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ORIGINAL RESEARCH

Red Blood Cell Transfusion at a Hemoglobin Threshold of 7 g/dl in Critically Ill Patients

A Regression Discontinuity Study

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Abstract

Rationale: In critically ill patients, a hemoglobin transfusion threshold of <7.0 g/dl compared with <10.0 g/dl improves organ dysfunction. However, it is unclear if transfusion at a hemoglobin of <7.0 g/dl is superior to no transfusion.

Objectives: To compare degrees of organ dysfunction between transfusion and no transfusion at a hemoglobin threshold of <7.0 g/dl among critically ill patients using quasiexperimental regression discontinuity methods.

Methods: We performed regression discontinuity analysis using hemoglobin measurements from patients admitted to intensive care units in three cohorts (Medical Information Mart for Intensive Care IV, eICU, and Premier Inc.), estimating the change in organ dysfunction (modified sequential organ failure assessment score) in the 24- to 72-hour window following each hemoglobin measurement. We compared hemoglobin concentrations just above and below 7.0 g/dl using a "fuzzy" discontinuity approach, based on the concept that measurement noise pseudorandomizes similar hemoglobin concentrations on either side of the transfusion threshold.

Results: A total of 11,181, 13,664, and 167,142 patients were included in the Medical Information Mart for Intensive Care IV (MIMIC-IV), eICU, and Premier Inc. cohorts, respectively. Patient characteristics below the threshold did not differ from those above the threshold, except that crossing below the threshold resulted in a >20% absolute increase in transfusion rates in all three cohorts. Transfusion was associated with increases in hemoglobin concentration in the subsequent 24–72 hours (MIMIC-IV, 2.4 [95% confidence interval (CI), 1.1 to 3.6] g/dl; eICU, 0.7 [95% CI, 0.3 to 1.2] g/dl; Premier Inc., 1.9 [95% CI, 1.5 to 2.2] g/dl) but not with improvement in organ dysfunction (MIMIC-IV, 4.6 [95% CI, −1.2 to 10] points; eICU, 4.4 [95% CI, 0.9 to 7.8] points; Premier Inc., 1.1 [95% CI, −0.2 to 2.3] points) compared with no transfusion.

Conclusions: Transfusion was not associated with improved organ dysfunction compared with no transfusion at a hemoglobin threshold of 7.0 g/dl, suggesting that evaluation of transfusion targets other than a hemoglobin threshold of 7.0 g/dl may be warranted.

Keywords: critical illness; anemia; blood transfusion; hemoglobin

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Anemia occurs in nearly all patients admitted to intensive care units (ICUs) (1) as a consequence of chronic disease, critical illness, and frequent laboratory testing (2, 3). In critically ill patients with anemia, the 1999 TRICC (Transfusion Requirements in Critical Care) trial (4) found that a strategy of red blood cell (RBC) transfusion based on a hemoglobin threshold of <7.0 g/dl was associated with fewer transfusions, lower organ dysfunction scores, and potentially lower mortality compared with a more liberal hemoglobin threshold (10.0 g/dl). Informed by these trial results and subsequent studies (5), guidelines (6, 7) recommend transfusions only when hemoglobin concentrations decrease below 7.0 g/dl, a practice that has become standard for ICU patients (2).

However, transfusion at a hemoglobin threshold of 7.0 g/dl has not been shown to improve outcomes in critically ill patients compared with no transfusion. Identifying optimal transfusion practice is important to preserve blood product supply and to limit adverse effects of transfusion such as organ dysfunction (8), volume overload (9), and acute lung injury (10). Although a randomized clinical trial (RCT) may best answer the question of the efficacy of transfusion versus no transfusion at a specific hemoglobin threshold, concerns about patient harm in withholding standard-of-care treatments (11) may make an RCT untenable. In the absence of RCTs, quasiexperimental study designs that leverage granular health record data can provide estimates of causal effects that approach clinical trial results (12). In this study, we assessed the effectiveness of RBC transfusion versus no transfusion at a hemoglobin threshold of <7.0 g/dl among patients admitted to the ICU using regression discontinuity study design (RDD).

