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Red Blood Cell Transfusions and Outcomes after Intracerebral Hemorrhage

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Abstract

Background: Low red blood cell (RBC) levels are associated with worse intracerebral hemorrhage (ICH) outcomes. However, relationships of RBC transfusions on ICH outcomes are unclear given the overlap of RBC transfusion, comorbidities, and disease severity. We investigated RBC transfusion relationships on ICH outcomes while accounting for comorbidities and disease severity.

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Methods: ICH hospitalizations between 2002–2011 and RBC transfusion exposure were identified from the Nationwide Inpatient Sample using ICD-9-CM codes. Logistic regression was used to study the relationship between RBC transfusion on outcomes after adjusting for demographics, baseline comorbidities, and markers of disease severity. Additional sensitivity analyses stratified by comorbidity burden and disease severity were performed.

Results: Of 597,046 ICH hospitalizations, RBC transfusions were administered in 22,904 (4%). RBC transfusion was associated with higher odds of in-hospital mortality (adjusted OR: 1.22 [95%CI: 1.10–1.35]). In sensitivity analyses, RBC transfusions resulted in poor outcomes regardless of the comorbidity burden, but attenuation in this relationship was notable with lower comorbidities (adjusted OR 1.43 [95%CI: 1.34–1.51] vs 1.18 [95%CI: 1.10–1.29]). There were no associations of RBC transfusions with poor outcomes in hospitalizations without mechanical ventilation (adjusted OR 0.88 [95%CI: 0.83–1.13]) and in cases requiring ventriculostomy drains (adjusted OR 1.05 [95%CI: 0.97–1.10]).

Conclusions: In a large, nationally representative sample, RBC transfusion was associated with poor ICH outcomes. However, there were variations in this relationship based on comorbidities and disease severity. Additional prospective studies are required to assess direct risks and benefits from RBC transfusions in ICH.

Keywords

intracerebral hemorrhage; red blood cell transfusions; comorbidities; outcome; administrative data

Introduction

Intracerebral hemorrhage (ICH) is associated with high morbidity and mortality. This is due to initial cerebral tissue injury as well as secondary brain injury that can occur in part due to either direct or indirect impairments of adequate cerebral tissue oxygen delivery. Unfortunately, there are no current treatment targets that have been shown to improve ICH outcomes. However, we and others have shown that low red blood cell (RBC) levels are associated with worse outcomes after ICH[1–3]. These findings are postulated to be due in part to impaired cerebral oxygenation, extrapolating findings from subarachnoid hemorrhage[4,5] and traumatic brain injury[6] patients and could suggest a potential role of RBC transfusions as a treatment modality in ICH. Though RBC transfusions are currently being explored in clinical treatment trials for subarachnoid hemorrhage and traumatic brain injury patients[7–9], no such trials exist for patients with ICH. While there may be observational evidence that RBC transfusions can improve survival in ICH patients[10], it is unclear if these single center findings are widely generalizable. Hence, we sought to explore the relationship between RBC transfusions and outcomes in a large, nationally representative sample of patients hospitalized with ICH while accounting for baseline medical comorbidities and medical and ICH disease severity.

Materials and Methods

Study Design and Sample

We performed a retrospective, cohort study using discharge data from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP) from 2002–2011. The NIS cohort represents a 20% stratified random sample of all inpatient admissions to non-federal US hospitals. The database provides information on patient demographics, hospital characteristics, primary and secondary diagnoses, inpatient procedures, comorbidities, and case-severity measures. All diagnoses and procedures are recorded using International Classification of Diseases version 9 Clinical Modification (ICD-9-CM) codes. Since the NIS database contains de-identified data, this study was exempt from the institutional review as determined by the Weill Cornell Medicine institutional review board.

