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Transfusion Practice in the Intensive Care Unit: A Ten-Year Analysis

Giora Netzer, MD, MSCE^{1,2}, Xinggang Liu, MD², Anthony D. Harris, MD, MPH², Bennett B. Edelman, MD³, John R. Hess, MD, MPH³, Carl Shanholtz, MD¹, David J. Murphy, MD⁴, and Michael L. Terrin, MD, MPH^{1,2}

¹Division of Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, Baltimore, MD

²Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD

³Department of Pathology, University of Maryland School of Medicine, Baltimore, MD

⁴Division of Pulmonary and Critical Care Medicine, The Johns Hopkins School of Medicine, Baltimore, MD

Abstract

Background—Clinical guidelines recommend a restrictive transfusion strategy in non-hemorrhaging critically ill patients.

Study Design and Methods—Retrospective observational study of 3533 single-admission patients, without evidence of acute coronary syndromes, hemorrhage or hemoglobinopathy admitted to the medical intensive care unit (MICU) of a large, academic medical center.

Results—MICU admission hemoglobin level (Hgb) did not change significantly over the study period. The proportion of transfused patients decreased from 31.0% in 1997–1998 to 18.0% in 2006–2007 ($p < 0.001$). Among patients receiving transfusion, the mean pre-transfusion Hgb decreased over time from 7.9 ± 1.3 to 7.3 ± 1.3 g/dL ($p < 0.001$). These changes in practice were not accounted for by differences in patient characteristics. The mean nadir Hgb in non-transfused patients decreased from Hgb 11.2 ± 2.2 g/dL in 1997–1999 to Hgb 10.4 ± 2.3 in 2006–2007 ($p < 0.001$). The mean number of units per patient transfused decreased during this time from 4.3 ± 4.7 to 3.0 ± 3.8 units ($p < 0.001$). The proportion of transfused patients who were transfused at Hgb < 7.0 g/dL increased by an estimated absolute increment of 3.2% (95% CI: 2.1 to 4.3%) per interval ($p < 0.001$), and the proportion of single unit transfusions during the first transfusion episode increased by 1.4% per interval (95% CI: 0.2 to 2.6%, $p = 0.03$) from 40.2% in 1997–1998 to 53.1% in 2006–2007.

Conclusions—Between 1997 and 2007, important and sustained changes have occurred in our MICU physician transfusion practices, with overall reductions in the proportion of patients transfused, mean pre-transfusion Hgb level, and nadir Hgb level in patients who were not transfused.

Corresponding author: Giora Netzer, MD, MSCE, Division of Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, 110 S. Paca St., 2nd Floor, Baltimore, MD 21201, gnetzer@medicine.umaryland.edu, Fax: 410 328-0177.

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Keywords

blood transfusion; erythrocyte transfusion; intensive care units; outcome and process adjustment; comparative effectiveness research; evidence-based practice; information dissemination; diffusion of innovation; benchmarking, health care; physician's practice patterns

Introduction

Transfusion is a frequently administered therapy among critically ill patients; between one third and one-half of patients are transfused at some point in the course of their intensive care unit (ICU) stays.^{1, 2} During the mid-20th Century, the decision to transfuse asymptomatic patients had been guided by the “10/30” rule, that a minimum acceptable hemoglobin level (Hgb) of 10.0 g/dL (and a hematocrit of approximately 30%), which continued for several decades.^{3, 4} With the recognition in 1982 that human immunodeficiency virus was a blood-borne pathogen⁵ and new data documenting physiologic tolerance of anemia, by the 1980s, this automatic transfusion threshold came into question (Table 1).^{6–8} In 1999, Hebert et al published the results of a Canadian, multi-center, randomized clinical trial evaluating a restrictive transfusion strategy among ICU patients, transfusing 1 unit of packed red blood cells (pRBCs) when the patient's hemoglobin (Hgb) level was <7.0 g/dL, compared to a strategy of transfusing at Hgb <10.0 g/dL.^{9, 10} This study, the Transfusion Requirements in Critical Care (TRICC) trial, found no statistically significant differences between the treatment groups in their outcomes. Subsequent practice guidelines reflected TRICC conclusions that similar or possibly improved outcomes could be obtained with a restrictive transfusion approach.¹¹

Other studies have evaluated transfusion practice in the short term and dichotomously before versus after publication of the TRICC findings. We describe and assess pRBC transfusion practice during the period 1997–2007 in a large, academic medical center, medical intensive care unit (MICU).

