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Early post-hospitalization hemoglobin recovery and clinical outcomes in survivors of critical illness: A population-based cohort study

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Summary

Anemia is common during critical illness, is associated with adverse clinical outcomes, and often persists after hospitalization. The goal of this investigation is to assess the relationships between post-hospitalization hemoglobin recovery and clinical outcomes after survival of critical illness. This is a population-based observational study of adults (≥18 years) surviving hospitalization for critical illness between January 1, 2010 and December 31, 2016 in Olmsted County, Minnesota, United States with hemoglobin concentrations and clinical outcomes assessed through one-year post-hospitalization. Multi-state proportional hazards models were utilized to assess the relationships between 1-month post-hospitalization hemoglobin recovery and hospital readmission or death through one-year after discharge. Among 6,460 patients that survived hospitalization for critical illness during the study period, 2,736 (42%) were alive, not hospitalized, and had available hemoglobin concentrations assessed at 1-month post-index hospitalization. Median (interquartile range) age was 69 (56, 80) years with 54% of male gender. Overall, 86% of patients had anemia at the time of hospital discharge, with median discharge hemoglobin concentrations of 10.2 (9.1, 11.6) g/dL. In adjusted analyses, each 1 g/dL increase in 1-month hemoglobin recovery was associated with decreased instantaneous hazard for hospital readmission (HR 0.87 [95% CI 0.84 – 0.90]; p<0.001) and lower mortality (HR 0.82 [95% CI 0.75 – 0.89]; p<0.001) through one-year post-hospitalization. The results were consistent in multiple pre-defined sensitivity analyses. Impaired early post-hospitalization hemoglobin recovery is associated with inferior

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clinical outcomes in the first year of survival after critical illness. Additional investigations are warranted to evaluate these relationships.

Keywords

Anemia; transfusion; critical illness; intensive care; hemoglobin; readmission

Introduction:

Anemia may be considered an unintended yet ubiquitous consequence of critical illness.[1–5] Indeed, more than 75% of critically ill adults experience anemia during hospitalization, with this number exceeding 95% for those with intensive care unit (ICU) durations greater than 7 days.[3] Causes of anemia are often multifactorial,[1,6,7] including anemia related to inflammation, bleeding, organ dysfunction, iron and other nutritional deficiencies, phlebotomy, cytotoxic medications, bone marrow failure, and hemolysis. Anemia experienced during critical illness is associated with increased rates of RBC transfusion,[3,5] prolonged hospitalization,[3,5] impaired post-hospitalization physical function,[8] and mortality.[3] Additionally, greater severity of anemia at the time of hospital discharge following critical illness is associated with reduced post-hospitalization survival.[2]

Importantly, anemia experienced during critical illness does not resolve with the completion of the initial critical care episode. Rather, this anemia may persist long after hospitalization.[2,9] Further, patients may experience differential rates of hemoglobin recovery, and it is unclear how hemoglobin recovery may relate to post-hospitalization clinical outcomes for critical illness survivors. By characterizing the relationships between early post-hospitalization hemoglobin recovery and clinical outcomes, care pathways could ultimately be designed to improve early identification, monitoring, and/or targeted interventions for patients at greatest risk for impaired hemoglobin recovery and adverse post-hospitalization clinical outcomes.

In this population-based investigation of critical illness survivors, we assess the associations between early post-hospitalization hemoglobin recovery and clinical outcomes through the first year after hospitalization for critical illness.

Methods:

This is a population-based observational cohort study conducted under approval from the appropriate local institutional review boards (Olmsted County, USA). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[9]

Study cohort:

This study employs the Rochester Epidemiology Project (REP), a comprehensive epidemiological database of population health information that links medical records for residents of Olmsted County, Minnesota, United States of America (USA) and the surrounding counties, such that complete medical records are available for >95% of the

population.[10,11] All consecutive adult residents of Olmsted County (age ≥18 years) who survived hospitalization for critical illness between January 1, 2010 through December 31, 2016 in this county were eligible for inclusion, as previously described,[2] with all included patients providing consent for medical record use in observational research. For patients with multiple hospitalizations during the study period, only the first hospitalization with an associated ICU admission was included such that patients were only included once. Patients dying within the first-month post-hospitalization, patients hospitalized at 1-month post-index hospitalization, and those without an available 1-month post-hospitalization hemoglobin concentration were excluded, as the study assesses outcomes from 1 month through 12 months post-hospitalization based upon 1-month hemoglobin data.