Methods

RDD is a quasiexperimental study method intended to estimate causal effects when a treatment decision is based on a continuous running variable crossing a specific threshold value (13, 14). In these situations, noise in the measurement of the running variable or factors exogenous to the causal structure (15) results in the pseudorandomization of patients who fall closely on either side of the running variable intervention threshold. Because of the threshold rule and measurement error in the running variable, patients just above/below the threshold are expected to have similar characteristics (16). In our study, the threshold rule was RBC transfusion at a hemoglobin concentration (running variable) of 7.0 g/dl (threshold). Hemoglobin concentration meets the criteria of a running variable measured with noise, with a coefficient of variation in measurement of approximately 2.2% (15). Thus, our study mimics a pragmatic clinical trial that randomizes ICU patients to RBC transfusion or no transfusion at a hemoglobin concentration of 7.0 g/dl.

Study Population

To study the effects of blood transfusion at a hemoglobin concentration of 7.0 g/dl, we created three patient cohorts with harmonized inclusion criteria from three data sources: *1*) the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (17, 18) (a high-resolution database of patients admitted to seven ICUs at Beth Israel Deaconess Medical Center from 2008 to 2019); *2*) the Philips eICU database (18, 19) (a multicenter U.S. database of patients admitted to ICUs that participated in Philips telehealth program from 2014 to 2015); and *3*) the Premier Inc. database (20) (an enhanced claims-based database consisting of ~20% of U.S. inpatient admissions from 2016 to 2020 with laboratory values and vital signs available for a subset of patients). We included adult (≥18 yr) patients admitted to an ICU with at least one hemoglobin measured between Days 2 and 28 of ICU admission. We excluded patients with hemoglobin concentrations recorded only on the first day of ICU admission because indications for transfusions during early critical illness (e.g., resuscitation) may not depend on hemoglobin concentration alone and only on the last day of ICU admission because outcome ascertainment was only available while patients remained in the ICU. In addition, in the MIMIC-IV and eICU cohorts, we excluded patients who only had hemoglobin concentrations recorded after patients had documented goals of care for "comfort measures only". In all cohorts, we excluded patients with diagnoses for myocardial infarction or major bleeding using previously validated definitions (21–24) because patients with these diagnoses may have alternative transfusion thresholds (25) and indications. To increase the likelihood that we were examining patients admitted to hospitals that routinely delivered RBC transfusions based on a hemoglobin threshold of 7.0 g/dl, we limited the multicenter eICU and Premier Inc. cohorts to hospitals that had higher percentages of patients given a transfusion at a hemoglobin concentration of 6.9 g/dl compared with 7.0 g/dl. For each included patient, we extracted the lowest hemoglobin value on a randomly selected day for evaluation as the running variable.

Exposure

The exposure in RDD is defined by where the running variable (i.e., hemoglobin concentration) falls relative to the treatment threshold. In this study, patients with a hemoglobin concentreation of <7.0 g/dl are characterized as "transfusion exposed", whereas those with a hemoglobin concentration of ⩾7.0 g/dl are characterized as "transfusion unexposed". The degree to which the running variable approximates transfusion exposure is measured by the difference in the proportion of hemoglobin measurements that were followed by transfusion in the next 24 hours just above and just below the hemoglobin threshold of 7.0 g/dl. As the Premier Inc. cohort contains transfusion data granular to the level of hospital-day we defined hemoglobin measurements followed by transfusion in the Premier Inc. cohort as transfusions that occurred on the same day as the hemoglobin measurement.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Outcomes

We sought to specify outcomes that were in close temporal relation to the administration of individual RBC transfusions, clinically meaningful, and similar to prior RBC transfusion trials (4). The primary outcome was a measure of organ dysfunction, the maximum sequential organ failure assessment (SOFA) (26) score in the 24- to 72-hour window after each hemoglobin measurement with a modification to account for the competing risk of death, such that patients who died in the 24- to 72-hour window were assigned a SOFA score of 25 (the maximum score of the unmodified SOFA is 24) (27). Patients with missing SOFA score elements (e.g., bilirubin for SOFA liver component score) were assigned a score of 0 for the corresponding SOFA organ component score. By limiting primary outcome ascertainment to the period shortly after each hemoglobin measurement, rather than longer periods (e.g., until ICU discharge), differences in the primary outcome are more likely because of changes in organ dysfunction attributable to each transfusion rather than changes in organ dysfunction due to cointerventions during critical illness, or due to subsequent transfusions in the same patient. Secondary outcomes were: *1*) first hemoglobin concentration in the 24–72 hours after each hemoglobin measurement; *2*) use of invasive mechanical ventilation in the 24–72 hours after each hemoglobin measurement; *3*) use of vasopressors in the 24–72 hours after each hemoglobin measurement; and *4*) overall hospital mortality from the time of hemoglobin measurement to hospital discharge. To approximate the 24- to 72-hour outcome ascertainment window in the less granular Premier Inc. cohort, we examined outcomes in the 2 days after the day of hemoglobin measurement.