Measurements

We identified ICH hospitalizations from 2002–2011 using the validated ICD-9-CM code 431 as previously described[11,12]. Hospitalizations of cases <18 years old were excluded. Cases transferred to another hospital were also excluded to avoid duplicate ICH case inclusions and to best account for entire hospitalization course[12]. Additionally, we did not include ICH hospitalizations with diagnostic codes suggesting an ICH from traumatic brain injury or other secondary etiologies of ICH including vascular malformation, aneurysm, or malignancy given the known heterogeneity of outcomes in these types of ICH. A cumulative score was calculated for each case using the Charlson comorbidity index[13,14] in order to capture baseline comorbidity status. This index is a weighted score of 17 different comorbidities using ICD-9-CM codes with higher scores indicating higher comorbidities. This score has been validated for outcome adjustment for administrative datasets on ischemic stroke and ICH[15,16].

Our exposure was RBC transfusions received during ICH hospitalization, identified using the ICD-9-CM code V58.2 and procedure code 99.04, which have both been used previously and validated with high levels of sensitivity and specificity[17–19]. Our primary outcomes were in-hospital mortality and home discharge. Secondary outcomes studied were a composite favorable outcome of discharge to home or rehabilitation, and a composite unfavorable outcome of discharge to skilled nursing facility, hospice or death. Discharge disposition has been shown to correlate with 90-day and 1-year modified Rankin Scale with discharge to home or rehabilitation indicating higher functional potential than discharge to skilled nursing facility[20].

Statistical analysis

Intergroup differences (RBC transfused vs non-RBC transfused ICH cases) were determined by applying Mann-Whitney-*U* or *t*-tests for continuous variables and $\chi 2$ or Fisher-exact tests for categorical variables. Binary logistic regression was used to evaluate the relationship between RBC transfusion and outcomes. Covariates in the model included baseline demographics (age, sex, race, insurance status), hospital-level characteristics (geographical location, teaching status, and bed size), comorbidities (diabetes, hypertension, hyperlipidemia, atrial fibrillation, valvular heart disease, congestive heart failure, and

chronic kidney disease), Charlson comorbidity index, surrogate markers of medical disease and ICH severity: infection (sepsis, urinary tract infections, and pneumonia), withdrawal of care, and procedures (ventriculostomy and mechanical ventilation).

Pre-specified sensitivity analyses were performed to investigate the differential relationship of RBC transfusion on outcome in patients with: a) varying levels of baseline medical comorbidity burden (stratified hospitalizations by Charlson comorbidity index ≥3 vs <3); b) different levels of active medical disease (mechanical ventilation vs no mechanical ventilation); c) and presumptive severity of neurological injury of the ICH (stratified hospitalization by external ventriculostomy drain placement[21,22]). Neurosurgical ventriculostomy placement is required for cerebrospinal fluid diversion for patients that have obstructive hydrocephalus and/or intraventricular hemorrhage (IVH), the presence of which is a marker of ICH severity[23]. These clinical parameters have been used in prior studies utilizing administrative data as surrogates of disease severity[12,24]. These sensitivity analyses were performed in attempts to best investigate the relationship of RBC transfusion, rather than underlying complication/indication, on outcome.

As recommended by HCUP, population estimates were obtained by complex sample analyses that consider weights, clustering, and stratification used for NIS sampling[25]. All analyses were performed by using IBM SPSS version 20 (IBM Corporation, NY, USA) with statistical significance set at $P<0.05$.

Results

Baseline Characteristics

Of the 619,166 ICH hospitalizations identified using ICD codes, 597,046 were ultimately included for analysis (figure 1). A total of 22,904 (4%) cases received an RBC transfusion during their ICH hospitalization. Cases receiving RBC transfusions were younger and more likely to be Black or Hispanic, compared to those who were not administered RBC transfusions. There also appeared to be geographic and hospital characteristic variations between cases receiving and not receiving RBC transfusions. Additionally, cases receiving RBC transfusions had more baseline risk factors including chronic kidney disease and anemia, a higher comorbidity burden as noted on the Charlson comorbidity scores, infections during hospitalization, as well as longer hospital length of stay (Table 1).

