 (7.7–21.6)	9.4 (5.1–17.0)	<0.01
Do Not Resuscitate Status, n(%)	162 (9.8)	6212 (10.0)	0.83
Hemodialysis, n(%)	64 (3.5)	2427 (4.0)	0.40
Cardiopulmonary Resuscitation, n(%)	59 (3.1)	2 260 (3.7)	0.29

IHT = interhospital transfer.

TABLE 2

Results of propensity-matched cohort analysis between transferred and non-transferred patients.

	Propensity Matched Cohort		
Covariates	**IHT (n=1 630)**	**No IHT (n=1 630)**	**p**
Age in years, mean (SD)	61.3 (15.9)	61.4 (16.3)	0.80
In-hospital mortality, n(%)	192 (12.3)	216 (12.7)	0.74
Female sex, n(%)	875 (54.6)	921 (56.8)	0.25
Insurance coverage, n(%)	1 528 (93.1)	1 529 (94.2)	0.25
Total Length of stay, median (IQR)	12.8 (7.7–21.6)	9.1 (5.1–17.0)	<0.01
Do Not Resuscitate Status, n(%)	162 (9.8)	146 (8.4)	0.17
Hemodialysis, n(%)	64 (3.5)	68 (3.5)	0.65

IHT = interhospital transfer.