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Authors

Mark, Dustin G
Huang, Jie
Plimier, Colleen
et al.

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Red blood cell transfusions for emergency department patients with gastrointestinal bleeding within an integrated health system

Dustin G. Mark, MD[a,b,c], **Jie Huang, PhD**[c], **Colleen Plimier, MPH**[c], **Mary E. Reed, DrPH**[c], **Gabriel J. Escobar, MD**[c], **David R. Vinson, MD**[c,d], **Nareg H. Roubinian, MD, MPHTM**[b,c,e]

[a]Department of Emergency Medicine Kaiser Permanente Medical Center 3600 Broadway Oakland, California, USA, 94611

[b]Department of Critical Care Kaiser Permanente Medical Center 3600 Broadway Oakland, California, USA, 94611

[c]Division of Research, Kaiser Permanente Northern California 2000 Broadway Oakland, California, USA, 94612

[d]Department of Emergency Medicine Kaiser Permanente Medical Center 1600 Eureka Road, 95661 Roseville, California, USA

[e]Division of Pulmonology Kaiser Permanente Medical Center 3600 Broadway Oakland, California, USA, 94611

Abstract

Study objective: To assess trends over time in red blood cell (RBC) transfusion practice among emergency department (ED) patients with gastrointestinal (GI) bleeding within an integrated healthcare system, inclusive of 21 EDs.

Methods: Retrospective cohort of ED patients diagnosed with GI bleeding between July 1st, 2012 and September 30th, 2016. The primary outcome was receipt of an RBC transfusion in the ED. Secondary outcomes included 90-day rates of RBC transfusion, repeat ED visits, rehospitalization, and all-cause mortality. Logistic regression was used to obtain confounder-adjusted outcome rates.

Results: A total of 24,868 unique patient encounters were used for the primary analysis. The median hemoglobin level in the ED prior to RBC transfusion decreased from 7.5 g/dl to 6.9 g/dl in the first versus last twelve months of the study period ($p<0.0001$). A small trend was observed in

Corresponding Author Dustin G. Mark, MD, Department of Emergency Medicine, Kaiser Permanente Medical Center, 3600 Broadway, Oakland, CA, 94611, Dustin.G.Mark@kp.org.

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the overall adjusted rate of ED RBC transfusion (absolute quarterly change of −0.1%, R2=0.18, p=0.0001) largely attributable to the subgroup of patients with hemoglobin nadirs between 7.0 and 9.9 g/dl (absolute quarterly change of −0.4%, R2=0.38, p<0.0001). Rates of RBC transfusions through 90 days likewise decreased (absolute quarterly change of −0.4%, R2=0.85, p<0.0001) with stable to decreased corresponding rates of repeat ED visits, rehospitalizations and mortality.

Conclusion: Rates of ED RBC transfusion decreased over time among patients with GI bleeding, particularly in those with hemoglobin nadirs between 7.0 and 9.9 g/dl. These findings suggest that ED providers are willing to adopt evidence-based restrictive RBC transfusion recommendations for patients with GI bleeding.

Keywords

red blood cell; transfusion; gastrointestinal bleeding; emergency department

1. INTRODUCTION

1.1 Background

Gastrointestinal (GI) bleeding is a common and occasionally life-threatening reason for emergency department (ED) care. Traditionally, transfusion of allogeneic red blood cells (RBC) has been recommended in the setting of GI bleeding with moderate or severe anemia (e.g. hemoglobin levels less than 10 g/dl) owing to associations between the severity of anemia and mortality, as well as theoretical hemostatic benefits at higher hemoglobin levels.[1–4] However, these theoretical benefits have been challenged[5], and over the past decade guideline support for a more restrictive approach to RBC transfusion in acute GI bleeding has emerged (e.g. using hemoglobin transfusion thresholds of less than 7 to 8 g/dl, absent overt circulatory shock or active ischemia), supported by evidence demonstrating both reduced healthcare utilization and equivalent safety, with possible mortality benefits.[6–11] At the same time, restrictive RBC transfusion practices have gained widespread endorsement for a variety of other conditions.[12–17]

1.2 Study Significance

Ultimately, knowledge translation is often a slow and incomplete process[18], and high rates of guideline-discordant transfusion practice within EDs have been recently documented.[19,20] Since most studies supporting restrictive transfusion practice have been conducted outside of the ED setting, it is understandable that ED clinicians would approach the concept of restrictive transfusion cautiously.[21] Patients with GI bleeding, however, do have an evidentiary base for restrictive transfusion that includes the ED setting[6,8], and thus may be harbingers of ED clinician willingness to adopt restrictive transfusion practices.

1.3 Goals of This Investigation

We sought to examine trends over time in RBC transfusion practice among ED patients diagnosed with GI bleeding within an integrated health system during a period when clinical trial data (beginning in 2013[6]) and subsequent guidelines increasingly supported a restrictive approach to RBC transfusion in patients with GI bleeding. We hypothesized that the proportion of ED patients with GI bleeding who received RBC transfusions during their ED

stay would decrease over time, and that this effect would be primarily observed among the subgroup of patients with ED hemoglobin nadirs in the 7.0 to 9.9 g/dl range, given the contemporaneously evolving evidence highlighted above. We further hypothesized that decreases in RBC transfusion rates would persist though the index hospitalization and out to 90 days, without associated changes in downstream healthcare utilization (hospital or ED readmission) or all-cause mortality.

2. MATERIALS AND METHODS

2.1 Study Setting and Design

We conducted a retrospective cohort study using electronic health records (EHR) from Kaiser Permanente Northern California (KPNC), and integrated health system which includes twenty-one medical center-based EDs, staffed by board-certified (or board-eligible) emergency physicians, serving a total population of 4 million health plan members with over 1.2 million annual ED visits.[22] KP members represent approximately 33% of the population in areas served and are highly representative of the surrounding population.[23] In 2015 the annual census of the 21 EDs ranged from 28,000 to 121,000, median 57,000 (interquartile range, 38,000–61,000). All medical centers are considered non-academic and community-based, though seven sites have at least one active graduate medical education program, four of which have residencies in either internal or family medicine.