Primary Analyses

The overall in-hospital mortality was 30% in our study and there was a higher mortality in cases exposed to RBC transfusion (35% vs 29%). In the unadjusted analysis, RBC transfusion was associated with an increased odds of in-hospital mortality (odds ratio [OR] 1.29; 95%CI: 1.25–1.33). We noted a continued association of RBC transfusion on hospital mortality after adjusting for relevant covariates (adjusted OR 1.22; 95%CI 1.10–1.35). Similarly, logistic regression models identified an association of RBC exposure and increased odds of unfavorable discharge disposition (adjusted OR 1.44; 95%CI: 1.36–1.51). Conversely, RBC transfusion was associated with a lower odds of home discharge (adjusted OR 0.45; 95%CI: 0.42–0.51) and favorable discharge disposition (adjusted OR 0.56; 95%CI:

0.54–0.60) (Table 2). In post-hoc analysis, we additionally included gastrointestinal hemorrhage, end stage renal disease on hemodialysis, and hospital length of stay as covariates in regression models and did not note a change in the relationship of RBC transfusion increased odds of mortality (adjusted OR 1.24; 95%CI: 1.16–1.35) or lower odds of home discharge (adjusted OR 0.73; 95%CI: 0.68–0.77).

Sensitivity Analyses

We additionally performed pre-specified sensitivity analyses. In the first analysis, RBC transfusion remained associated with poor ICH outcomes regardless of baseline comorbidity burden as stratified by Charlson comorbidity index ≥3 vs <3 (adjusted OR 1.43 [95%CI: 1.34–1.51] vs adjusted OR 1.18 [95%CI: 1.10–1.29] respectively). However, it was notable that there was an attenuation of the association of RBC transfusion exposure on poor outcomes in cases with less baseline comorbidities. In our second analysis, we similarly identified a variation in the relationship of RBC transfusion on ICH outcome when stratifying the cohort based on need for mechanical ventilation, a surrogate marker of medical disease severity. While RBC transfusion was associated with poor outcomes in cases requiring mechanical ventilation, there was no association in cases not requiring mechanical ventilation (adjusted OR 1.33 [95%CI: 1.27–1.39] vs adjusted OR 0.88 [95%CI: 0.83–1.13] respectively). In our third analyses, we stratified cohorts by external ventriculostomy drain use as a surrogate measure of ICH specific disease severity. RBC transfusion was associated with poor ICH outcomes (adjusted OR 1.51; 95%CI: 1.46–1.57) among hospitalizations not requiring ventriculostomy. However, there was no relationship between RBC transfusion and poor outcomes in cases receiving ventriculostomy (adjusted OR 1.05; 95%CI: 0.97–1.10). Additional analyses were performed stratifying for both anemia and gastrointestinal hemorrhage complication diagnostic codes and there continued to be associations of RBC transfusions on poor outcome regardless of the presence/absence of diagnosis (table 3). There were no interactions between RBC transfusion and the stratification variable for each outcome.

Discussion

In a large, nationally representative cohort of hospitalizations with non-traumatic ICH, approximately 4% of cases received an RBC transfusion during their ICH hospitalization. Intergroup differences in hospital characteristics, geographic location of the hospital, and baseline demographics were seen in ICH hospitalizations requiring RBC transfusions compared to those that did not. Expectedly, we also identified that cases receiving RBC transfusions had higher medical comorbidities and surrogate markers of severity of illness during hospitalization (infections, procedures) compared to cases not requiring RBC transfusions. While RBC transfusions were associated with poor ICH outcomes even after adjusting for these comorbidities, the relationship of RBC transfusion on outcome appeared to vary based on baseline comorbidities as well as presumed medical and neurological injury severity.