Outcomes and Exposures:

The outcomes of interest were unplanned hospital readmissions and all-cause mortality from 1 month through 12 months following hospital discharge. Unplanned hospital readmissions were defined as admissions through the Emergency Department (ED), direct transfers from other acute care facilities, or admissions immediately following emergency surgery or procedural interventions. Anticipated hospital admissions (e.g. admissions following elective surgery or procedures, admissions for chemotherapy) were not included. The primary exposure of interest was 1-month post-hospitalization hemoglobin recovery defined as the absolute change in hemoglobin concentration from hospital discharge to 1-month post hospitalization (i.e. 1-month post-hospitalization hemoglobin concentration minus hospital discharge hemoglobin concentration), with 1-month hemoglobin concentrations obtained between 8- and 35-days following hospitalization, selecting the value closest to 30 days when multiple measurements were available. This time window (i.e. from 2 through 5 weeks post-index hospitalization) was chosen a priori based upon the collective expertise of study authors as representing the earliest window for clinically relevant hematinic recovery after acute illness while also facilitating early outcome assessment. Additional variables of interest included the hospital discharge hemoglobin concentration (i.e. the value closest to hospital dismissal but no more than 5 days before discharge), pre-hospitalization hemoglobin concentrations (i.e. the outpatient hemoglobin concentration occurring closet to index hospital admission, which could be obtained at any time in the 12 months up to 1 day before hospital admission), patient demographics (age, patient-reported gender, patient-reported race), baseline clinical characteristics (comorbidities, Charlson comorbidity index), hospitalization characteristics (ICU admission type [surgical vs. non-surgical], admission Acute Physiology and Chronic Health Evaluation [APACHE] III scores, ICU length of stay, hospital length of stay, invasive mechanical ventilation during hospitalization), and the total number of allogeneic RBC units transfused during hospitalization.

Statistical Approach:

Exposure variables and index hospitalization features were summarized overall and for patients achieving or not achieving at least 1 g/dL of hemoglobin recovery as median (interquartile range [IQR]) for continuous variables and number (percentage) for categorical variables. To estimate the relationship between 1-month hemoglobin recovery and outcomes of readmission and mortality in the one year following index hospitalization, we used an illness-death with recovery multi-state hazard model to estimate hazard ratios for each

state transition (e.g. transitions from not hospitalized to hospitalized or death, transition from hospitalized to not hospitalized or death; Supplemental Figure 1). We constrained the model to fit a shared coefficient for the relationship between 1-month hemoglobin recovery and transitions from not hospitalized and hospitalized to death. That is, we estimate a common association between 1-month hemoglobin recovery and death whether the patient is hospitalized or not. All models were adjusted for factors selected a priori that may influence hemoglobin concentrations and post-hospitalization outcomes, including patient age, gender, surgical vs. medical admission, Charlson score, admission APACHE III score, invasive mechanical ventilation, hospital duration, and hemoglobin at the time of hospital discharge. Hazard ratios associated with a 1 g/dL increase in 1-month hemoglobin recovery along with 95% confidence intervals and p-values are reported. Estimated instantaneous probability for readmission or death (i.e. the proportion of subjects either hospitalized or dead at a given time point) is presented graphically for the overall population, for patients with hemoglobin recovery of at least 1 g/dL vs. those without, and for two representative hypothetical patients with identical demographic and clinical features but distinct 1-month hemoglobin recovery. To estimate the cumulative rather than instantaneous incidence of unplanned hospital readmission between 1-month and 1-year post critical illness (i.e. any readmission in the first year), a competing events analysis was used with death defined as the competing event and follow-up ending at time of first hospital admission. Aalen-Johansen estimates and 95% confidence limits are shown graphically.