Covariables

We included covariables that were plausibly associated with both transfusion and organ dysfunction to improve estimate precision (28, 29). Included covariables were *1*) age, *2*) sex, *3*) Charlson Comorbidity score (21, 22), *4*) baseline SOFA score at the time of hemoglobin measurement, *5*) use of invasive mechanical ventilation at the time of hemoglobin measurement, *6*) use of vasopressors at the time of hemoglobin measurement, and *7*) transfusion in the 24 hours before hemoglobin measurement. For each covariable, we estimated the discontinuity at the hemoglobin threshold to check if clinical variables other than RBC transfusion exposure were discontinuous at the hemoglobin threshold (i.e., imbalanced), which would potentially decrease the validity of using RDD.

Statistical Analysis

Exposure to transfusion may not be determined by hemoglobin threshold alone (i.e., some hemoglobin concentrations of $<$7.0 g/dl do not lead to transfusion, and some hemoglobin concentrations of $\geq$7.0 g/dl lead to transfusion). Thus, the decision rule for transfusion leads to a "fuzzy" RDD. In a fuzzy RDD, the difference at the threshold is an estimate of the intention-to-treat (ITT) effect of having a hemoglobin concentration just below versus above the threshold. In addition to the ITT effect, the threshold rule can be used as an instrumental variable to estimate the effect of the treatment itself for so-called "compliers" (i.e., patients who would receive transfusion owing to having hemoglobin below the threshold and who would not receive transfusion owing to having hemoglobin above the threshold) (13, 16). This effect is known as the complier average causal effect (CACE). CACE is a causal estimate of the effect of transfusion on outcomes while accounting for crossover between treatment arms. CACE rescales the ITT effect by the degree of measured compliance with the treatment at the threshold (13).

Both ITT and CACE are of clinical/policy interest. The ITT effect can be interpreted as the effect of raising (or lowering) the threshold (one potential guideline change). CACE can be interpreted as the effect of transfusion itself among those patients induced to have a transfusion because of the threshold rule. The CACE estimand is arguably of greater clinical relevance, as clinicians would implicitly compare this effect with other individual-level medical interventions for this population. Thus, we chose the CACE as the primary estimand of interest and also reported ITT effects for each outcome at the hemoglobin threshold. Both ITT and CACE estimates are identified at the threshold and may not be generalizable to patients with hemoglobin values far from 7.0 g/dl.

The effect estimates for each outcome were as follows: *1*) primary outcome (difference in modified SOFA score points); *2*) hemoglobin concentration (difference in hemoglobin concentrations [g/dl]); *3*) use of invasive mechanical ventilation (risk difference [RD]); *4*) use of vasopressors (RD); and *5*) overall hospital mortality (RD). We quantified discontinuity in the exposure, covariables, and outcomes consistent with the approach used by Goulden and colleagues (29) (local linear regression with triangular kernel weights and automatic asymmetric bandwidth selection). We used bias-corrected estimators and confidence intervals (CIs) to reduce coverage error and the effect of local linear regression tuning parameter selection (30). In an individual patient-level meta-analysis, we combined the three cohorts and repeated the primary CACE analysis using robust estimators and CIs to account for clustering by cohort. Table E1 in the online supplement shows checks to evaluate the required assumptions for RDD in our study (31).

Sensitivity Analyses

We performed sensitivity analyses to assess the robustness of our results to alternative model tuning parameters and functional forms of hemoglobin measurements: *1*) half bandwidth, *2*) double bandwidth, *3*) local quadratic regression, *4*) global polynomial approach (third, fourth, and fifth order), and *5*) symmetric bandwidths. We calculated an E-value to determine the strength of association between a theoretical unmeasured confounder, transfusion, and the modified SOFA score that the unmeasured confounder must have to bring the observed effect estimate to the null (32, 33).