In 2010, KPNC initiated a comprehensive blood conservation educational program targeting emergency physicians, hospitalists, anesthesiologists and surgeons regarding the management of anemia, adoption of evidence-based transfusion practices, and implementation of blood transfusion guidelines across its facilities.[24] To further support these efforts, in May 2012 electronic clinical decision support was integrated into the EHR which recommended (but did not mandate) transfusion of the minimum number of RBC units to return patients to an evidence-based safe hemoglobin range (e.g. above 7 g/dl in stable patients without cardiac ischemia, or above 8 g/dl in stable patients with cardiac ischemia). Notably, however, active bleeding was a listed exception to guideline adherence, and no specific educational program or decision support was provided for the management of patients with active bleeding.

All KPNC hospitals, clinics and EDs employ a common EHR (Epic, Verona, WI) which was fully deployed for inpatient use in 2010. Data were derived principally from the KPNC Virtual Data Warehouse, a research database resource that centralizes data from EHRs and other legacy health system source files into standardized formats and data tables.[25] All data were electronically extracted from the EHR using unique encounter and medical record numbers. Manual chart review was not used for data validation except where noted as previously performed. The study was approved with a waiver for informed consent by the KPNC Institutional Review Board, which has jurisdiction over all hospitals in this report.

2.2 Cohort selection

To assemble the study cohort, we identified all adult KPNC health plan members who presented to a KPNC ED between July 1st, 2012 and September 30th, 2016. The July 1st,

2012 starting point was chosen due to limitations in clearly separating ED from inpatient-based diagnostic codes prior to this date. Patients were eligible for principal cohort inclusion if they had an International Classification of Diseases, 9th revision (ICD-9) or 10th revision (ICD-10) ED physician-coded diagnosis of GI bleeding (supplemental appendix Table e1), laboratory measurement of a complete blood count while in the ED, and continuous KPNC health plan membership for 90 days (excepting loss of coverage due to death) following the index visit to allow for capture of 90-day outcome events. The principal cohort was further restricted to only include the first study-eligible ED encounter to allow for per-patient analyses of 90-day outcomes. Patients were also stratified a priori by their hemoglobin nadir in the ED into three categories, with cut-offs determined by relevance to restrictive transfusion evidence and guidelines; hemoglobin 6.9 g/dl or less; hemoglobin between 7.0 and 9.9 g/dl (the subgroup of prime interest) and hemoglobin of 10.0 g/dl and above.

2.3 Patient Characteristics

Patient-level variables included age, sex, comorbid diseases, anticoagulant use, and laboratory measurements obtained during the ED stay. Laboratory values included platelet counts (nadir), hemoglobin levels (nadir) and International Normalized Range (INR) values for prothrombin time (peak). Comorbidities were obtained from the active problem list at the time of the ED visit and were categorized using the Health Care Utilization Project Elixhauser Comorbidity Software (www.ahrq.gov/data/hcup).[26] Anticoagulant use was defined as a prescription fill for warfarin or a direct oral anticoagulant (rivaroxaban, apixaban, dabigatran) in the 90 days prior to the index ED visit using data from an internal prescription database. For additional risk adjustment we also determined if patients received GI endoscopy (upper and/or lower) using corresponding Common Procedural Terminology billing codes.

2.4 Outcome Measures

All outcomes are reported as a percentage of study population per study quarter (rate), adjusted for confounders as noted below. The primary outcome of interest was the receipt of any RBC transfusion during the ED stay. Secondary outcomes included any RBC transfusion during the index hospitalization (inclusive of the ED stay), as well as any RBC transfusion, repeat ED visit, repeat hospital admission or death within 90 days following the index ED visit. RBC transfusion events were identified from blood bank transfusion records including ED, inpatient, and outpatient encounters though the 90-day endpoint. The RBC transfusion data have been previously validated.[27] Repeat ED visits or hospital admissions were determined from KPNC EHR records, supplemented by queries of a claims-based database to capture events occurring outside of KPNC. Mortality was determined using a composite death database of internal KPNC mortality statistics cross-referenced with state (California Death Index) and federal (Social Security Death Index) data.

2.5 Data Analysis

Data are presented as medians with interquartile ranges (IQR) or proportions with 95% confidence intervals (CI). Missing INR values were imputed using the median (normal range) value for the cohort, under the assumption that a lack of INR measurement represented clinical assumption of normal range values, and thus was not missing at random.

[28] Unadjusted differences between multiple proportions and medians were assessed using the chi-squared and Kruskal-Wallis rank test, respectively. P values of 0.005 or less were considered statistically significant to provide a greater degree of confidence in the results.[29] Bonferroni adjustment was added for the hemoglobin nadir subgroup analyses (p value of 0.001 or less considered statistically significant).

Mixed-effects logistic regression models were used to provide adjusted rates of RBC transfusion. The models included age, lowest hemoglobin value, lowest platelet value, highest INR value, sex, comorbidities (iron-deficient anemia, congestive heart failure, chronic lung disease, chronic kidney disease stage 3 or higher, diabetes, malignancy), anticoagulant use, and performance of GI endoscopy (during the respective outcome timeframe) as patient-level fixed effects. Continuous variables (age and laboratory values) were modeled using restricted cubic splines. An interaction term between anticoagulant prescription and highest INR value was used to help differentiate between INR elevations due to intrinsic coagulation factor deficiencies from those due to anticoagulant use. The index visit facility was treated as a random effect to account for any lack of independence at the hospital level. Additional adjustment for clustering by provider did not improve the model goodness-of-fit, as determined by the likelihood ratio test, likely due to the low number of transfusions ordered by any given provider.

Adjusted rates for both repeat ED visits and hospital admissions through 90 days were determined using logistic regression models including age, baseline laboratory values and Elixhauser-categorized comorbidities. Given the very low observed mortality rates, a more parsimonious logistic regression model was used to avoid overfitting (age, hemoglobin nadir, malignancy). For these three models, introducing index treating facility as a random-effect did not result in significant improvement in model goodness-of-fit, as determined by the likelihood ratio test, and thus fixed effect models were used. Multicollinearity in all models was assessed using the variance inflation factor.

Using the logistic regression models described above, adjusted rates of the respective outcomes were summarized by study quarter (3-month interval). These adjusted rates were plotted (rate per quarter), and the magnitude of trend over time was determined using the slope of the best fit linear line, reported in absolute and relative terms (the latter using a baseline value indicated by the y-intercept of the line). Strength and consistency of observed trends was reported using the coefficient of determination (R^2), and statistical significance was determined by regressing the study time unit (quarter) against corresponding adjusted rates.