Several pre-specified sensitivity analyses were performed, including analyses limited to those with anemia at the time of hospital discharge (n=2352), with anemia being defined according to World Health Organization (WHO) guidelines as <12.0 g/dL in females and <13.0 g/dL in males,[12] and analyses with additional incorporation of pre-hospitalization hemoglobin concentrations as a covariate, given that baseline pre-illness hemoglobin concentrations may influence anticipated post-hospitalization hemoglobin recovery. Further, we explored interactions between 1-month hemoglobin recovery and outcome relationships by index admission type (medical vs. surgical), the presence (any vs. none) as well as the number of RBC transfusions during index admission, index hospitalization discharge hemoglobin concentrations, index hospital length of stay, age, and gender. In interaction analyses, we fit shared coefficients for the interaction terms as well as the corresponding main effects for transitions to the death state. Additionally, we repeated the primary analysis with inclusion of all critical illness survivors alive and not hospitalized at 1-month post-hospitalization by imputing 1-month hemoglobin values for those patients with missing values (full details available as Supplemental Content 1). Finally, we repeated the primary analyses by exclusion of patients with post-hospitalization hemoglobin measurements that were obtained during emergency department or inpatient admissions (i.e., limiting analyses to patients with outpatient hemoglobin assessments only), given that these may be influenced greatly by acute illness and may not provide an accurate assessment of hemoglobin recovery. Analyses were done using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). P-values <0.05 were considered statistically significant.

Results:

Among 6,460 patients that survived hospitalization for critical illness during the study period, 2,736 (42%) remained under follow-up, had available 1-month post-hospitalization hemoglobin assessment, were not hospitalized at 1 month following index hospitalization, and were included in the analysis (Figure 1). Patients without available 1-month hemoglobin data were modestly younger with lower comorbidity burden, shorter hospital durations, and less severe anemia at hospital discharge than those with 1-month hemoglobin data (Supplemental Table 1). For included subjects, the median (IQR) time for post-hospitalization hemoglobin assessment was 24 (16, 30) days. The median (IQR) age was 69 (56, 80) years, with 54% male (Table 1). Surgical admissions accounted for 44% of index hospitalizations. Pre-hospitalization hemoglobin data was available for 88% of patients, with median (IQR) concentrations of 12.7 (11.2, 14.1) g/dL. 2,352 patients (86%) had anemia at hospital discharge, with median hemoglobin concentrations of 10.2 (9.1, 11.6) g/dL. A total of 988 patients (36%) were transfused with allogeneic RBCs during their hospitalization, with a median of 2 (2, 4) units administered. Median ICU and hospital lengths of stay were 1.2 (0.9, 2.3) and 5.7 (3.6, 9.2) days.

The median (IQR) hemoglobin recovery in the first month post-hospitalization was 1.0 (0.1, 1.9) g/dL with 1,402 patients (51.2%) achieving hemoglobin recovery of at least 1 g/dL. Differences in clinical and demographic features were generally limited between patients achieving or not achieving at least 1 g/dL of hemoglobin recovery; however, patients with greater recovery were more likely to be surgical ICU admissions (49% vs. 39%), had modestly higher pre-hospitalization hemoglobin concentrations (median [IQR] 13.0 [11.5, 14.3] vs. 12.5 [10.9, 13.9] g/dL), lower discharge hemoglobin concentrations (9.6 [8.8, 11.0] vs. 10.7 [9.6, 12.2] g/dL), lower rates of chronic kidney disease (17% vs. 23%), higher transfusion rates during hospitalization (39% vs. 33%), and higher rates of mechanical ventilation (37% vs. 28%).

A total of 949 patients (35%) experienced unplanned hospital readmission (Supplemental Figure 2) and 356 patients (13%) died between 1- and 12-months post-hospitalization (Figure 2). In adjusted analyses using a multi-state model (Table 2), each 1 g/dL increase in 1-month hemoglobin recovery was associated with a 13% reduction in the instantaneous hazard for readmission [HR 0.87 (95% CI: 0.84 – 0.90); $p<0.001$] and an 18% reduction in the hazard for mortality [HR 0.82 (0.75 – 0.89); $p<0.001$]. The estimated probability of being alive and hospitalized and the estimated probability of death overtime for patients with or without at least 1 g/dL of hemoglobin recovery are displayed in Figure 3, with the cumulative incidence of readmission displayed in Supplemental Figure 3. Additionally, estimated outcome probabilities for two hypothetical 65-year-old females are displayed in Supplemental Figure 4 and Supplemental Figure 5.