Subgroup Analyses

We conducted subgroup analyses to test for effect modification (34) between patients with sepsis and those without sepsis and between patients admitted to cardiac ICUs versus and those admitted to other ICUs, as these subgroups might be expected to differentially benefit from the improved oxygen-carrying capacity associated with RBC transfusion (35, 36).

R (version 4.0.2) with package rdrobust (37, 38) was used for analyses. α was two-sided and set at 0.05. The code used to generate the study cohort and conduct the analyses is available at https://github.com/nabosch/Bosch-Lab. This study was designated not human subjects research by Boston University's institutional review board (#H-41795).

Table 1. Characteristics at the time of hemoglobin measurement

Variable at the Time of Hemoglobin Measurement	MIMIC-IV		eICU		Premier Inc.	
	Cohort (*n* = *11,181*)	Discontinuity at the Hemoglobin Threshold of 7.0 g/dl (95% CI)*	Cohort (*n* = *13,644*)	Discontinuity at the Hemoglobin Threshold of 7.0 g/dl (95% CI)	Cohort (*n* = *167,142*)	Discontinuity at the Hemoglobin Threshold of 7.0 g/dl (95% CI)
Age, yr, median (IQR)	66 (54–77)	0.5 (−4.1 to 5.1)	65 (53–75)	2.2 (−5.1 to 0.6)	66 (55–75)	0.3 (−0.7 to 1.3)
Female sex, *n* (%)	5,239 (46.9)	11.1 (−1.8 to 24.0)	6,225 (45.6)	−5.1 (−14.4 to 4.1)	74,984 (44.9)	2.3 (−0.7 to 5.3)
SOFA score, points, median (IQR)	4 (2–6)	−0.1 (−1.2 to 0.9)	6 (3–9)	1.4 (0.3 to 2.4)	1 (0–3)	0.1 (−0.1 to 0.3)
Charlson Comorbidity Score, points, median (IQR)	5 (4–7)	0.6 (−0.3 to 1.4)	0 (0–1)	−0.1 (−0.2 to 0.1)	2 (1–3)	0.0 (−0.1 to 0.1)
Use of invasive mechanical ventilation, *n* (%)	2,441 (21.8)	2.5 (−9.7 to 14.6)	4,992 (36.5)	3.7 (−5.8 to 13.2)	71,957 (43.1)	0.0 (−2.9 to 2.9)
Use of vasopressors, *n* (%)	1,774 (15.9)	−6 (−18.2 to 6.3)	2,615 (19.1)	5.0 (−3.5 to 13.5)	30,558 (18.3)	−0.1 (−2.7 to 2.4)
Prior use of RBC transfusion†, *n* (%)	544 (4.9)	6.4 (−1.8 to 14.5)	576 (4.2)	0.2 (−5.2 to 8.9)	10,278 (6.1)	−0.3 (−2.4 to 1.8)

Definition of abbreviations: CI = confidence interval; IQR = interquartile range; MIMIC-IV = Medical Information Mart for Intensive Care IV; RBC = red blood cell; SOFA = sequential organ failure assessment.
*Crossing from higher hemoglobin to lower hemoglobin concentration (i.e., from lower proportion of transfusion to higher proportion of transfusion).
†In the 24 hours before hemoglobin measurement.

Results

We included 11,181 patients from the MIMIC-IV cohort, 13,664 patients from the eICU cohort, and 167,142 patients from the Premier Inc. cohort (Figures E1–E3). The median hemoglobin concentration was >9 g/dl in all cohorts (MIMIC-IV, 9.7 g/dl [interquartile range (IQR), 8.6–11.2 g/dl]; eICU, 9.7 g/dl [IQR, 8.3–11.3 g/dl]; Premier Inc., 10.3 g/dl [IQR, 8.6–12.1 g/dl]) (Figure E4). There was no evidence of discontinuity (i.e., imbalance) crossing the hemoglobin threshold from higher to lower concentration for any of the examined covariables except for a 1.4 (95% CI, 0.3–2.4)-point increase in baseline SOFA score in the eICU cohort (Table 1 and Figures E5–E7). Table E2 shows large differences in covariables when stratified by transfusion exposure (e.g., akin to a "traditional" Table 1), highlighting the risk for strong confounding if we had used traditional modeling techniques to examine the comparative effectiveness of blood transfusion to no transfusion. Crossing the hemoglobin threshold of 7.0 g/dl from higher to lower hemoglobin resulted in a >20% increase (discontinuity) in transfusion rate in all cohorts (MIMIC-IV, 22.9% [95% CI, 8.4%–37.4%]; eICU, 36.1% [95% CI, 27.4%–44.7%]; Premier Inc., 25.4% [95% CI, 22.1%–28.7%]) (Figure 1).