Materials and Methods

We conducted a single-center, retrospective, observational study of patients admitted to the University of Maryland Medical Center (UMMC) MICU between October 1, 1997 and December 31, 2007. These dates reflect the earliest availability of complete electronic clinical data and the most recent full year of data available to us at the time of data extraction. UMMC is a 705-bed teaching hospital with a closed-model¹² MICU, in which patients are managed only by defined and designated medical intensivists. During this time period, 27 attending physicians worked with house staff and nurse practitioners in the MICU, for a total of 123 attending staffing years. Of this total, 6 physicians attended every year, comprising 66 staffing years (53.7%), while 8 faculty attended only in the years 2006–2007, totaling 12 staffing years (9.8%). During the study period, no unit- or hospital-specific transfusion protocols or guidelines were promulgated.

TRICC excluded patients with acute coronary syndromes and hemorrhage; most subsequent published guidelines did not apply to these patients. We excluded patients with ICD-9-CM codes for acute coronary syndromes (410 and 411)¹³ and adapted a published set of ICD-9-CM codes validated for the evaluation of risks of warfarin therapy to exclude patients with hemorrhage.¹⁴ We also excluded patients with ICD-9-CM codes for intracranial bleeding (800, 801, 803, 804, 852, 853), hemothorax (860) and hemorrhage complicating procedures (998.11). Additionally, we excluded patients with ICD-9-CM codes for hemoglobinopathies (282 and 517.3), as different indications apply for the management of their anemias.^{15, 16}

Patients <13 years of age were excluded. We evaluated only patients with single admissions on the data file to protect independence of observations and, to a lesser extent, comparability of the clinical courses studied. These data were abstracted from the hospital's electronic medical and blood bank record systems.

Multiple-unit transfusion events were identified on the basis of the number of units issued by the blood bank to a patient within a 6-hour period with no intervening check of patient Hgb level. The pre-transfusion Hgb level was the last laboratory value preceding the release of the first unit of pRBCs by the blood bank. Transfusion practices between October 1, 1997, and December 31, 2007 were evaluated in nine intervals created around the annual calendar, data availability, and February 11, 1999, the date of TRICC publication: October 1, 1997—February 10, 1999 (1997–1998); the seven 12-month periods in February 11, 1999—February 10, 2006 (1999–2005); and February 11, 2006—December 31, 2007 (2006–2007).

Baseline MICU admission characteristics in transfused and non-transfused are presented as mean values with standard deviations, and compared using two-sample t-tests for continuous variables,¹⁷ and comparisons of proportions for categorical variables.¹⁸ Mean Hgb level at the time of MICU admission, pre-transfusion Hgb level, and nadir Hgb among the nontransfused, number of transfused pRBC units per patient and proportion of single and multiple unit transfusion over time were described by interval and evaluated using linear regression, which was also used for assessment of case-fatality rates.¹⁷ The proportion of patients transfused each year, according to three pre-transfusion Hgb level strata, Hgb <7.0 g/dL, Hgb ≥7.0 g/dL and <10.0 g/dL, and Hgb ≥10.0 g/dL, was evaluated with linear and logistic regression^{17, 19} and presented with 95% confidence intervals (CI). These strata were selected on the basis of the TRICC findings and older guidelines. Splines, piece-wise polynomial fit functions which can compare different linear slopes, were used to compare slopes of aggregated interval sequences.²⁰ To assess effects of patient characteristics on transfusion practice, regression analyses were also performed with the variables of age, gender, race, first-level Agency for Healthcare Research and Quality (AHRQ) Clinical Classifications Software (CCS) 2010 diagnostic category,^{21, 22} Charlson score,^{23, 24} and admission laboratory values (hemoglobin, white blood cell count, creatinine, sodium, potassium, glucose, and bicarbonate).^{25–30}

Analyses were performed using SAS v.9.1.3. We applied the traditional definition of $p \leq 0.05$ for statistical significance,³¹ $p \leq 0.01$ to indicate more evidence that differences did not result from chance, and $p < 0.001$ to indicate strong evidence.