Study results were consistent in pre-defined sensitivity analyses limited to those with anemia at the time of hospital discharge [HR 0.86 (95% CI: 0.83 – 0.89), $p<0.001$ for readmission; HR 0.81 (95% CI: 0.74 – 0.88, $p<0.001$ for mortality] and with incorporation of pre-hospitalization hemoglobin concentrations [HR 0.90 (95% CI: 0.86 – 0.94), $p=0.006$ for readmission; HR 0.86 (95% CI: 0.77 – 0.95, $p=0.005$ for mortality]. There were no

significant interactions based upon admission type, RBC transfusion status or quantity, discharge hemoglobin concentrations, hospital length of stay, or patient gender. There was a significant interaction between hemoglobin recovery and readmissions by patient age (p=0.034), such that older adults experienced lower hazard for readmission for each 1 g/dL increase in hemoglobin recovery compared to their younger counterparts (HR [95% CI] per 1 g/dL increase in hemoglobin for patients 55, 65, and 80 years [25th, 50th, and 75th percentiles of age] of 0.88 [0.83, 0.95], 0.86 [0.81, 0.92], and 0.83 [0.78, 0.89] respectively, all p<0.001). The primary results were also consistent in a sensitivity analysis with imputation of 1-month hemoglobin concentrations for those with missing values, such that each 1 g/dL increase in 1-month hemoglobin recovery was associated with decreased hazard for readmission [HR 0.90 (95% CI: 0.87 – 0.94); p<0.001] and mortality [HR 0.78 (95% CI 0.71–0.86); p<0.001). Moreover, the results were consistent when limiting analyses only to those patients with post-hospitalization hemoglobin concentrations obtained in outpatient settings (n=2521), with each 1 g/dL increase in hemoglobin recovery associated with lower readmissions [HR 0.88 (95% CI: 0.85, 0.91; p<0.001] and mortality [HR 0.80 (95% CI 0.74, 0.88); p<0.001).

Discussion:

In this population-based study of early post-hospitalization hemoglobin recovery in critical illness survivors, higher 1-month hemoglobin recovery was associated with reductions in mortality and hospital readmissions through the first-year post-hospitalization. These relationships were consistent across medical and surgical ICU admissions, in those with varying degrees of anemia severity at hospital discharge, and in those with varying hospital lengths of stay. This suggests that early hemoglobin assessment may be important for the identification of patients at risk for adverse post-hospitalization outcomes. Given that more than 85% of patients were anemic at the time of hospital discharge, there is a considerable opportunity to identify high-risk patients early in their post-hospitalization course and potentially modify outcome trajectories. However, future studies are clearly necessary to determine if interventions designed to improve the rate and magnitude of hemoglobin recovery, or to employ additional focused interventions or care strategies targeted to anemic patients, result in improved post-hospitalization clinical outcomes.

Anemia is seemingly ubiquitous in critical illness, with an incidence exceeding 90% for those with ICU durations greater than 3 days.[1,3] Only a small minority of patients leave the hospital after critical illness with preservation of normal hemoglobin concentrations.[2,3,5,13] In light of numerous restrictive vs. liberal RBC transfusion trials over the past 20 years,[16–20] anemia associated with critical illness is often tolerated by clinicians until hemoglobin concentrations drop below a given threshold (i.e. <7 g/dL), at which point transfusion may be triggered. An unanticipated consequence of these trials has been the framing of allogeneic transfusion, a liquid transplant with a host of adverse clinical consequences, as a primary treatment for anemia. Transfusion reduction and avoidance certainly remain worthwhile goals for hospitalized patients, and broad adoption of evidence from landmark transfusion trials has been successful in achieving these aims.[19,21] However, it remains critical to recognize that anemia is not benign and may persist long after critical illness.[9,14] At 12-months post-hospitalization, nearly 50% of critical illness survivors discharged

with anemia remain anemic.[2] Additionally, anemia experienced during critical illness is associated with impairments in physical performance months after hospitalization, including activities of daily living and ambulatory capacity.[8]