In the primary analyses, treatment with transfusion among compliers was associated with an increase in hemoglobin concentrations (MIMIC-IV, 2.4 g/dl [95% CI, 1.1 to 3.6 g/dl]; eICU, 0.7 g/dl [95% CI, 0.3 to 1.2 g/dl]; Premier Inc., 1.9 g/dl [95% CI, 1.5 to 2.2 g/dl]) and potentially increased organ dysfunction (MIMIC-IV, 4.6 [95% CI, −1.2 to 10.4] points, $P = 0.12$, E-value = 3.5; eICU, 4.4 [95% CI, 0.9 to 7.8] points, $P = 0.01$, E-value = 3.3; Premier Inc., 1.1 [95% CI, −0.2 to 2.3] points, $P = 0.09$, E-value = 1.7) in the 24–72 hours after hemoglobin measurement (Figure 1). In the individual patient-level meta-analyses, crossing the hemoglobin threshold of 7.0 g/dl from higher to lower hemoglobin resulted in a 25.3% (95% CI, 22.8% to 27.8%) increase in transfusion rates but no improvement in organ dysfunction owing to transfusion among compliers (1.3 [95% CI, −3.4 to 6.1] points). In the ITT results, the CIs suggest that the policy of routine transfusion at a hemoglobin threshold of 7 g/dl potentially increases organ dysfunction (MIMIC-IV, 1.2 [95% CI, −0.6 to 3.1] points; eICU, 2.0 [95% CI, 0.6 to 3.4] points; Premier Inc., 0.3 [95% CI, −0.1 to 0.7] points). Sensitivity analyses evaluating alternative model bandwidths and functional forms were similar to the primary analyses (Table 2 and Figures E8–E10). In subgroup analyses, associations between transfusion and organ dysfunction in the Premier Inc. cohort suggested effect modification for patients with sepsis: RBC transfusion was associated with increased organ dysfunction among patients with sepsis (2.8 [95% CI, 1.0 to 4.6] points) but not in patients without sepsis (−0.2, [95% CI, −1.4 to 1.1]; P value for interaction = 0.04). There was no evidence of effect modification among patients admitted to cardiac versus noncardiac ICUs (Table E3).

For the secondary outcomes, there were no clear differences across study cohorts in the primary CACE analyses or ITT analyses for the use of invasive mechanical ventilation or the use of vasopressors in the 24–72 hours after hemoglobin measurement, or for overall hospital mortality (Table 3).

Discussion

We used RDD to assess *1*) the effectiveness of RBC transfusion versus no transfusion at a hemoglobin threshold of <7.0 g/dl owing to crossing the hemoglobin threshold and *2*) the effects of a policy of routine transfusion