The IRB of the University of Maryland Baltimore reviewed and approved this study with waiver of consent.

Results

Of the 7128 patients admitted to our MICU during the study period, 3569 patients met inclusion criteria, of whom 36 (1%) patients with unavailable Hgb levels (distributed over the 9 intervals, and with mean length of stay 0.5 ± 0.8 days) were not included in the analysis, resulting in 3533 patients whose data were analyzed (Fig. 1). Patients who were transfused presented with lower MICU admission Hgb values and higher Charlson Scores (Table 2). There were no statistically significant differences in the baseline age, admission Hgb, gender, or race of transfused and non-transfused patients before and after the TRICC publication date. The proportions of primary ICD-9-CM for respiratory disease decreased from 31.8% before TRICC to 22.1% afterwards ($p < 0.001$). There was no important change over time in mean MICU admission Hgb level from 1997–2007, 11.4 ± 2.7 g/dL versus

11.4±2.5 g/dL (−0.02 g/dL estimated per interval, 95% CI −0.051 to 0.007, linear regression $p=0.13$). The total MICU length of stay (LOS) for non-transfused patients was greater than the LOS prior to first transfusion in transfused patients ($p=0.01$).

The percentage transfused (Figure 2) decreased from 31.0% in 1997–1998 to 18.0% in 2006–2007 (logistic regression $p<0.001$). Over the nine intervals, there were small, annual decreases in the percentage transfused in the Hgb <7.0 g/dL stratum and the Hgb ≥10.0 g/dL stratum (Figure 3). There was a larger decrease over time among patients with Hgb ≥7.0 g/dL and <10.0 g/dL. In the Hgb ≥7.0 g/dL and <10.0 g/dL stratum, the decrease was greater for the years 1997–2001 than 2002–2007, while in the other strata the rates were similar comparing 1997–2001 with 2001–2007. These results were consistent after adjustment for age, gender, race, first-level AHRQ CCS diagnostic category, Charlson score, and abnormal laboratory values (Table 3). Changing the spline knot point to 2000 or 2002 yielded similar results.

Among non-transfused patients (Figure 4), mean nadir Hgb decreased from 11.2±2.2 g/dL in 1997–1999 to 10.4±2.3 in 2006–2007 (linear regression $p<0.001$). This decrease in mean nadir Hgb remained after adjustment for age, gender, race, first-level AHRQ CCS diagnostic category, Charlson score, and abnormal lab values. During this time period the mean pre-transfusion Hgb decreased from 7.9±1.3 to 7.3±1.3 g/dL (linear regression $p<0.001$), which remained apparent after adjustment for age, gender, race, first-level AHRQ CCS diagnostic category, Charlson score, and abnormal laboratory values. The mean number of pRBC units transfused per MICU patient, (all patients, both transfused and non-transfused) decreased over time from 1.3±3.3 units in 1997–1999, to 0.5±2.0 units in 2006–2007 (linear regression $p<0.001$). In patients receiving transfusion, the mean number of units transfused per patient decreased from 4.3±4.7 units (1997–1998) to 3.0±3.8 units (2006–2007) per patient transfused (linear regression $p<0.001$), a 0.17 unit/patient transfused reduction estimated per interval (95% CI: 0.07 to 0.28). The proportion of patients transfused who had pre-transfusion Hgb <7.0 g/dL increased by an absolute increment of 3.2% (95% CI: 2.1 to 4.3%, $p<0.001$) per interval. The proportion of single unit transfusions during the first transfusion episode also increased over time, by an absolute percentage of 1.4% ($p=0.03$) per interval (95% CI: 0.2 to 2.6%) from 40.2% in 1997–1998 to 53.1% in 2006–2007. The case-fatality rate started the time period studied at 18.8% and decreased to 16.7% with large interval to interval variability and no strong, consistent pattern ($p=0.06$ on linear regression).