The results of the current investigation suggest that early hemoglobin assessment may be one marker to identify patients at greatest risk for adverse outcomes after critical illness. Indeed, patients with impaired 1-month hemoglobin recovery experienced higher rates of unplanned hospital readmission and death. It is therefore important to consider strategies to prevent, attenuate, and treat anemia rather than assuming anemia to be an innocent and inevitable bystander of critical illness.[17] Importantly, several clinical factors were identified in this investigation that may be associated with impaired early post-hospitalization hemoglobin recovery, including non-surgical ICU admissions, lower pre-hospitalization hemoglobin concentrations, and the presence of chronic kidney disease. Interestingly, there were no meaningful differences in hemoglobin recovery across patient age or gender. However, hemoglobin recovery and outcome relationships differed by age, such that older patients had greater signal for benefit (i.e. lower hazard for unanticipated hospital readmission) with greater hemoglobin recovery when compared to their younger counterparts. Hence, early assessment of post-hospitalization hemoglobin recovery, while likely important for all critical illness survivors, may be of particular importance in those with advanced age.

The pressing question remains whether we can modify patient outcomes by addressing anemia before, during, or after critical illness. Given the unanticipated nature of most critical illness not related to planned surgery, optimization of anemia prior to hospitalization is unlikely to be uniformly possible. In surgical patients, however, there is often time for adequate preoperative optimization. Indeed, there is strong evidence to suggest that preoperative anemia management may improve hemoglobin recovery through the perioperative and early post-hospitalization periods.[7, 23–25] Similar trials in critical illness with both erythropoietic stimulation and intravenous iron therapy have shown improved hemoglobin recovery throughout hospitalization,[21–26] though data regarding longer-term hemoglobin recovery and post-hospitalization clinical outcomes are lacking. One recent multicenter trial randomized approximately 400 patients with anemia during critical illness to receive intravenous iron therapy, with or without erythropoietin (EPO), at the time of ICU discharge versus standard care.[27] While there was no difference in the primary outcome of hospital length of stay, those in the intervention arm had a substantial reduction in 90-day mortality (8% vs. 17%). A similar trial of IV iron therapy delivered between ICU and hospital discharge is underway.[28] Additionally, meta-analyses suggest that EPO may improve survival in critical illness,[30, 31] and recent guidelines from the French Society of Anesthesia & Intensive Care Medicine (SFAR) recommend the use of EPO in critically ill non-bleeding anemic patients to reduce transfusion utilization and mortality.[29] Future studies are warranted to evaluate the impact and optimal timing of anemia management strategies, which may include pharmacological therapies and/or practice improvement initiatives to minimize iatrogenic anemia, on post-hospitalization clinical outcomes.

There are several limitations of this investigation. First, it is observational in design, and the presented associations do not represent causal relationships. To this end, impaired

hemoglobin recovery after critical illness may be a marker of persistent chronic illness, and interventional trials, some of which have recently been completed or are ongoing,[33, 35] are necessary to determine if anemia prevention, mitigation, or treatment strategies translate into improvement in post-hospitalization clinical outcomes. Second, 1-month hemoglobin data was not available in all critical illness survivors, which reflects the real-world experience of post-hospitalization follow-up; hence, our primary results are only applicable to those with available 1-month outpatient hemoglobin data. Patients without 1-month follow-up hemoglobin data were modestly younger with lower comorbidity burden, shorter hospital durations, and less severe anemia than those with available hemoglobin data. While the relationships between hemoglobin recovery and clinical outcomes in this group are unknown, the results of a sensitivity analysis employing multiple imputation of missing 1-month hemoglobin concentrations were consistent with the primary analysis. As an additional limitation, patients who died or were readmitted at 1-month post-index hospitalization were excluded, such that we are unable to comment on the role of anemia recovery in those with impaired early post-hospitalization outcomes. Third, we adjusted for a variety of factors that may influence hemoglobin concentrations and outcomes in critical illness survivors, including patient demographics, comorbidities, and acute illness features. However, we were unable to account for all factors (e.g., discharge disposition) and the possibility of residual confounding remains. Fourth, we did not assess the potential associations between non-transfusion-based anemia treatments (e.g. iron, EPO) during or after hospitalization on hemoglobin recovery or clinical outcomes, though only a small minority of patients received any non-RBC-based treatment of anemia. Thorough assessment of these relationships will be critical to inform future interventions. Fifth, we were unable to obtain etiologies of anemia, and future investigations should be designed to evaluate the role of anemia etiology in hemoglobin recovery and outcomes. Finally, the results of this study are representative of a relatively homogeneous group of individuals residing in the Midwestern United States. Generalizability to other practice settings is unclear.