Sensitivity analyses were performed by 1) including both patients without continuous health plan membership or with multiple eligible ED encounters during the study period to assess for principal cohort selection bias (reporting ED and index hospitalization RBC transfusion outcomes only, adjusting for same patient correlations) and 2) restricting analysis to principal cohort patients who were hospitalized at the index ED visit (to exclude patients with lower-risk GI bleeds and assess for effect modification). Statistical analyses were performed using Stata Version 13.1 (StataCorp LLC, College Station, Texas, USA).

3. RESULTS

3.1 Principal Cohort Selection and Characteristics

Out of 34,202 ED patients with both a complete blood count and a diagnosis of GI bleeding during the study period, 24,868 eligible principal cohort encounters were identified after exclusions for multiple ED visits (n=5,892) and absence of continuous health plan membership for 90 subsequent days (n=3,442). Of these, 2,457 (9.9%) had an index ED hemoglobin nadir value of 6.9 g/dl or less, 7,752 (31.2%) had values between 7.0 and 9.9 g/dl, and 14,660 (59.0%) had values of 10.0 g/dl of greater. A CONSORT diagram of study cohort selection is presented in Figure 1.

The median age was 67 years, 50.1% were female, and 22.2% had a history of iron deficiency anemia. A total of 13.2% patients underwent RBC transfusion during the ED visit, while 32.1% underwent RBC transfusion through 90 days. The annualized median hemoglobin nadir in the ED did not vary significantly over the course of the study (range 10.8–11.0 g/dl), nor was there a statistically significant quarterly trend (odds ratio = 0.99, 95% CI 0.99–1.0, p=0.07). However, the annualized median hemoglobin prior to ED RBC transfusion did decrease during the study period, starting at 7.5 g/dl in the first 12 months and ending at 6.9 g/dl in the final 12 months, resulting in an average annual decrease of just over 0.1 g/dl ($p<0.0001$). Demographics and unadjusted outcomes for the overall cohort are presented in an annualized format in Table 1, and by hemoglobin nadir strata in Table 2. The quarterly distribution of principal cohort eligible ED encounters was well balanced and is presented in supplemental appendix Figure e1.

3.2 Primary and Secondary Outcomes

Results for the principal cohort are presented in Table 3. For the primary outcome of regression model-adjusted rates of RBC transfusion during the index ED visit, we observed a small (absolute quarterly change of −0.1%) and weak (R^2=0.18) overall trend during the study period. However, there was a larger (absolute quarterly change of −0.4%) and stronger (R^2=0.82) trend towards decreasing RBC transfusions during the index hospitalization, and this persisted out to 90 days. At the same time, rates of 90-day repeat ED visits and rehospitalizations remained relatively unchanged without notable linear trends (R^2 of 0.05 and 0.11, respectively). 90-day mortality rates, which remained consistently below 1%, did demonstrate a trend towards lower rates over time. Plots of adjusted rates used in the primary analysis are presented in Figure 2 (RBC transfusions), and Figure 3 (90-day repeat ED visits, rehospitalizations and mortality).

3.3 Subgroup Analyses

Subgroup analysis stratified by hemoglobin nadir values in the ED revealed a larger (absolute quarterly change of −0.4%) and more consistent (R^2=0.38) trend towards decrease in ED RBC transfusions among the subgroup of prime interest, patients with values between 7.0 and 9.9 g/dl, as compared to the overall cohort. A very small (absolute quarterly change of −0.04%) but similarly consistent (R^2=0.34) trend was seen towards decreased transfusion among patients with hemoglobin values of 10.0 g/dl and above. No consistent change in ED RBC transfusions was seen among patients with hemoglobin nadir values of 6.9 g/dl or less

(R^2 of 0.13). For secondary outcomes, similar trends were seen in each hemoglobin nadir subgroup as compared to the primary cohort (data not shown).

3.4 Sensitivity Analyses

Two sensitivity analyses were performed, neither of which substantially altered the findings. The first assessed for principal cohort selection bias by analyzing all 34,202 encounters (including patients without continuous health plan membership or repeated ED encounters) and found no difference in results for RBC transfusions while in the ED or during the index hospitalization (Table 4). The second assessed for effect modification by restricting the analysis to principal cohort patients who were hospitalized at the index encounter (thus excluding patients with lower-risk GI bleeds) and likewise did not demonstrate any changes in magnitude or strength of the observed trends, including 90-day outcomes (Table 5).

4. DISCUSSION

In this retrospective cohort, the proportion of patients presenting to the ED with GI bleeding who subsequently underwent RBC transfusion steadily decreased over the course of several years. This apparent practice change was evident not only in the ED setting (most notable among patients with hemoglobin nadirs between 7.0 and 9.9 g/dl) but also during the index hospitalization and up to 90 days following the index encounter, inclusive of the outpatient setting. Accordingly, there was a gradual and steady lowering of the annualized median hemoglobin nadir value among patients with GI bleeding who were transfused in the ED.

The observed decrease in ED RBC transfusion among GI bleeding patients with hemoglobin nadirs between 7.0–9.9 g/dl is consistent with evolving guidelines supporting hemoglobin “triggers” of 7.0 or 8.0 g/dl for RBC transfusion in acute GI bleeding, and is perhaps representative of a growing awareness and acceptance of these guidelines by ED physicians over time.[9–11] This is particularly notable in the context of earlier studies demonstrating poor adherence to restrictive transfusion practice recommendations among ED physicians.[19,20] These findings also complement data demonstrating an increase in anemia tolerance and restrictive RBC transfusion practice for all hospitalized patients at the health system level.[24]

In terms of utilization and safety, the proportion of patients with a rehospitalization or repeat ED visits out to 90 days was constant over time, suggesting that restrictive RBC transfusion practice did not result in increased utilization and/or morbidity, consistent with existing literature.[30,31] Similarly, mortality was decreased over time, a finding which, while possibly attributable to general temporal trends[32], is consistent with clinical trial findings supporting the safety and potential survival benefit of restrictive transfusion practices among patients with GI bleeding.[6,7] Thus, while none of these findings are evidence of non-inferiority or benefit in themselves, given the observational nature of this study, they are reassuring in the context of similar findings from other health-system and patient population settings. Additionally, a recent large observational study from our health system had similar outcome findings in association with increased restrictive transfusion practice among a heterogenous hospitalized patient population.[33]