There is increasing recognition that anemia or low RBC levels correlate with poor ICH outcomes due in part to impaired cerebral oxygenation[1–3]. Subsequently, RBC levels have

been considered a potential therapeutic target to improve outcomes in these patients. While the logical next step would be to examine if RBC transfusion has any therapeutic benefit in ICH as has been initiated in other diseases of acute brain injury[7,9], there is a paucity of RBC transfusion data on this topic in ICH. A single center cohort study from a tertiary care center identified better survival with RBC transfusions after ICH[10]. In this context, our findings from a much larger cohort of ICH cases across the United States suggesting poor outcomes after RBC transfusion did not confirm these single center observational study results. However, rather than directly contradicting these observational ICH study findings, it is possible that our results reinforce observations seen in other studies of primarily non-brain injured patients which similarly identified that RBC transfusions were associated with poor outcomes[26]. It is worth noting that these studies in non-brain injured patients cautioned that the relationships of RBC transfusions with increased morbidity/mortality did not imply causality and could reflect the significant overlap of baseline comorbidities, severity of illness during hospitalization with low RBC levels, RBC transfusion requirements, and subsequent outcomes. Perhaps in line with this concept is that we noted an attenuation of the relationship of RBC transfusion exposure on poor outcome when looking at ICH cases with lower baseline comorbidities. Similarly, there was no association of RBC transfusions with poor outcomes in ICH cases that did not require mechanical ventilation.

Because cerebral oxygen delivery is paramount in settings of severe neurological injury, we attempted to address the differential impact of RBC transfusions amongst cases with different degrees of neurologic injury utilizing ventriculostomy placement as a surrogate marker of increased neurologic injury. An intriguing observation from our data was that while RBC transfusions had a deleterious relationship with outcomes among hospitalizations not requiring ventriculostomy placement, there was no relationship with outcomes when ventriculostomies were placed. Because patients receiving ventriculostomies are more likely to have intraventricular hemorrhage, larger hematoma volumes, deep ICH location, and poor mental status, all of which independently portend poor prognosis, it could be speculated that brain injury severity can mask any potential underlying outcome effect (either deleterious or beneficial) of RBC transfusion. It is unclear whether our study further suggests that patients with less severe neurological injury may be more susceptible to the risks rather than benefits associated with RBC transfusions. However, at the very least our findings appear to indicate that future studies will need to account for measures of both acute medical and neurological critical illness, such as physiologic scores (APACHE), ICH location, ICH score[23], hematoma expansion[1], in addition to baseline comorbidities when addressing the relationship of RBC transfusions on outcome. It could be possible that RBC transfusions indicated for cerebral oxygenation delivery may have different, and potentially beneficial relationships with outcomes compared to those transfusions given for blood loss or conditions related to medical illness severity.

Though our study strengths included a very large sample of nationally represented ICH hospitalizations and attempts to adjust for potential confounders, the results need to be interpreted with caution due to inherent limitations of administrative databases. The absence of granular data, specifically hemoglobin laboratory levels and indication for transfusions in such databases prohibit a closer look at the relationship of RBC transfusion themselves (rather than underlying disease/indication) on outcome. While we attempted to adjust for

medical comorbidities, active disease severity, and also performed analyses while excluding those encountering hemorrhagic complications in order to estimate the relationship of RBC transfusion itself on outcome, further work using prospective datasets will be required to elucidate this complex relationship. Coding errors and misclassification are additional inherent limitations to administrative datasets, however in order to address this issue, we utilized well-validated codes to identify ICH cases and RBC transfusion exposure[18,19]. Similarly, while random ICD-9-CM coding errors are possible, they would bias the results toward the null, and are hence unlikely to account for the measured differences in mortality rates found in this study. Further limitations included the absence of well-validated ICH severity measures, such as ICH volume, ICH location, and Glasgow Coma Scale in our data. The use of ventriculostomy procedure codes as a surrogate marker of ICH severity may be limited in certain scenarios and a closer look at specific ICH characteristics will be important to elucidate in future studies. It is also possible that our analyses could be limited by treatment bias, where patients not receiving RBC transfusions could simply be patients who did not receive aggressive treatment due to withdrawal of care practices. However, we attempted to account for this by incorporating withdrawal of care as a covariate in all models. Additional limitations included the inability to assess the number of transfusions and temporality of the transfusion in relation to the day of hospitalization in this dataset. This prevented us from looking at the known relationship between RBC transfusions and incident complications (infections and thrombosis) to identify whether our relationships of RBC transfusions and poor outcomes were driven by inherent risks of RBC transfusions themselves.