In summary, hemoglobin concentrations in the first month after hospitalization for critical illness are associated with hospitalizations and survival through 12 months. Specifically, patients with greater 1-month hemoglobin recovery experienced improved post-hospitalization outcomes. Future studies are necessary to confirm these relationships and to assess the potential impact of anemia management strategies on the modification of post-hospitalization hemoglobin recovery and clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Competing Interests:

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Take home message:

In a population-based observational study of survivors of critical illness, greater 1-month post-hospitalization hemoglobin recovery was associated with fewer hospital readmissions and lower mortality through 12-months. Patients with impaired recovery from anemia after critical illness are at heightened risk for adverse clinical outcomes.

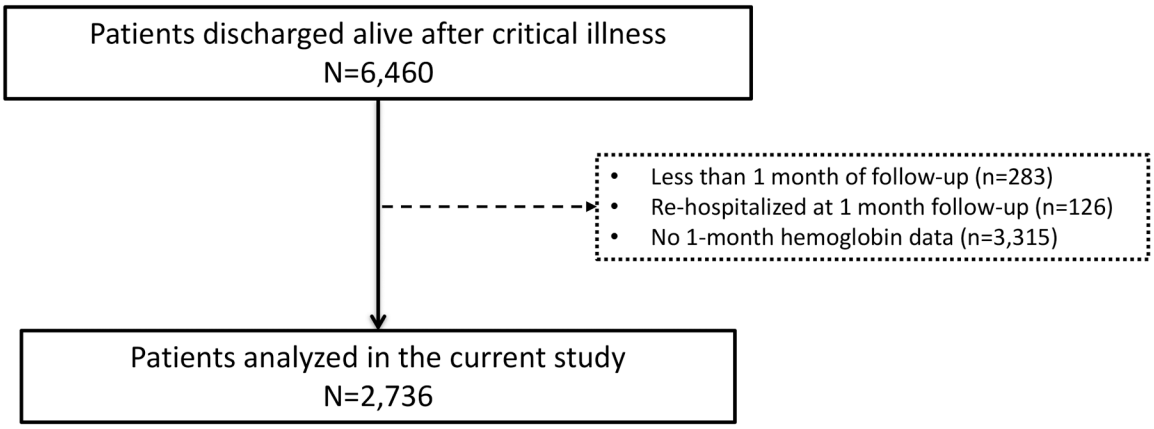

Figure 1.
Patient flow diagram.