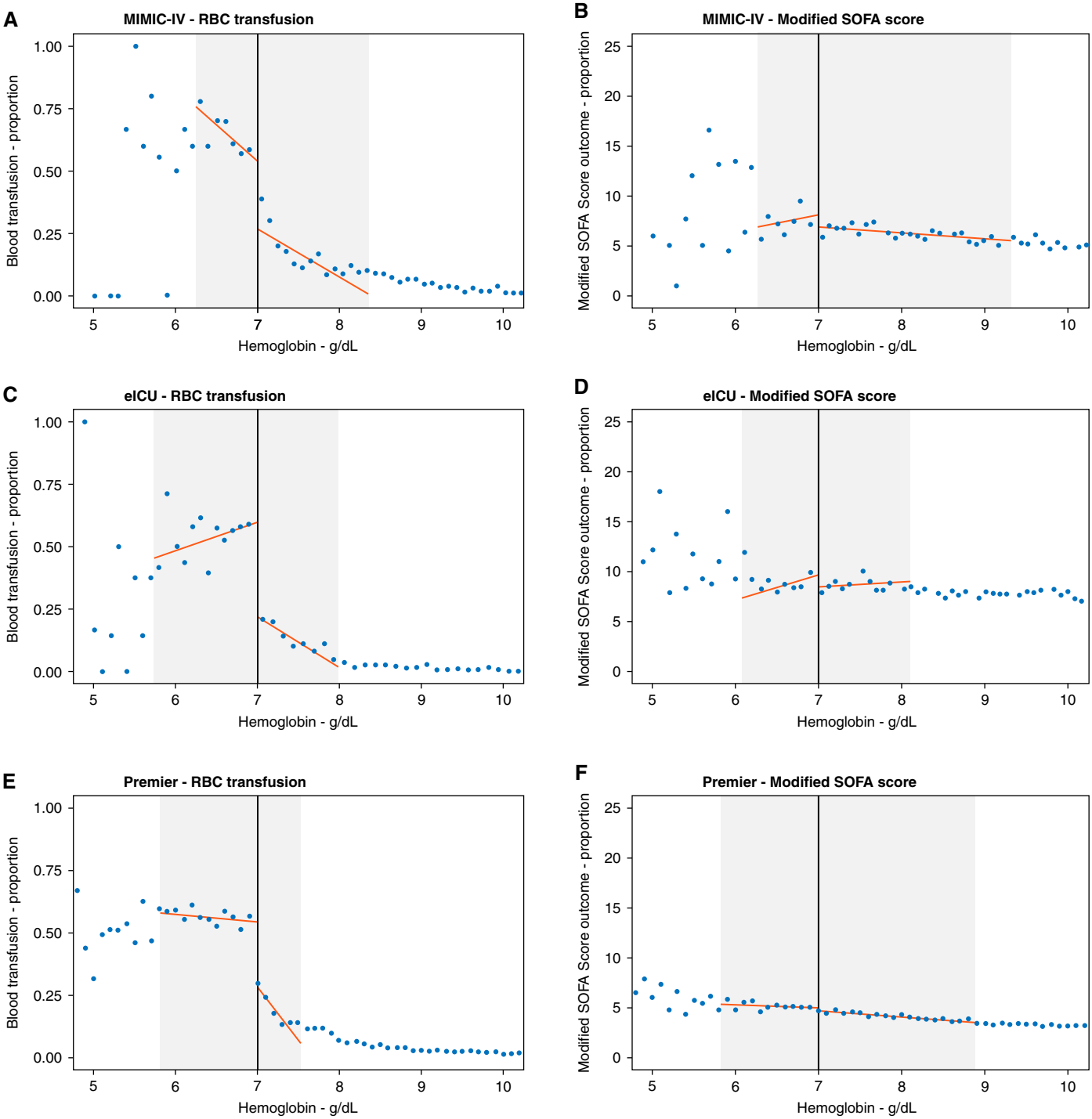

Figure 1. Exposure and outcome discontinuity at the hemoglobin threshold. Shown are estimates of the discontinuity in blood transfusion and the primary outcomes at the hemoglobin threshold of 7 g/dl. *A*, *C*, and *E* show discontinuity in the proportion of blood transfusions administered at the hemoglobin threshold in the MIMIC-IV, eICU, and Premier Inc. cohorts, respectively. *B*, *D*, and *F* show discontinuity in the modified SOFA score primary outcome at the hemoglobin threshold in the MIMIC-IV, eICU, and Premier Inc. cohorts, respectively. Solid blue dots correspond to binned hemoglobin concentrations at intervals of 0.1 g/dl. Gray areas correspond to the optimal bandwidth selected by the data-driven procedure for the local linear regression. Red lines correspond to local linear regression lines fitted to the binned hemoglobin concentrations below and above the hemoglobin transfusion threshold. MIMIC-IV = Medical Information Mart for Intensive Care IV; RBC = red blood cell; SOFA = sequential organ failure assessment.

Table 2. Model specification sensitivity analyses for the association between RBC transfusion and the modified sequential organ failure assessment score organ dysfunction primary outcome using fuzzy regression discontinuity design