Study strengths include the multicenter composition and large size of the cohort, both of which bolster the internal validity of the results. While unknown or unmeasured factors are a limitation in any adjusted analysis, and particularly in this study given the limitations of electronic retrospective data, we were able to control for age, comorbidities, primary hematologic laboratory values, anticoagulant use, endoscopy (encompassing interventions to decrease bleeding rates and risk), and facility level variation in practice. While there was a notable increase in endoscopy rates over the course of the study, largely driven by more procedures being performed during the ED visit and index hospitalization, these interventions were controlled for in all the models excepting mortality. Though it is conceivable that increased endoscopy rates may have played a role in supporting a restrictive transfusion approach and/or decreasing downstream utilization and mortality, contemporaneous studies examining early endoscopy for either upper or lower GI bleeding have not demonstrated associated decreased rates of downstream re-bleeding, RBC transfusions or mortality.[34–38]

Additional limitations of this study include an inability to reliably stratify into upper versus lower GI sources of bleeding (including the type of endoscopy performed), unavailability of reliable antiplatelet medication use data (owing to over-the-counter aspirin use), lack of alternative measures of altered coagulation status (e.g. thromboelastography), and lack of control for other potentially confounding variables related to transfusion decisions, given the limits of the available retrospective electronic data as noted above (e.g. hemodynamic instability, apparent volume of blood loss, clinical symptoms attributable to anemia, personal healthcare preferences). However, it is unlikely that the prevalence and/or relative proportions of these unmeasured factors varied significantly over the course of the study. Additionally, previous predictive modeling work on the likelihood of RBC transfusions among hospitalized patients, and more specifically amongst patients with GI bleeding, demonstrated that measures of severity of illness contributed minimal predictive value beyond that provided by the admission hemoglobin level alone.[39] Likewise, while it is possible that a relatively small group of patients with GI bleeding were missed due to alternative diagnostic coding (e.g. anemia, hemorrhagic shock), these occurrences are unlikely to have altered the findings. Finally, the study involved patients treated within an integrated health system, which may have increased clinician comfort with deferral of transfusion, particularly amongst outpatients. However, the results were consistent when restricting the analysis to patients hospitalized at the index encounter, thus improving the potential generalizability of the findings to non-integrated systems as well.

It is also notable that these observations were made in the context of an active system-wide blood product conservation initiative. However, the initiative did not promote restrictive transfusion for patients with uncontrolled active bleeding. Rather, when clinicians placed electronic orders for RBC transfusion in the ED or hospital, active bleeding was presented as a specific exclusion criterion alongside recommended hemoglobin “transfusion trigger” thresholds. Thus, it is likely that some passive diffusion of evidence and practice guidelines specific to GI bleeding had a role to play, albeit primed by a framework supporting general restrictive transfusion practices.

5. CONCLUSIONS

We observed a gradual decrease in the proportion of ED patients with GI bleeding who subsequently underwent RBC transfusion, without corresponding increases in measures of utilization or mortality. The largest decrease in rates of ED RBC transfusion was observed amongst patients with hemoglobin nadirs between 7.0 and 9.9 g/dl, corresponding to the clinical scenarios most likely to be impacted by evolving clinical evidence and guidelines. These findings suggest that ED physicians are willing to adopt restrictive transfusion practices for patients with GI bleeding and can serve as benchmarks for future efforts concerning optimal transfusion practices in the setting of GI bleeding.[7,8]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

CI	confidence interval
ED	emergency department
EHR	electronic health record
GI	gastrointestinal
INR	International Normalized Ratio
IQR	Interquartile range
KPNC	Kaiser Permanente Northern California
RBC	red blood cell

REFERENCES

1. Consensus conference. Perioperative red blood cell transfusion. JAMA 1988;260:2700–3. [PubMed: 3054179]
2. Silvain J, Abtan J, Kerneis M, et al. Impact of red blood cell transfusion on platelet aggregation and inflammatory response in anemic coronary and noncoronary patients: the TRANSFUSION-2 study (impact of transfusion of red blood cell on platelet activation and aggregation studied with flow cytometry use and light transmission aggregometry). J Am Coll Cardiol 2014;63:1289–96. [PubMed: 24361322]
3. Silvain J, Pena A, Cayla G, et al. Impact of red blood cell transfusion on platelet activation and aggregation in healthy volunteers: results of the TRANSFUSION study. Eur Heart J 2010;31:2816–21. [PubMed: 20591842]
4. British Society of Gastroenterology Endoscopy C. Non-variceal upper gastrointestinal haemorrhage: guidelines. Gut 2002;51 Suppl 4:iv1–6. [PubMed: 12208839]
5. Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal haemorrhage. Br J Surg 1986;73:783–5. [PubMed: 3533203]

6. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11–21. [PubMed: 23281973]
7. Odutayo A, Desborough MJ, Trivella M, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials. Lancet Gastroenterol Hepatol 2017;2:354–60. [PubMed: 28397699]
8. Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet 2015;386:137–44. [PubMed: 25956718]
9. Strate LL, Gralnek IM. ACG Clinical Guideline: Management of Patients With Acute Lower Gastrointestinal Bleeding. Am J Gastroenterol 2016;111:459–74. [PubMed: 26925883]
10. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015;47:a1–46. [PubMed: 26417980]
11. Oakland K, Chadwick G, East JE, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. Gut 2019;68:776–89. [PubMed: 30792244]
12. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409–17. [PubMed: 9971864]
13. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 2010;304:1559–67. [PubMed: 20940381]
14. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453–62. [PubMed: 22168590]
15. Holst LB, Wetterslev J, Perner A. Hemoglobin threshold for transfusion in septic shock. N Engl J Med 2015;372:91–2.
16. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2016;10:CD002042. [PubMed: 27731885]
17. Halpern SD, Becker D, Curtis JR, et al. An official American Thoracic Society/American Association of Critical-Care Nurses/American College of Chest Physicians/Society of Critical Care Medicine policy statement: the Choosing Wisely(R) Top 5 list in Critical Care Medicine. Am J Respir Crit Care Med 2014;190:818–26. [PubMed: 25271745]
18. Westfall JM, Mold J, Fagnan L. Practice-based research--"Blue Highways" on the NIH roadmap. JAMA 2007;297:403–6. [PubMed: 17244837]
19. Beyer A, Rees R, Palmer C, Wessman BT, Fuller BM. Blood product transfusion in emergency department patients: a case-control study of practice patterns and impact on outcome. Int J Emerg Med 2017;10:5. [PubMed: 28155184]
20. Diaz MQ, Borobia AM, Garcia Erce JA, et al. Appropriate use of red blood cell transfusion in emergency departments: a study in five emergency departments. Blood Transfus 2017;15:199–206. [PubMed: 27416566]
21. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA 2016;316:2025–35. [PubMed: 27732721]
22. Selevan J, Kindermann D, Pines JM, Fields WW. What Accountable Care Organizations Can Learn from Kaiser Permanente California's Acute Care Strategy. Popul Health Manag 2015;18:233–6. [PubMed: 25856631]
23. Gordon N, Lin T. The Kaiser Permanente Northern California Adult Member Health Survey. Perm J 2016;20:15–225.
24. Roubinian NH, Escobar GJ, Liu V, et al. Decreased red blood cell use and mortality in hospitalized patients. JAMA Intern Med 2014;174:1405–7. [PubMed: 24978650]
25. Ross TR, Ng D, Brown JS, et al. The HMO Research Network Virtual Data Warehouse: A Public Data Model to Support Collaboration. EGEMS (Wash DC) 2014;2:1049. [PubMed: 25848584]
26. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8–27. [PubMed: 9431328]

27. Roubinian NH, Escobar GJ, Liu V, et al. Trends in red blood cell transfusion and 30-day mortality among hospitalized patients. Transfusion 2014;54:2678–86. [PubMed: 25135770]
28. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393. [PubMed: 19564179]
29. Ioannidis JPA. The Proposal to Lower P Value Thresholds to .005. JAMA 2018;319:1429–30. [PubMed: 29566133]
30. Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. Transfusion 2017;57:1347–58. [PubMed: 28150313]
31. Mazer CD, Whitlock RP, Fergusson DA, et al. Six-Month Outcomes after Restrictive or Liberal Transfusion for Cardiac Surgery. N Engl J Med 2018.
32. Ma J, Ward EM, Siegel RL, Jemal A. Temporal Trends in Mortality in the United States, 1969–2013. JAMA 2015;314:1731–9. [PubMed: 26505597]
33. Roubinian NH, Murphy EL, Mark DG, et al. Long-Term Outcomes Among Patients Discharged From the Hospital With Moderate Anemia: A Retrospective Cohort Study. Ann Intern Med 2018.
34. Nigam N, Ham SA, Sengupta N. Early Colonoscopy for Diverticular Bleeding Does Not Reduce Risk of Post-Discharge Recurrent Bleeding-A Propensity Score Matching Analysis. Clin Gastroenterol Hepatol 2018.
35. Nagata N, Niikura R, Sakurai T, et al. Safety and Effectiveness of Early Colonoscopy in Management of Acute Lower Gastrointestinal Bleeding on the Basis of Propensity Score Matching Analysis. Clin Gastroenterol Hepatol 2016;14:558–64. [PubMed: 26492844]
36. Kouanda AM, Somsouk M, Sewell JL, Day LW. Urgent colonoscopy in patients with lower GI bleeding: a systematic review and meta-analysis. Gastrointest Endosc 2017;86:107–17 e1. [PubMed: 28174123]
37. Kumar NL, Cohen AJ, Nayor J, Claggett BL, Saltzman JR. Timing of upper endoscopy influences outcomes in patients with acute nonvariceal upper GI bleeding. Gastrointest Endosc 2017;85:945–52 e1. [PubMed: 27693643]
38. Mohammed N, Rehman A, Swinscoe MT, Mundre P, Rembacken B. Outcomes of acute upper gastrointestinal bleeding in relation to timing of endoscopy and the experience of endoscopist: a tertiary center experience. Endosc Int Open 2016;4:E282–6. [PubMed: 27004244]
39. Roubinian NH, Murphy EL, Swain BE, et al. Predicting red blood cell transfusion in hospitalized patients: role of hemoglobin level, comorbidities, and illness severity. BMC Health Serv Res 2014;14:213. [PubMed: 24884605]