Finally, our study lacked functional outcome data at discharge as well as long-term follow-up which is a critical measure of outcome in neurological disease. While we used discharge disposition, a validated, accurate surrogate for functional outcomes[20] in these settings at discharge, further work is required to establish the relationship of RBC transfusions on long term functional and cognitive outcomes.

Conclusions

In this nationally representative study, RBC transfusions were associated with poor outcomes after ICH. However there appeared to be variations in the relationship of RBC transfusion on poor outcomes based on comorbidities and hospitalization related medical and ICH severity. In order to disentangle the complex relationship of RBC transfusions, underlying medical indication/disease, and their confounders on clinical ICH outcome, further prospective work is required to elucidate the specific risks and benefits of RBC transfusion for patients with ICH. And ultimately, further work is required to clarify whether ICH patients necessitate different hemoglobin threshold triggers for RBC transfusions.

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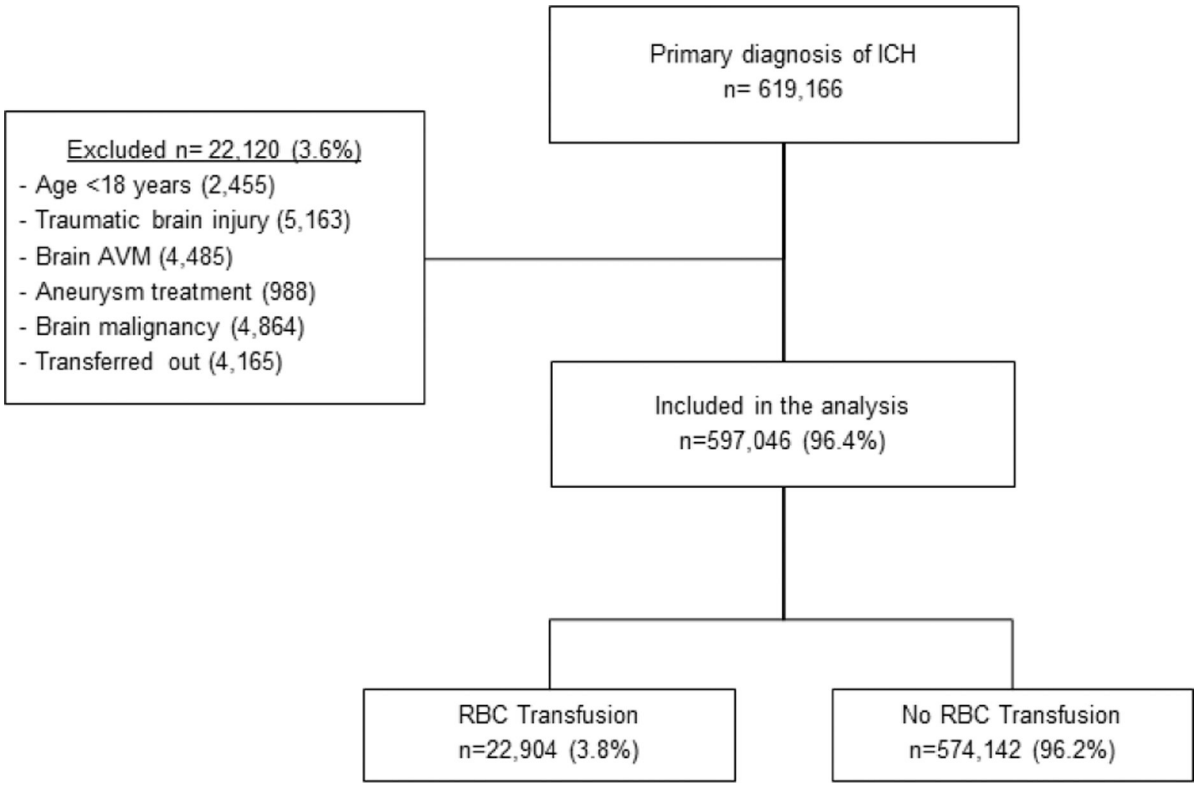