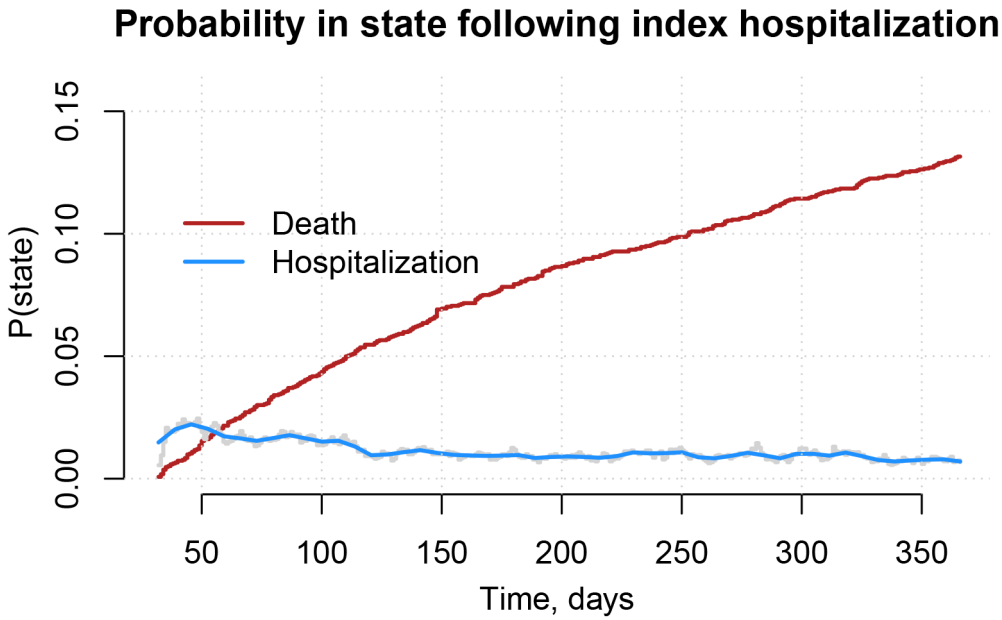

Figure 2.

Probability of hospitalization or death in the year after hospitalization for critical illness. Probability of hospitalization represents the instantaneous probability of being hospitalized (i.e., unanticipated readmission) at any given time in the year following survival of critical illness. Probability of death is cumulative over time.

*Patients alive and under follow-up 1 month following index hospitalization

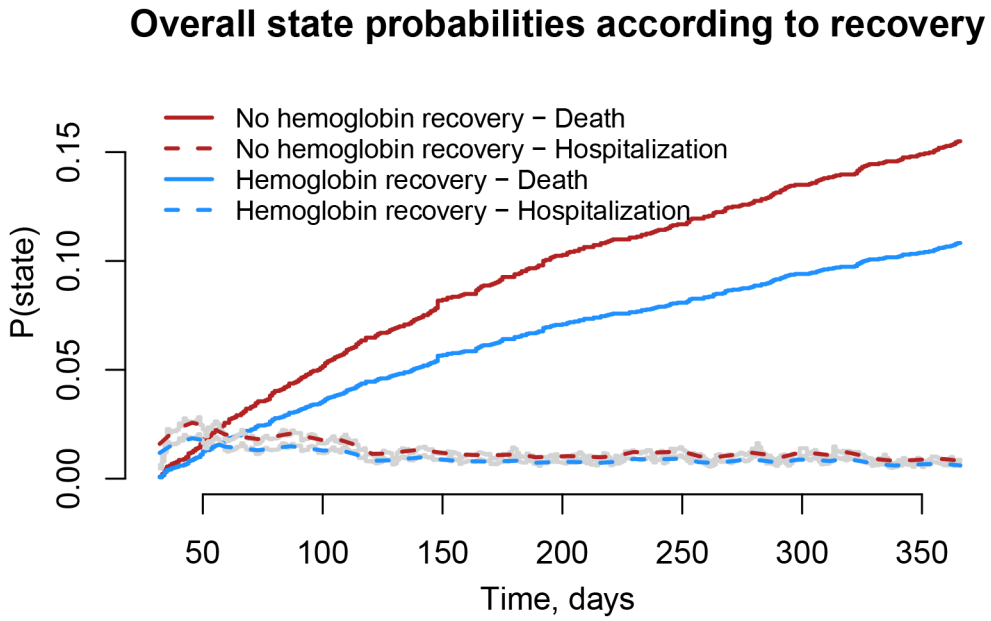

Figure 3.

Probability of hospitalization or death in the year after hospitalization for critical illness for patients with or without at least 1 g/dL of early hemoglobin recovery

Probability of hospitalization represents the instantaneous probability of being hospitalized (i.e., unanticipated readmission) at any given time in the year following survival of critical illness. Probability of death is cumulative over time.

*Patients alive and under follow-up 1 month following index hospitalization

Table 1.