Analysis	MIMIC-IV			eICU			Premier		
	Lower BW	Upper BW	CACE (95% CI)	Lower BW	Upper BW	CACE (95% CI)	Lower BW	Upper BW	CACE (95% CI)
Half BW	0.4	1.2	−0.2 (−9.6 to 9.1)	0.5	0.5	6.8 (0.5 to 11.7)	0.6	0.9	1.2 (−0.7 to 3.1)
Double BW	1.5	4.7	3.0 (−0.6 to 6.7)	1.8	2.2	3.2 (0.8 to 5.6)	2.4	3.8	1.0 (0.2 to 1.7)
Symmetric BW	0.6	0.6	11.4 (−2.5 to 25.4)	0.8	0.8	5.3 (1.4 to 9.2)	0.9	0.9	1.4 (−0.2 to 3.0)
Local quadratic regression	0.8	3.5	−2.8 (−12.8 to 7.1)	1.1	2.2	7.4 (2.2 to 12.6)	1.4	3.2	1.1 (−0.7 to 2.9)
Global polynomial (third order)	5.0	12.9	4.9 (−1.0 to 10.9)	4.1	12.9	3.4 (0.3 to 6.5)	5.9	12.9	1.4 (0.2 to 2.6)
Global polynomial (fourth order)	5.0	12.9	9.9 (−0.5 to 19.9)	4.1	12.9	5.8 (1.1 to 10.4)	5.9	12.9	0.6 (−1.1 to 2.3)
Global polynomial (fifth order)	5.0	12.9	−2.6 (−15.4 to 10.3)	4.1	12.9	8.5 (2.8 to 14.1)	5.9	12.9	0.9 (−1.2 to 2.9)

Definition of abbreviations: BW = bandwidth; CACE = complier average causal effect; CI = confidence interval; MIMIC-IV = Medical Information Mart for Intensive Care IV; RBC = red blood cell.

at a hemoglobin concentration of 7.0 g/dl. Blood transfusion owing to crossing the hemoglobin threshold of 7.0 g/dl was associated with increased hemoglobin concentrations but no improvement in organ dysfunction (and potential worse organ dysfunction, especially among patients with sepsis). Our results suggest that routine transfusion at a hemoglobin threshold of 7.0 g/dl is not associated with clinical improvement.

Our study (in the context of previous RCTs) calls the standard practice of routine transfusion at a fixed hemoglobin threshold of 7.0 g/dl in the ICU into question. The 1999 TRICC trial (4) showed that critically ill patients who were randomized to a restrictive hemoglobin threshold of <7.0 g/dl received fewer transfusions and had less organ dysfunction compared with patients randomized to a hemoglobin threshold of 10 g/dl. Results from the TRICC trial suggest that the effect of transfusion is more favorable with a restrictive hemoglobin threshold compared with a liberal threshold but, importantly, do not clarify if transfusion at a restrictive threshold is more favorable to no transfusion. The results from our study show that the effects of a policy of routine transfusion at a hemoglobin of 7.0 g/dl do not improve SOFA and may actually increase organ dysfunction. Thus, future clinical trials should compare the effectiveness of transfusion at a hemoglobin threshold of 7.0 g/dl with that at lower thresholds where transfusion effects may be more favorable (e.g., hemoglobin threshold of 6.0 g/dl) with dynamic measures (e.g., relative decrease in hemoglobin [39]), patient-centered measures (e.g., symptoms of anemia [40]), or measures of oxygen delivery to evaluate the risk/benefit ratio of transfusion in critically ill patients.

Strengths and Limitations

Our study has several strengths. Unlike traditional retrospective cohort studies that

Table 3. Outcomes for the effect of transfusion at a hemoglobin threshold of 7.0 g/dl, regression discontinuity analyses