Discussion

Because of blood's immunomodulatory and pro-inflammatory effects,³² as well as blood's scarcity and cost, physician utilization of transfusion merits close attention.^{1, 2, 33–38} Important changes have occurred in physician transfusion practices over time. Six years prior to publication of the TRICC findings, Hebert et al found that the mean pre-transfusion Hgb in 6 Canadian tertiary critical care centers was 8.6±1.3 g/dL, and 80% of orders were for two units of pRBCs.³ In the U.S. in an academic medical center ICU in 1990, Corwin et al found a mean pre-transfusion hematocrit of 27%.³⁹

After TRICC publication, observational studies were performed in Great Britain, Australasia and the United States, evaluating transfusion behavior from February 1999 to April 2001. These studies, varying in length between 2 weeks and 9 months, showed variable penetration of restrictive transfusion strategies into clinical practice, with pre-transfusion Hgb levels ranging from median 7.8 g/dL (interquartile range 7.4–8.4) to mean 8.6±1.7 g/dL.^{1, 2, 40–43} Studies evaluating transfusion between 2003–2006 found lower pre-transfusion Hgb levels. An American 22-month prospective study of patients with acute lung

injury who were admitted between 2004 and 2006 found the prevalence of transfusion was 47%, with a mean pre-transfusion Hgb of 7.7 ± 1.1 g/dL.⁴⁴

These studies above did not assess how transfusion practice changed over time. Ours is the longest MICU transfusion practice time period evaluated in the literature, and the first to assess temporal effects and evaluate transfusion practices for over a decade, including before and after publication of the TRICC trial findings. By evaluating patient-specific data over a decade of MICU practice, we identified not only change over time, but that this change varied by interval and patient Hgb level. We found clear and substantial changes in practice, concentrated in the early years of the decade in temporal association with TRICC and related guidelines. These changes were sustained in the latter half of our decade of observation. These changes reflected physician decision-making and were associated independently of changes in patient baseline characteristics, chronic disease, or acuity of illness.

Because the likelihood of transfusion increases with length of stay (LOS), we evaluated the LOS in the non-transfused to assess whether the decision to transfuse was a reflection of the patient's LOS. We found that the MICU LOS for non-transfused patients was longer than the time to first transfusion in those patients who were transfused. We interpret these data to mean this that the decision to withhold transfusion was not a consequence of shorter ICU courses in these patients. The stability of admission Hgb levels over time suggests that the lower rate of transfusion was not reflective of higher patient Hgb or reduced incidence of anemia. Our multivariable analysis confirms that the decreases in nadir and pre-transfusion Hgb were not due to patient characteristics.

The assessment of nadir Hgb levels in the non-transfused, in addition to evaluating the pre-transfusion Hgb and the proportion transfused, differentiates our study from most prior studies methodologically.^{2, 3, 39–43} Changes in pre-transfusion Hgb may not reflect change in the amount of blood used if the proportion transfused (or the nadir Hgb in the non-transfused) is unchanged. We found: the proportion of patients transfused decreased over the time; mean pre-transfusion Hgb levels decreased over time; non-transfused nadir Hgb levels decreased over time; and the units of blood transfused per MICU patient decreased over time. This set of consistent observations provides convincing evidence of a change in transfusion practices, even more convincing than the decrease in the mean number of units transfused per transfused patient or the isolated observation of a lower pre-transfusion Hgb level because the entirety of the MICU patient population's hematologic status and blood usage is taken into account.

Different patterns of clinical implementation have been noted after the publication of clinical trials and the creation of guidelines for several practice settings,⁴⁵ including the treatment of hyperlipidemia with statin medications,^{46–48} treatment of patients after acute myocardial infarction with beta-blockers,^{49, 50} and therapy for heart failure.^{51–53} In the critical care setting, a minority of ICUs have adopted daily sedation interruptions and spontaneous breathing trials despite evidence of their benefit.⁵⁴ Numerous barriers to the implementation of guidelines have been identified, including lack of awareness, familiarity and agreement among clinicians; and reluctance to change previous practices.⁵⁵ The time period evaluated in these studies of guideline implementation varies from months to years.