Figure 1: Patient Selection and Screening from NIS

ICH: intracerebral hemorrhage; AVM: arteriovenous malformation; RBC: red blood cells

Table 1.

Baseline Characteristics of ICH Hospitalizations

Characteristic	RBC transfusion N=22,904	No transfusion N=574,142	P value
Age, years			
18–64	9,625 (42.0)	207,261 (36.1)	<0.001
65–79	7,874 (34.4)	201,340 (35.1)	
80 or more	5,406 (23.6)	165,541 (28.8)	
Female	12,068 (52.7)	301,643 (52.5)	<0.001
Race			
White	10,676 (46.5)	312,002 (54.3)	<0.001
Black	4,735 (20.7)	75,697 (13.2)	
Hispanic	2,406 (10.5)	42,945 (7.5)	
Asian	1,053 (4.6)	21,049 (3.6)	
Other	888 (3.9)	16,466 (2.9)	
Missing	3,147 (13.7)	105,983 (18.5)	
Hospital geographic region			
Northeast	5,335 (23.3)	105,392 (18.4)	<0.0001
Midwest	3,452 (15.1)	122,424 (21.3)	
South	9,086 (41.1)	228,200 (39.7)	
West	5,032 (21.9)	118,126 (20.6)	
Urban hospital	21,881 (95.5)	546,638 (95.2)	0.045
Academic hospital	14,214 (62.1)	341,083 (59.4)	<0.001
Hospital size			
Small	1,210 (5.3)	44,029 (7.7)	<0.001
Medium	5,079 (22.2)	120,443 (20.9)	
Large	16,524 (72.1)	409,670 (71.4)	
Health insurance			
Medicare	13,473 (58.8)	365,204 (63.6)	<0.001
Medicaid	2,985 (13.0)	42,930 (7.5)	
Private insurance	4,439 (19.4)	115,778 (20.2)	
Other	1,984 (8.7)	58,230 (10.1)	
Comorbidities			
Anemia	10,758 (46.9)	61,881 (10.8)	<0.001
Dyslipidemia	3,932 (17.2)	140,269 (24.4)	<0.001
Coronary Artery Disease	4,845 (21.2)	115,852 (20.1)	<0.001
Atrial Fibrillation	5,221 (22.8)	103,278 (17.9)	<0.001
Hypertension	15,975 (69.7)	449,786 (78.3)	<0.001
Diabetes	5,226 (22.8)	123,371 (21.5)	<0.001
Chronic kidney disease	3,117 (13.6)	38,417 (6.7)	<0.001
Charlson Comorbidity Index			<0.001