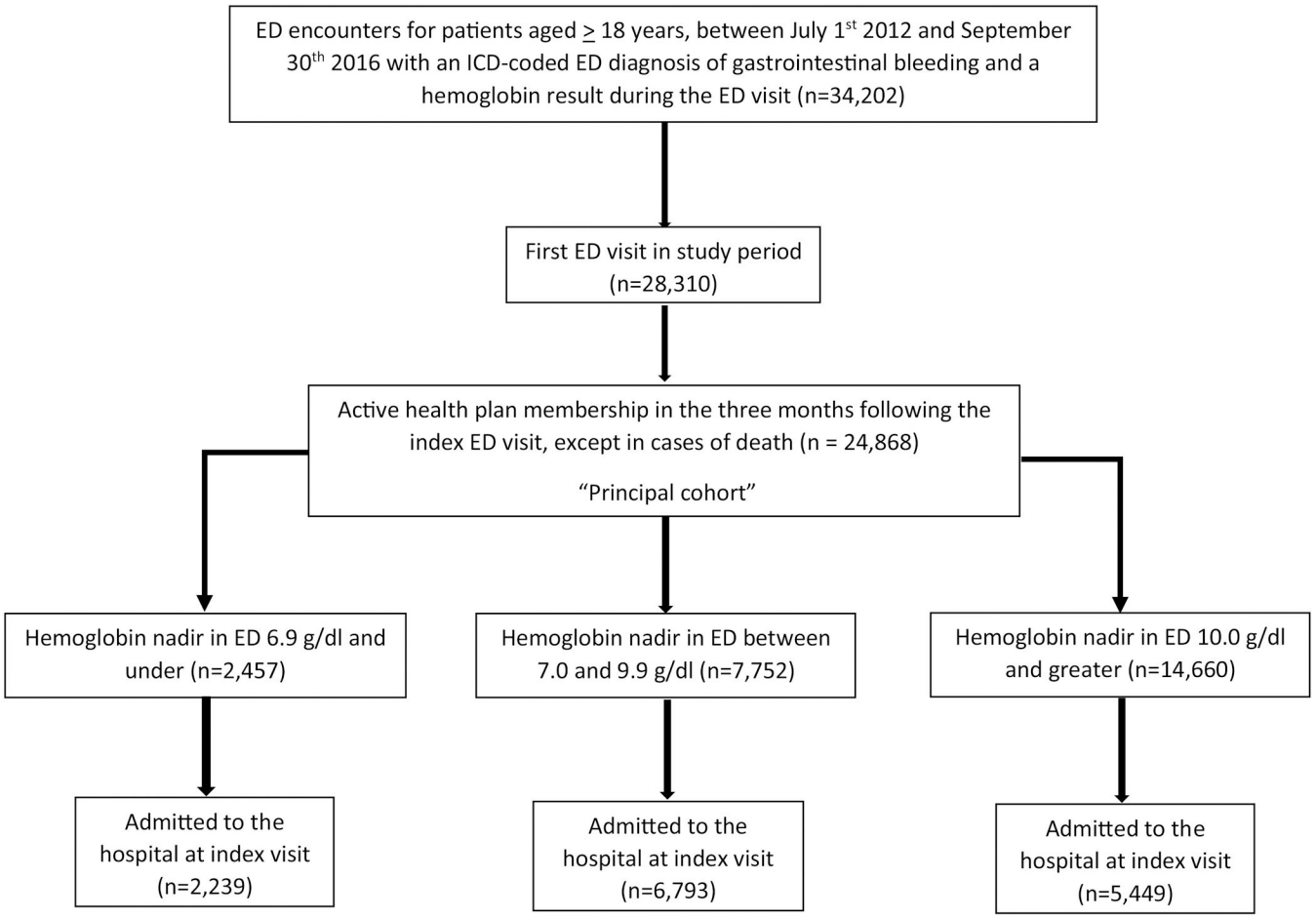

Figure 1.
CONSORT diagram of principal cohort and subgroup selection

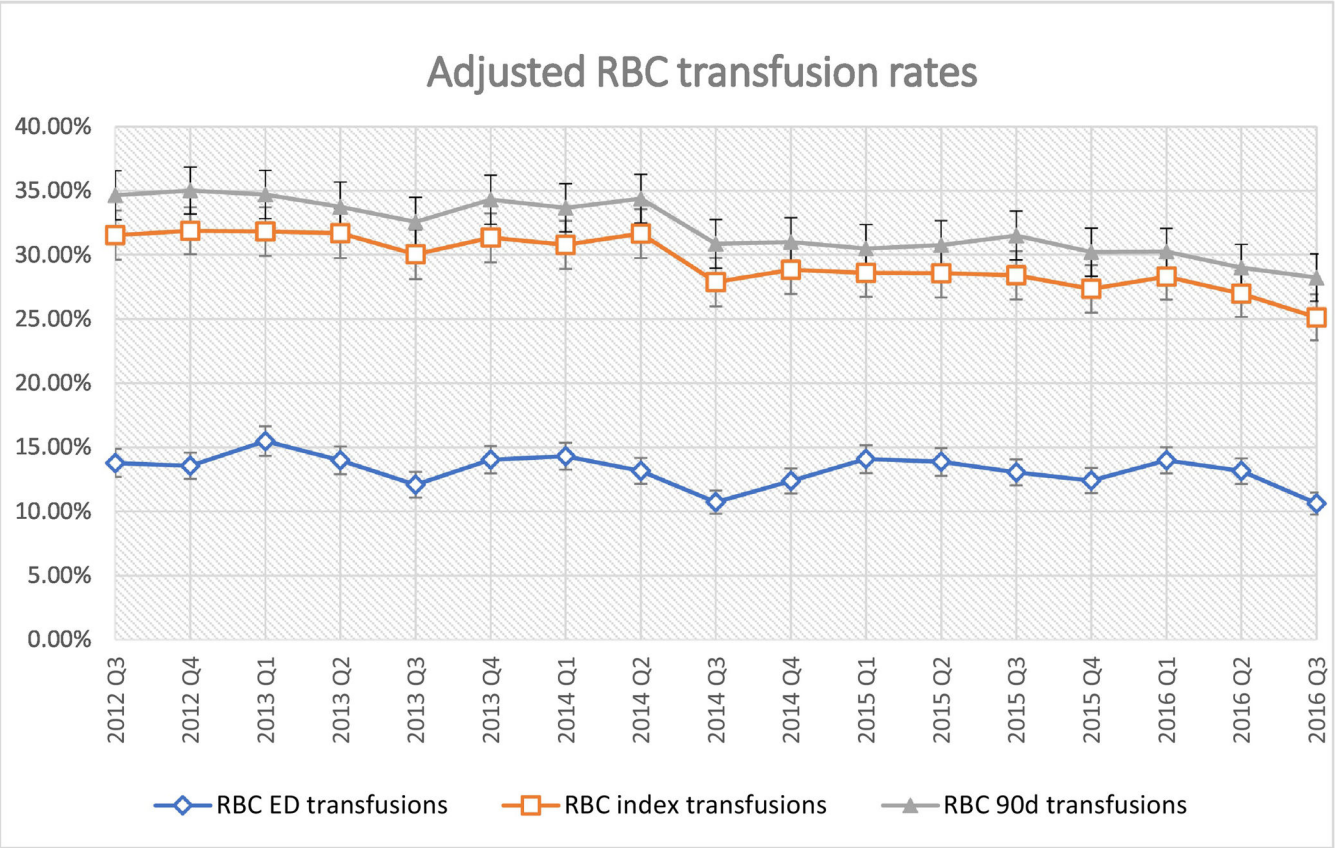

Figure 2.