Studies evaluating treatment practices may be limited by a time period too short to capture or exclude meaningful change. After the publication of a clinical trial showing the survival benefit of low tidal volume ventilation for the treatment of the acute respiratory distress syndrome,⁵⁶ multiple studies of 12–26 month duration concluded that there was little change in practice.^{57–60} However, a study by Checkley et al evaluating a 10-year interval,

including 5 years post-publication, did find an important decrease in the set ventilator tidal volume.⁶¹ This study found, as did our study, that the rate of change in practice varied over time. Thus, the short intervals used in many studies evaluating practice before and after publication of trials and guidelines may be inadequate to properly assess real effects. While we found that the largest magnitude of change started in the interval after the publication of the TRICC trial, the period of large-magnitude change lasted 5 years and subsequent smaller magnitude change persisted for another 5 years. Limiting our study to a few months or a one-year period, as prior studies were limited, could have missed the changes and pattern of change we found over the decade. The length of time studied in our analysis furthers our understanding of the complexities in assessing changes in transfusion practice over time.

While our data reflect increasing adoption of best practices over time, they show also that UMMC MICU physicians may not have fully implemented restrictive transfusion policies by 2007. Because the use of threshold Hgb values is predicated on patients being asymptomatic and individual tolerance to anemia varies, it would not be expected that 100% of patients would be managed according to restrictive transfusion policies. Still, our findings that the majority of transfusions continued to be above the restrictive Hgb threshold of 7.0 g/dL, and that physicians transfused single units close to 50% of the time suggest that physicians in our MICU have not yet fully embraced the restrictive strategy of the TRICC trial. On the other hand, retrospective data collection using ICD-9-CM codes to identify ACS and hemorrhage may have failed to capture some of these patients who should have been excluded from the analysis. Mistaken inclusion of these patients, who are typically transfused more aggressively, may have led us to underestimate the extent of change over time and may mean that there is less room for further restriction of transfusion.

The stability of our MICU's physician staffing suggests the change represents change in physician practice rather than change in physicians. Our study is of equal or greater size and covers a longer time interval than previously published multi-center studies.^{2, 40, 42-44, 62} As a single-center study, our results may not be generalizable to other settings. TRICC treatment recommendations may not have been adopted similarly in other critical care settings; a study of transfusion in surgical patients in our state's health care database during this period found an increase in transfusion rates.⁶³ Pre-transfusion Hgb levels in our MICU were lower than published data from other U.S. intensive care units.^{1, 64} Given the absence of transfusion protocols or guidelines in our MICU, the mechanisms underlying the adoption of this more restrictive transfusion strategy are unclear. As a teaching hospital, these practice changes may also reflect changes in house officer education and training over time. It would be interesting to analyze data from a variety of MICUs, including non-teaching institutions over this extended time interval for comparison. We observed a decrease in the case fatality rate over the time period studied that was not statistically significant. Our study design was not appropriate to test for associations between transfusion practice and clinical outcomes.

Conclusion

Our study shows this group of MICU physicians altered transfusion practice after the publication of the TRICC trial results and that, in the years following, transfusion practice has remained closer to the restrictive transfusion strategy proposed by the TRICC investigators than to older conventions. The rate of change varied over time interval and according to patient MICU admission Hgb level. The rate of change in transfusion practice decreased over time, but implementation of more restrictive transfusion strategies continued years after the initial large shifts in practice. These changes occurred without an internal dictum. Though important change occurred in our MICU, the potential may exist for further application of evidence-based guidelines to our transfusion practices. Institutions should review their ICU blood transfusion practices and consider interventions that may be

effective in reducing inappropriate pRBC use.⁶⁵ These practices should be assessed over a period of time sufficient for their evaluation—perhaps on the order of a decade.

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Figure 1. Enrollment of study participants

UMMC, University of Maryland Medical Center; *MICU*, Medical Intensive Care Unit; *ICD-9-CM*, International Classification of Diseases, 9th Revision, Clinical Modification; *ACS*, Acute Coronary Syndrome; *Hgb*, Hemoglobin

Figure 2. Percentage of patients transfused, by interval

Linear regression estimated a 1.1% absolute reduction in percentage of patients transfused per interval (95%CI: 0.6% to 1.6%, $p < 0.001$).

