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Development and Validation of a Transfusion Risk Score for Patients Receiving Maintenance Hemodialysis

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Key Points

- Variables most predictive of transfusion were previous transfusion, hemoglobin, ferritin, and length of hospitalization at baseline.
- Our transfusion prediction risk score performed well. It could be further developed into a clinically useful tool.
- The score could allow clinicians to identify hemodialysis patients most likely to benefit from an anemia treatment to avoid transfusions.

Abstract

Background In patients on dialysis with anemia, avoiding red blood cell transfusions is preferable. We sought to develop and validate a novel transfusion prediction risk score for patients receiving maintenance hemodialysis.

Methods This retrospective cohort study used United States Renal Data System data to create a model development cohort (patients who were point prevalent and on hemodialysis on November 1, 2012) and a validation cohort (patients who were point prevalent and on hemodialysis on August 1, 2013). We characterized comorbidity, inflammatory conditions, hospitalizations, anemia and anemia management, iron parameters, intravenous iron use, and vitamin D use during a 6-month baseline period to predict subsequent 3-month transfusion risk. We used logistic least absolute shrinkage and selection operator regression. In an exploratory analysis, model results were used to calculate a score to predict 6- and 12-month hospitalization and mortality.

Results Variables most predictive of transfusion were prior transfusion, hemoglobin, ferritin, and number of hospital days in the baseline period. The resulting c-statistic in the validation cohort was 0.74, indicating relatively good predictive power. The score was associated with a significantly increased risk of subsequent mortality (hazard ratios 1.0, 1.22, 1.26, 1.54, 1.71, grouped from lowest to highest score), but not with hospitalization.

Conclusions We developed a transfusion prediction risk score with good performance characteristics that was associated with mortality. This score could be further developed into a clinically useful application, allowing clinicians to identify patients on hemodialysis most likely to benefit from a timely, proactive anemia treatment approach, with the goal of avoiding red blood cell transfusions and attendant risks of adverse clinical outcomes.

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Introduction

Anemia is a near-universal complication of advanced CKD and in patients with ESKD receiving maintenance hemodialysis (1). Because anemia is associated with adverse outcomes, including hospitalization and mortality, for patients on hemodialysis (2–7), anemia management is a major focus of their care. Anemia therapies consist primarily of erythropoiesis-stimulating agents (ESAs), intravenous (iv) iron, and, in severe or acute cases, red blood cell (RBC) transfusions.

Unfortunately, RBC transfusions carry risks, including immune-related reactions, infections, and, possibly, increased sensitization to human leukocyte antigens (8). Therefore, avoiding transfusions is recommended in patients with CKD and ESKD, and is the main US FDA-approved indication for ESA use in patients on dialysis (9).

Given that transfusion avoidance is a key goal for patients receiving maintenance dialysis and the lack of existing tools to predict transfusion at the individual patient level, we sought to develop and validate an RBC transfusion prediction model for patients on hemodialysis. Further, in an exploratory analysis, we ascertained the model's performance by determining how the model's risk score was associated with risks of mortality and hospitalization over the ensuing year. To develop a score with optimal performance

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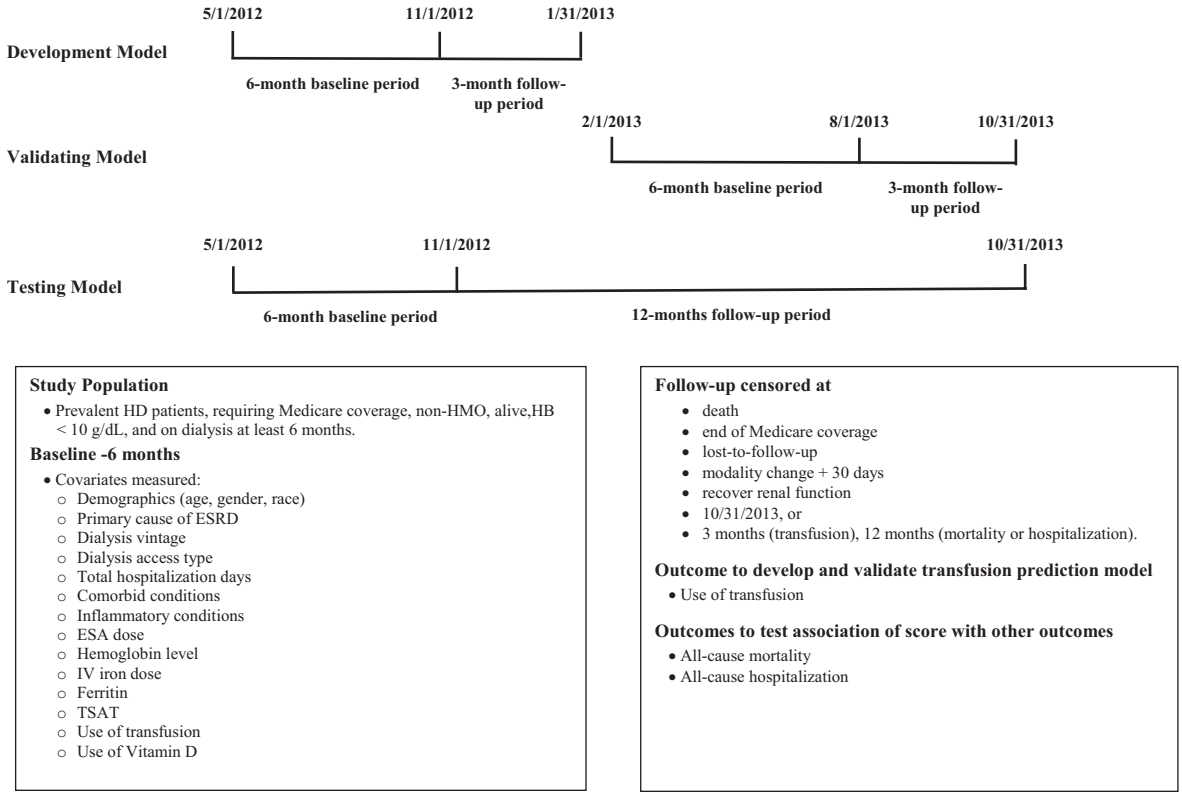