Adjusted rates of RBC transfusion while in the ED, during the index hospitalization and through 90 days (principal cohort, n=24,868)

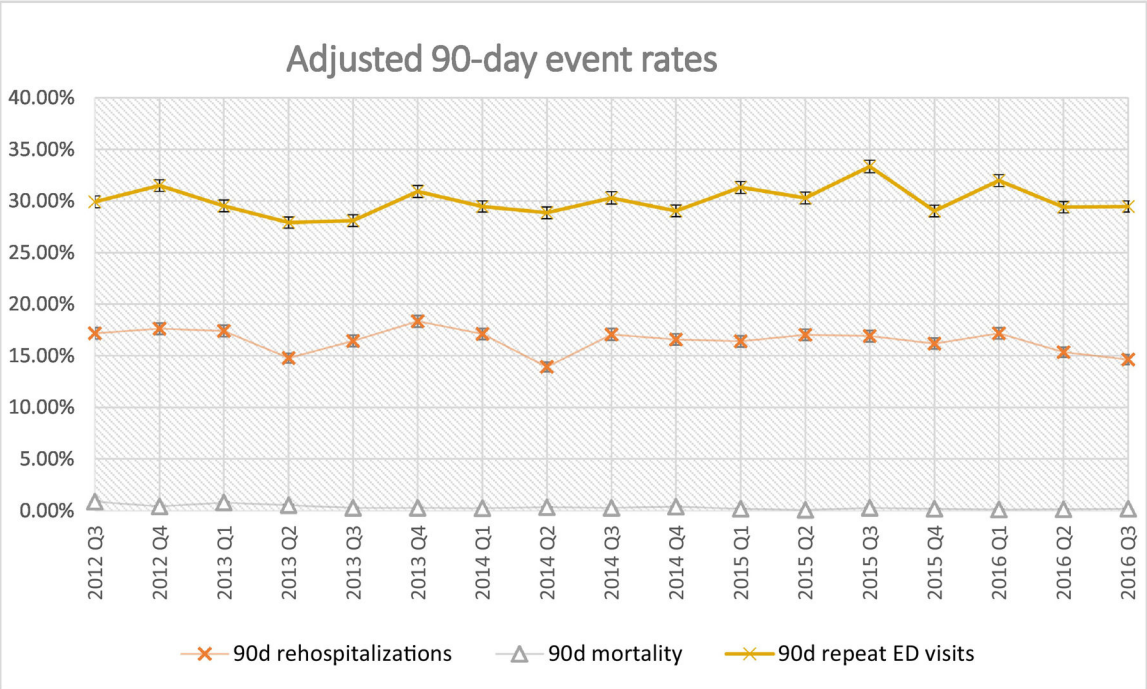

Figure 3.

Adjusted rates of 90-day events, including repeat emergency department visits, rehospitalizations and mortality. (principal cohort, n=24,868)

Table 1

Cohort characteristics by year (n = 24868)

Year	All years	2012	2013	2014	2015	2016	P value
# of patients	24,868	2976	5642	5795	5812	4643	
Age (median, IQR)	67 (52–79)	66 (52–79)	67 (52–79)	67 (53–79)	66 (52–79)	66 (52–79)	0.57
Female (%)	50.1	49.7	50.0	51.2	49.4	49.8	0.34
Iron-deficient anemia (%)	22.2	24.7	23.3	23.9	22.4	17.1	<0.001
Congestive heart failure (%)	10.6	10.9	10.9	10.6	10.4	10.1	0.74
Chronic lung disease (%)	22.4	21.7	22.1	22.9	22.2	22.8	0.65
Chronic kidney disease (%)	21.3	20.7	21.5	22.2	21.8	19.6	0.017
Diabetes (%)	20.8	20.7	21.2	20.7	21.4	19.9	0.42
Malignancy (%)	2.9	3.6	3.2	3.2	2.9	3.0	0.35
Warfarin prescription (%)	10.7	10.6	10.6	10.7	10.4	11.1	0.85
Direct oral anticoagulant prescription (%)	0.5	0.4	0.4	0.4	0.7	0.5	0.13
Platelet count $\times 10^3$ (median, IQR)	204 (158–256)	199 (151–251)	201 (155–252)	205 (159–258)	206 (161–256)	208 (161–259)	<0.001
Hemoglobin g/dL (median, IQR)	10.9 (8.4–13.1)	10.9 (8.6–13.1)	10.8 (8.6–13.1)	10.8 (8.4–13.0)	10.9 (8.3–13.2)	11.0 (8.1–13.2)	0.42
INR (median, IQR)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.0 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	<0.001
Endoscopy in the ED (%)	6.7	4.2	6.0	5.5	8.2	9.1	<0.001
Endoscopy during index hospitalization (%)	37.4	30.2	32.1	36.5	42.1	43.8	<0.001
Endoscopy within 90 days (%)	48.6	46.0	46.8	45.2	51.1	53.3	<0.001
Discharged home from ED (%)	41.8	40.7	41.8	39.8	42.2	44.4	<0.001
ED length of stay in hours, (median, IQR)	4.4 (3.1–6.6)	4.4 (3.1–6.5)	4.5 (3.1–6.7)	4.3 (3.0–6.4)	4.4 (3.1–6.5)	4.6 (3.1–7.0)	<0.001
RBC transfusion in the ED (%)	13.2	13.7	13.9	12.7	13.4	12.7	0.22
Hemoglobin nadir among those transfused in ED, g/dl (median, IQR)	7.2 (6.2–8.1)	7.4 (6.4–8.3)	7.5 (6.4–8.4)	7.2 (6.2–8.2)	7.1 (6.1–7.9)	6.9 (6.0–7.7)	<0.001
RBC transfusion during index hospitalization (%)	29.4	31.7	31.2	29.8	28.2	26.9	<0.001
RBC transfusion within 90 days (%)	32.1	34.8	33.8	32.5	30.7	29.2	<0.001
Repeat ED visit 90 days (%)	30.0	30.7	29.1	29.4	31.0	30.3	0.15
Days to next ED visit (median, IQR)	22 (5–70)	23 (7–50)	21 (7–47)	21 (6–48)	22 (7–51)	23 (7–50)	0.65
Rehospitalization within 90 days (%)	16.5	17.4	16.8	16.2	16.6	15.8	0.35
90-day mortality (%)	0.3	0.7	0.5	0.3	0.2	0.2	<0.001

Abbreviations: ED – emergency department; RBC – red blood cell; INR- international normalized ratio; IQR – Interquartile range