Figure 3. Proportion of patients transfused, by strata, by interval

The proportion of transfused patients decreased over time in all three hemoglobin strata. Linear regression estimated a -2.0% absolute reduction per interval in Hgb < 7g/dL stratum (95% CI: -3.8% to -0.2% , $p=0.031$), a -3.1% absolute reduction in ≥ 7.0 g/dL and < 10 g/dL stratum (95% CI: -3.9% to -2.4% , $p<0.001$), a -0.2% absolute reduction in Hgb ≥ 10 g/dL stratum (95% CI: -0.4% to 0.0% , $p=0.045$).

Figure 4. Mean nadir hemoglobin and mean pre-transfusion hemoglobin by interval

In non-transfused patients, mean nadir hemoglobin decreased from 11.2 ± 2.2 g/dL (1997–1998) to 10.4 ± 2.3 g/dL (2006–2007), linear regression model estimated a -0.077 g/dL change in mean nadir hemoglobin per interval (95% CI: -0.106 g/dL to -0.047 g/dL, $p < 0.001$). After Adjustment for age, gender, race, first-level Agency for Healthcare Research and Quality (AHRQ) Clinical Classifications Software (CCS) 2010 diagnostic category, Charlson score, and admission laboratory values (white blood cell count, hemoglobin, creatinine, sodium, potassium, WBC, glucose, bicarbonate) change per interval was -0.055 g/dL (-0.083 g/dL to -0.028 g/dL), $p < .0001$.

In transfused patients, mean pre-transfusion hemoglobin decreased from 7.9 ± 1.3 g/dL (1997–1998) to 7.3 ± 1.3 g/dL (2006–2007), linear regression model estimated a -0.078 g/dL change in Mean MICU admission hemoglobin per interval (95% CI: -0.109 g/dL to -0.047 g/dL, $p < 0.001$). After Adjustment for age, gender, race, first-level AHRQ CCS 2010 diagnostic category, Charlson score, and admission laboratory values (white blood cell count, hemoglobin, creatinine, sodium, potassium, WBC, glucose, bicarbonate) change per interval was -0.083 g/dL (-0.116 g/dL to -0.051 g/dL), $p < .0001$.

Table 1

Selected studies and guidelines

Year	Organization/Publication	Comments
1951	Mollison, 1 st Ed.66	Threshold for “anemia chronic sepsis” Hgb 10 g/dL, for aplastic anemia/“refractory anemia”/ leukemia 11 g/dL
1961	Mollison, 3 rd Ed.67	Pre-operative Hgb 13.5 g/dL for men recommended
1983	Mollison, 7 th Ed.68	Post-operative Hgb 8 g/dL in healthy patients, 10 g/dL in those with cardiac or pulmonary disease
1988	NIH69	Perioperative transfusion justifiable at Hgb 7 g/dL in most situations
1992	ACP7	“Normovolemic hemoglobin, 7–10 g/dL can be well tolerated”
1996	ASA70	“Red blood cell transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and it is almost always indicated when it less than 6 g/dL”
1997	CMA71	“Transfusion is more likely to be beneficial when (Hgb) is less than 60 g/L, but not when Hgb is greater than 80 g/L”
1998	Weiskopf et al72	Acute isovolemic reduction of blood Hgb concentration to 50 g/L in conscious healthy resting humans does not produce evidence of inadequate systemic TO_2
1999	Hebert et al9	“A restrictive strategy of red cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients”
2001	BSH11	“Indicated when the Hgb is <7 g/dL,” 2 units pRBCs should be given
2003	MAC of American Red Cross, New England Region73	“patients...may become symptomatic when the Hgb falls below 8 g/dL,” “patients with cardiac, pulmonary, or cerebrovascular disease may become symptomatic with Hgb<10 g/dL
2005	Mollison, 11 th Ed.74	No threshold; Hgb 7–10 g/dL based on individual patient
2006	ASA75	“agree that red blood cells should usually be administered when the Hgb is less than 6 g/dL and strongly agree that red blood cells are usually unnecessary when the level is more than 10 g/dL
2007	American Red Cross76	“transfusion is rarely indicated when the Hgb is above 10 g/dL and almost always indicated in patients when the Hgb is below 6 g/dL”