Characteristic	RBC transfusion N=22,904	No transfusion N=574,142	P value
0	6,435 (28.1)	245,819 (42.8)	
1	5,748 (25.1)	159,045 (27.7)	
2	4,340 (18.9)	86,440 (15.1)	
3 or more	6,287 (27.4)	82,539 (14.4)	
Mechanical Ventilation	12,554 (54.8)	163,322 (28.4)	<0.001
External Ventriculostomy	3,682 (16.1)	35,782 (6.2)	<0.001
Sepsis	2,906 (12.7)	16,957 (2.9)	<0.001
Pneumonia	5,036 (21.9)	78,235 (13.6)	<0.001
Urinary tract infection	4,740 (20.7)	38,940 (6.8)	<0.001
Gastrointestinal hemorrhage	1,265 (5.5)	5,694 (1.0)	<0.001
ESRD requiring dialysis	1,674 (7.3)	10,039 (1.7)	<0.001
Length of stay, mean [SD]	17.0 (20.1)	8.0 (10.5)	<0.001

Abbreviations: ICH: intracerebral hemorrhage; RBC, red blood cell; ESRD: end stage renal disease; SD: standard deviation

Table 2.

Logistic Regression Analysis Evaluating the Relationship between RBC Transfusion and ICH Outcomes

	RBC Transfusion*	No RBC Transfusion*	Adjusted OR (95% Cl)	P value
In-hospital mortality	7,927 (34.6)	173,738 (29.1)	1.22 (1.10–1.35)	**<0.001**
Home discharge/Self-care	2,135 (9.3)	121,166 (20.3)	0.45 (0.42–0.51)	**<0.001**
Unfavorable discharge (SNF/hospice/inpatient death)	11,312 (61.9)	264,020 (52.2)	1.44 (1.36–1.51)	**<0.001**
Favorable discharge* (Home/Rehabilitation)	3,891 (21.3)	172,591 (34.1)	0.56 (0.54–0.60)	**<0.001**

Abbreviations: CI, confidence interval; ICH, intracerebral hemorrhage; OR, odds ratio; RBC, red blood cell; SNF, skilled nursing facility.

Logistic regression models adjusted for age, sex, modified Charlson Comorbidity Index, hypertension, diabetes, dyslipidemia, atrial fibrillation, mechanical ventilation, insurance status, teaching status of hospital, chronic kidney disease, ventriculostomy procedure, infections, and withdrawal of care

*Data represented as N (%) unless otherwise specified

Table 3.

Sensitivity Analysis of the Association between RBC Transfusion and ICH Outcomes[1]

Characteristic	In-hospital Mortality	Home Discharge/Self-Care
	OR (95% Cl)	OR (95% Cl)
Modified Charlson's index ≥ 3	1.43 (1.34–1.51)*	0.45 (0.39–0.52)*
Modified Charlson's index <3	1.18 (1.10–1.29)*	0.33 (0.30–0.40)*
Cases with mechanical Ventilation	1.33 (1.27–1.39)*	0.98 (0.94–1.04)
Cases without mechanical Ventilation	0.88 (0.83–1.13)	0.64 (0.61–0.68)*
Cases with EVD	1.05 (0.97–1.10)	0.91 (0.78–1.05)
Cases without EVD	1.51 (1.46–1.57)*	0.69 (0.66–0.73)*
Excluding cases with Gl hemorrhage	1.23 (1.18–1.29)*	0.66 (0.61–0.69)*
Cases with anemia only	1.48 (1.41–1.55)*	0.58 (0.54–0.62)*
Cases without anemia	1.55 (1.48–1.62)*	0.31 (0.29–0.33)*
Patients with ESRD on dialysis	1.23 (1.02–1.34)*	0.54 (0.49–0.61)*
Patients without ESRD	1.18 (1.13–1.24)*	0.65 (0.60–0.72)*

Abbreviations: CI, confidence interval; EVD, external ventriculostomy drain; GI: gastrointestinal; ESRD: end stage renal disease; OR, odds ratio; RBC, red blood cell.

[1] Logisitc regression models adjusted for age, sex, modified Charlson Comorbidity Index, hypertension, diabetes, dyslipidemia, atrial fibrillation, mechanical ventilation, insurance status, teaching status of hospital, chronic kidney disease, ventriculostomy procedure, infections, and withdrawal of care

* Indicates p value < 0.05