Table 2

Primary cohort characteristics by hemoglobin nadir strata in the ED

	ED hemoglobin nadir ≤ 6.9 g/dl (n = 2457)	**ED hemoglobin nadir 7–9.9 g/dl (n = 7752)**	**ED hemoglobin nadir ≥ 10.0 g/dl (n =14660)**
Age (median, IQR)	71 (60–81)	72 (60–82)	62 (46–76)
Female (%)	48.4	50.2	50.5
Iron-deficient anemia (%)	50.0	36.1	10.2
Congestive heart failure (%)	19.5	15.0	6.7
Chronic lung disease (%)	22.8	24.1	21.4
Diabetes (%)	31.9	27.6	15.4
Chronic kidney disease (%)	35.8	30.1	14.2
Cancer (%)	4.3	4.3	2.2
Warfarin prescription (%)	10.7	10.7	10.7
Direct oral anticoagulant prescription (%)	0.5	0.5	0.5
Platelet count, $\times 10^3$ (median, IQR)	178 (126–246)	181 (134–236)	217 (177–264)
Hemoglobin, g/dL (median, IQR)	6.2 (5.5–6.6)	8.4 (7.8–9.2)	12.8 (11.5–14.0)
INR (median, IQR)	1.2 (1.1–1.6)	1.2 (1.0–1.3)	1.1 (1.0–1.2)
Endoscopy in the ED (%)	6.3	7.9	6.2
Endoscopy during index hospitalization (%)	61.4	55.5	23.9
Endoscopy within 90 days (%)	67.8	61.6	38.4
Discharged home from ED (%)	8.9	12.4	62.8
ED length of stay in hours, (median, IQR)	4.7 (3.5–7.0)	4.9 (3.6–7.2)	4.1 (2.8–6.3)
RBC transfusion in the ED (%)	59.9	21.6	1.0
RBC transfusion during index hospitalization (%)	97.0	57.8	3.1
RBC transfusion within 90 days (%)	97.4	62.3	5.1
Repeat ED visit 90 days (%)	38.4	35.0	26.0
Days to next visit (median, IQR)	24 (10–47)	22 (8–48)	21 (5–51)
Rehospitalization at 90 days (%)	27.5	23.2	11.1
90-day mortality (%)	0.8	0.6	0.1

Abbreviations: ED – emergency department; RBC – red blood cell; INR- international normalized ratio; IQR – Interquartile range

Table 3

Principal cohort analysis results (n=24,868)

	Adjusted range	y-intercept (baseline)	Absolute quarterly change (slope)	Relative quarterly change	R^2	P value
RBC transfusion in ED	10.5–15.5%	14.2%	−0.1%	−0.7%	0.18	0.0001
Subgroup 1 (Hgb ≤6.9 g/dl)	52.1–70.6%	63.1%	−0.4%	−0.6%	0.13	P<0.0001
Subgroup 2 (Hgb 7.0–9.9 g/dl)	14.3–27.3%	25.4%	−0.4%	−1.6%	0.38	P<0.0001
Subgroup 3 (Hgb ≥ 10.0 g/dl)	0.4–1.8%	1.4%	−0.04%	−4.0%	0.34	P<0.0001
RBC transfusion during index hospitalization	25.1–31.9%	32.8%	−0.4%	−1.1%	0.82	<0.0001
RBC transfusion in 90 days	28.2–35.0%	35.7%	−0.4%	−1.1%	0.85	<0.0001
90-day repeat ED visit	27.9–33.3%	29.5%	+0.06%	+0.2%	0.05	<0.0001
90-day rehospitalization	13.9–18.4%	17.2%	−0.08%	−0.5%	0.11	<0.0001
90-day mortality	0.1–0.9%	0.6%	−0.03%	−4.7%	0.61	<0.0001

Results are presented using the best fit linear line to the plotted data of adjusted outcomes rates (as determined by the respective logistic regression models) and where the adjusted outcome rate = (bx + y) and b = absolute quarterly change (slope), x = quarter (time) and y = intercept (baseline). Relative quarterly changes are calculated by dividing the absolute quarterly change by the extrapolated baseline values (y-intercept).

Abbreviations – ED = emergency department; Hgb = hemoglobin; RBC = red blood cell

Table 4

Sensitivity analysis, including both patients with multiple ED visits during study and those without continuous health plan coverage through 90 days (n=34,225)

	Adjusted range	y-intercept (baseline)	Absolute quarterly change	Relative quarterly change	R^2	P value
RBC transfusion in ED	12.5–18.2%	16.3%	−0.06%	−0.4%	0.05	0.008
RBC transfusion during index hospitalization	29.6–36.0%	36.1%	−0.3%	−0.8%	0.64	<0.0001

Results are presented using the best fit linear line to the graphed data, where the adjusted outcome rate = bx + y and b = absolute quarterly change (slope), x = quarter (time) and y = intercept (baseline). Relative quarterly changes are calculated by dividing the absolute quarterly change by the extrapolated baseline values (y-intercept).

Abbreviations – ED = emergency department; RBC = red blood cell

Table 5

Sensitivity analysis restricted to patients hospitalized at the index ED visit (n=14,480)

	Adjusted range	y-intercept (baseline)	Absolute quarterly change (slope)	Relative quarterly change	R^2	P value
RBC transfusion in ED	15.8–21.1%	20.3%	−0.1%	−0.5%	0.12	0.0007
RBC transfusion during index hospitalization	42.3–51.4%	51.4%	−0.5%	−1.0%	0.82	<0.0001
RBC transfusion in 90 days	44.7–54.0%	54.0%	−0.5%	−0.9%	0.87	<0.0001
90-day repeat ED visit	30.7–36.7%	31.7%	+0.09%	+0.3%	0.05	<0.0001
90-day rehospitalization	17.3–22.1%	21.2%	−0.05%	−0.2%	0.03	0.003
90-day mortality	0.1–1.4%	0.9%	−0.05%	−5.5%	0.52	<0.0001

Results are presented using the best fit linear line to the graphed data, where the adjusted outcome rate = bx + y and b = absolute quarterly change (slope), x = quarter (time) and y = intercept (baseline). Relative quarterly changes are calculated by dividing the absolute quarterly change by the extrapolated baseline values (y-intercept).

Abbreviations – ED = emergency department; RBC = red blood cell