Analysis	MIMIC-IV			eICU			Premier Inc.		
	Lower BW	Upper BW	Estimate (95% CI)	Lower BW	Upper BW	Estimate (95% CI)	Lower BW	Upper BW	Estimate (95% CI)
Primary outcome modified SOFA score in the 24–72 h after hemoglobin measurement, points									
CACE	0.7	2.3	4.6 (−1.2 to 10.4)	0.9	1.1	4.4 (0.9 to 7.8)	1.2	1.9	1.1 (−0.2 to 2.3)
ITT	0.7	2.8	1.2 (−0.6 to 3.1)	0.7	3.3	2.0 (0.6 to 3.4)	1.2	2.8	0.3 (−0.1 to 0.7)
Hemoglobin level in the 24–72 h after hemoglobin measurement, g/dl									
CACE	0.7	1.6	2.4 (1.1 to 3.6)	1.2	1.7	0.7 (0.3 to 1.2)	1.1	0.9	1.9 (1.5 to 2.2)
ITT	0.6	1.3	0.6 (0.3 to 0.9)	0.9	0.8	0.1 (0.1 to 0.4)	0.9	0.6	0.4 (0.3 to 0.5)
Use of IMV in the 24–72 h after hemoglobin measurement, %									
CACE	0.8	2.1	−16.7 (−57.7 to 24.3)	1.1	1.0	24.1 (−0.3 to 48.4)	1.1	0.8	5.6 (−5.9 to 17.0)
ITT	0.9	1.8	−6.1 (−18.4 to 6.2)	0.7	3.2	10.4 (0.4 to 20.0)	1.2	2.4	0.0 (2.9 to 2.8)
Use of vasopressors in the 24–72 h after hemoglobin measurement, %									
CACE	0.7	2.1	−23.0 (−59.7 to 13.7)	1.2	2.3	14.7 (−0.5 to 29.8)	1.4	1.4	5.6 (−2.3 to 13.5)
ITT	0.7	2.3	−6.5 (−17.4 to 4.4)	0.7	2.7	11.5 (4.0 to 19.0)	1.4	2.4	1.8 (−0.5 to 4.2)
Hospital mortality, %									
CACE	1.0	2.3	15.7 (−18.8 to 50.2)	1.2	1.4	9.3 (−9.1 to 27.7)	1.1	1.4	7.4 (−0.5 to 15.3)
ITT	1.0	2.6	4.8 (−6.2 to 15.7)	0.9	2.8	4.2 (−3.1 to 11.6)	1.2	2.5	1.6 (−0.7 to 3.9)

Definition of abbreviations: BW = bandwidth; CACE = complier average causal effect; CI = confidence interval; IMV = invasive mechanical ventilation; ITT = intention-to-treat; MIMIC-IV = Medical Information Mart for Intensive Care IV; SOFA = sequential organ failure assessment.

may have substantial unmeasured residual confounding, RDD minimizes both measured and unmeasured confounding (13, 14). Our analyses showed similar patient characteristics near the transfusion threshold of 7.0 g/dl, supporting exchangeability and a low risk for unmeasured confounding near the transfusion threshold. In addition, our results were robust to multiple sensitivity analyses addressing the functional form of hemoglobin measurement that increases the likelihood that our results estimate the true effects of RBC transfusion at a hemoglobin threshold of <7.0 g/dl. In addition, the robustness of our findings across three separate and unique cohorts, including two large multicenter cohorts, increases the external validity of our findings and confidence in the stability of the effect estimates.

Our study also has limitations. First, the results of our study apply only to patients with a narrow range of hemoglobin levels close to the threshold of 7.0 g/dl. The effects of blood transfusion at higher and lower hemoglobin thresholds are not evaluable within the context of this study. Second, lower hemoglobin levels are associated with worse outcomes (41). Thus, the data-driven bandwidths in our study may be large enough to introduce confounding by severity of illness, which may be suggested by the reversal in effect estimate direction in the half-bandwidth sensitivity analysis in the MIMIC-IV cohort. However, the triangular kernel regression approach used in our study preferentially weights hemoglobin concentrations closest to the threshold to maximize comparisons between similar hemoglobin concentrations, and the effect estimate from the half-bandwidth sensitivity analyses in the larger eICU and Premier Inc. cohorts were consistent with the primary analyses. In addition, the E-values of more than 1.5 suggest that only a strong unmeasured confounder would influence our findings. We purposefully examined outcomes that were in close temporal relation to hemoglobin transfusion because we thought it was unlikely that we could detect differences in organ dysfunction due to a single blood transfusion at later time points with retrospective data; thus, our results may be less meaningful (compared with later "hard" outcomes like 30-day mortality [4]) for patients and families weighing the implications of blood transfusion and should not be used as evidence that blood transfusions are ineffective for time points beyond 72 hours. Finally, it is possible that patients who were transfused were also monitored more closely with follow-up laboratory and vital sign assessments. Thus, given that missing SOFA score elements were assigned a SOFA organ component score of 0, it is possible that ascertainment bias may partially explain the trend toward worse organ dysfunction with transfusion.

Conclusions

RBC transfusion at a hemoglobin threshold of 7.0 g/dl among critically ill patients was not associated with improved organ dysfunction as measured by the SOFA score compared with no transfusion. These results suggest that evaluation of transfusion indications other than a hemoglobin threshold of <7.0 g/dl should be considered. ■

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