NIH, National Institute of Health; ACP, American College of Physicians; ASA, American Society of Anesthesiologists; CMA, Canadian Medical Association; BSH, British Society for Haematology; MAC, Medical Advisory Committee; TO_2 : Critical oxygen delivery level

Table 2

Study patient characteristics by transfusion status

Characteristics [*]	Transfused	Not-Transfused	p value [†]	Total (N=3533)
	(n=753)	(n=2780)		
Age, years	54.1±15.7	52.8±16.9	0.05	53.1±16.6
MICU LOS prior to transfusion or total LOS, days [‡]	2.7±4.2	3.2±4.0	0.01	3.1±4.0
MICU Charlson Score, 0–20	2.7±2.5	2.3±2.5	<.0001	2.4±2.5
MICU admission hemoglobin, g/dL	9.3±2.1	12.0±2.3	<.0001	11.4±2.5
Gender, Male	372 (49.4)	1299 (46.7)	0.19	1671 (47.3)
Race, White	338 (44.9)	1187 (42.7)	0.28	1525 (43.2)
MICU Primary diagnosis [¶]				
Diseases of the respiratory system	155 (20.6)	672 (24.2)		827 (23.4)
Infectious and parasitic diseases	167 (22.2)	353 (12.7)		520 (14.7)
Diseases of the circulatory system	52 (6.9)	428 (15.4)		480 (13.6)
Injury and poisoning	58 (7.7)	255 (9.2)	<.0001	313 (8.9)
Neoplasm	130 (17.3)	168 (6.0)		298 (8.4)
Diseases of the digestive disease	50 (6.6)	142 (5.1)		192 (5.4)
Other	141 (18.7)	762 (27.4)		903 (25.6)

* Continuous values are presented as mean ± SD, and categorical values are presented as no. (%).

[†] For continuous variables, p values were obtained from Two-sample t-tests; For categorical variable, p values were obtained from tests of comparison of proportions.

[‡] MICU Stay prior to first unit of transfusion: number of days from MICU admission to first unit of RBC transfusion in transfused patients or total length of stay in non-transfused patients.

[¶] Primary diagnosis: first-level Agency for Healthcare Research and Quality Clinical Classifications Software 2010 diagnostic category

MICU, Medical Intensive Care Unit; LOS, Length of stay

Table 3

Rate of change by strata

Hemoglobin stratum Number transfused/total	1997-2001 vs. 2001-2007 (unadjusted)			1997-2001 vs. 2001-2007 (adjusted [*])		
	Time coefficient slope, 1997-2001 ¹	Time coefficient slope, 2001-2007 ²	Test for equal slopes (1997-2001 vs. 2001-2007)	Time coefficient slope, 1997-2001 ³	Time coefficient slope, 2001-2007 ⁴	Test for equal slopes (1997-2001 vs. 2001- 2007)
<7 g/dL	1.5%	-3.2%		-0.7%	-1.9%	
237/336	(-5.3% to 8.3%)	(-6.0% to -0.3%)	p=0.300	(-8.0% to 6.6%),	(-5.0% to 1.3%),	0.799
	p=0.668	p=0.031		p=0.86	p=0.242	
≥7.0 g/dL and <10.0 g/dL	-9.3%	-0.6%		-9.3%	-0.5%	
490/1630	(-12.0% to -6.5%)	(-1.9% to 0.7%)	p<0.0001	(-12.0% to -6.7%),	(-1.8% to 0.8%),	<0.0001
	p<0.0001	p=0.353		p<0.0001	p=0.474	
≥10g/dL	-0.5%	-0.1%		-0.4%	0.0%	
26/1567	(-1.3% to 0.3%)	(-0.5% to 0.3%)	p=0.466	(-1.2% to 0.4%),	(-0.4% to 0.4%),	0.536
	p=0.211	p=0.619		p=0.342	p=0.839	

Test for heterogeneity across strata:

¹ p<0.0001,

² p=0.082,

³ p<0.001,

⁴ p=0.391

* Adjusted for age, gender, race, first-level Agency for Healthcare Research and Quality Clinical Classifications Software 2010 diagnostic category, Charlson score, and admission laboratory values (white blood cell count, hemoglobin, creatinine, sodium, potassium, WBC, glucose, bicarbonate).