Patient demographic and hospitalization characteristics by hemoglobin recovery (n=2,736)

	No recovery (<1 g/dL) (N=1,334)	Recovery (≥1 g/dL) (N=1,402)	Total (N=2,736)
Age, y	70 (57, 81)	68 (54, 79)	69 (56, 80)
Male	715 (54%)	774 (55%)	1489 (54%)
Race			
White	1217 (91%)	1283 (92%)	2500 (91%)
Black	36 (3%)	31 (2%)	67 (2%)
Asian	38 (3%)	26 (2%)	64 (2%)
American Indian	1 (0%)	5 (0%)	6 (<1%)
Other/Chose not to disclose	42 (3%)	57 (4%)	99 (4%)
Surgical admission	516 (39%)	684 (49%)	1200 (44%)
Charlson comorbidity index	3 (1, 5)	2 (1, 4)	2 (1, 5)
Myocardial infarction	160 (12%)	151 (11%)	311 (11%)
Congestive heart failure	295 (22%)	219 (16%)	514 (19%)
Peripheral vascular disease	328 (25%)	333 (24%)	661 (24%)
Cerebrovascular disease	201 (15%)	204 (15%)	405 (15%)
Dementia	65 (5%)	49 (3%)	114 (4%)
COPD	404 (30%)	410 (29%)	814 (30%)
Peptic ulcer disease	80 (6%)	74 (5%)	154 (6%)
Diabetes	113 (8%)	106 (8%)	219 (8%)
Hemiplegia	27 (2%)	32 (2%)	59 (2%)
Renal disease	311 (23%)	240 (17%)	551 (20%)
Liver disease	106 (8%)	117 (8%)	223 (8%)
Cancer	336 (25%)	334 (24%)	670 (24%)
Rheumatologic disease	76 (6%)	63 (4%)	139 (5%)
Pre-hospitalization Hb (n=2,382; g/dL)	12.5 (10.9, 13.9)	13.0 (11.5, 14.3)	12.7 (11.2, 14.1)
Males	13.0 (11.2, 14.5)	13.4 (11.8, 14.8)	13.2 (11.4, 14.6)
Females	12.0 (10.7, 13.2)	12.5 (11.3, 13.7)	12.3 (11.0, 13.5)
Discharge Hb, g/dL	10.7 (9.6, 12.2)	9.6 (8.8, 11.0)	10.2 (9.1, 11.6)
Males	11.0 (9.8, 12.6)	9.8 (8.8, 11.3)	10.4 (9.1, 12.0)
Females	10.4 (9.5, 11.6)	9.5 (8.7, 10.6)	10.0 (9.1, 11.1)
Anemia at discharge	1055 (79%)	1297 (93%)	2352 (86%)
RBC transfusion during hospitalization	439 (33%)	549 (39%)	988 (36%)
RBC units (n=988)	3 (2, 5)	2 (2, 4)	2 (2, 4)
Iron or EPO for anemia	87 (7%)	81 (6%)	168 (6%)
Admission APACHE III score	60 (45, 74)	58 (46, 74)	59 (46, 74)
Invasive mechanical ventilation	374 (28%)	517 (37%)	891 (33%)
ICU length of stay, d	1.2 (0.9, 2.2)	1.2 (0.9, 2.4)	1.2 (0.9, 2.3)
Hospital length of stay, d	5.7 (3.4, 9.1)	5.8 (3.7, 9.2)	5.7 (3.6, 9.2)

Values are number (percent) for categorical variables and median (25th, 75th) for continuous variables. Number of observations with complete data is listed when not all data were available.

APACHE – acute physiology and chronic health evaluation; COPD – chronic obstructive pulmonary disease; EPO – erythropoietin; Hb – hemoglobin; ICU – intensive care unit; RBC – red blood cell.

Table 2.

Hazard for hospitalization or death by each 1 g/dL increase in 1-month hemoglobin recovery in a multi-state model

	HR	95% CI	P
Hospital readmission	0.87	0.84 – 0.90	<0.001
Death	0.82	0.75 – 0.89	<0.001

HR – hazard ratio; CI – confidence interval.

HR represents the hazard for hospitalization or death, adjusted for age, gender, surgical vs. medical admission, Charlson score, admission APACHE III score, invasive mechanical ventilation, hospital duration, and hemoglobin at the time of hospital discharge. Patients experiencing hospital readmission may transition out of the hospital and remain at risk for additional readmissions or death.