Figure 1. | **Study design.** ESA, erythropoiesis-stimulating agent; HD, hemodialysis; HMO, health maintenance organization; iv, intravenous; TSAT, transferrin saturation.

characteristics, we considered not only "traditional" factors, such as hemoglobin, ESA requirements, and comorbid conditions, but also variables related to inflammation, iron status, and vascular access. This risk-prediction model could be further developed into a clinically useful bedside application, such as for a smartphone, permitting nephrologists to assess individuals at risk for future transfusion need and, possibly, allowing other anemia-management therapies to be used in a timely fashion.

Methods

Data Sources

This study used data from the 2012–2013 United States Renal Data System ESRD database. This database contains information from the ESRD Medical Evidence Report (Centers for Medicare & Medicaid Services [CMS]-2728 form), which includes patient demographic information, renal history, comorbid conditions, and selected information on pre-ESKD therapy (*e.g.*, ESA use). The database also includes information from the ESRD Death Notification (CMS-2746 form), which reports date and cause of death; the Medicare enrollment file, which includes patient demographic information and Medicare coverage status in each month; and the standard analytic file (SAF) claims. The SAFs contain data from Parts A, B, and D final action claims, submitted for Medicare beneficiaries, in which all adjustments have been resolved. In addition, the ESRD clinical CROWNWeb data were used to derive patient information on laboratory tests, including hemoglobin, ferritin, and transferrin saturation (TSAT). Although the Medical Evidence Report and the Death Notification form are required for all patients with ESKD, the SAFs, and CROWNWeb data are available for patients with ESKD with fee-for-service Medicare coverage, approximately two thirds of all patients with ESKD (10).

Study Design

The study samples consisted of two point-prevalent cohorts of individuals receiving maintenance hemodialysis: a training, or development, cohort (point prevalent on November 1, 2012), and a validation cohort (point prevalent on August 1, 2013). Members of both cohorts were required to have at least 6 months of Medicare Parts A and B coverage before the point-prevalent dates (baseline period), and at least 1 month with hemoglobin, TSAT, and ferritin values during the last 3 months of the baseline period. The cohorts were further limited to patients with mean hemoglobin <10 g/dl during the last 2 months of the baseline period, received ESAs, and were aged ≥ 20 years. Individuals in both cohorts were followed for <3 months. A testing cohort was also assessed, consisting of the same patients included in the November 1, 2012 cohort, followed for up to 12 months for outcomes. Figure 1 displays diagrams of these cohorts.

The transfusion score was developed using the study cohort defined on November 1, 2012. The 6-month baseline period was used to define comorbid conditions,

inflammatory conditions, and measures of hemoglobin, ESA dosage, ferritin, TSAT, use of iv iron, use of transfusion, and use of vitamin D. The 3-month follow-up period was used to assess transfusion use, and patients were followed until death, end of Medicare coverage, loss to follow-up, recovery of renal function, kidney transplant, or 30 days after switching to peritoneal dialysis. Use and definitions of baseline and follow-up for the August 1, 2013 point-prevalent validation cohort were similar to those for the development cohort.

In an exploratory analysis, the testing cohort was used to assess the relationship between the transfusion risk score and subsequent outcomes. Patients were followed for up to 1 year after November 1, 2012, for death and hospitalization. Patients were followed until end of Medicare coverage, loss to follow-up, recovery of renal function, transplant, or 30 days after switching to peritoneal dialysis.

Covariates

Covariates included demographic factors (age, sex, race), primary cause of ESKD (diabetes, hypertension, glomerulonephritis, other), time since dialysis initiation (dialysis duration), and a broad range of comorbid conditions defined from the CMS-2728 form or *via* International Classification of Diseases, Ninth Revision, Clinical Modification codes. A comorbid condition was defined as present by at least one inpatient, skilled nursing facility, or home health claim, or at least two outpatient or physician/supplier claims on different days. Comorbid conditions were identified during the baseline period. Other inflammatory conditions were also assessed, including glomerulonephritis, chronic infections, Crohn's disease, ulcerative colitis, hepatitis C, gout, and rheumatoid arthritis (Supplemental Table 1). Additionally, number of total hospital days during the baseline period was included as a covariate. Other covariates included dialysis access type, hemoglobin concentration (mean of months 5–6), serum ferritin level (mean of months 5–6), TSAT percentage (mean of months 5–6), and use of ESA (mean dose over months 5–6) iron, transfusion (yes/no), or activated vitamin D (yes/no) during the baseline period.

Outcomes

For developing and validating the transfusion score, the outcome defined in the 3-month follow-up period was transfusion use. For testing the association of outcomes and the score, the outcomes defined in the follow-up periods (6 and 12 months) included all-cause death and all-cause hospitalization.

Statistical Analyses

Descriptive data are displayed as percentages and means with standard deviations, where applicable. For the development cohort, we used logistic least absolute shrinkage and selection operator regression for variable selection to predict transfusion during the 3-month follow-up period. Logistic least absolute shrinkage and selection operator regression is a method that performs variable reduction and shrinkage of parameter estimates to avoid overfitting. The risk score on the basis of the final logistic regression model was created using the $\sum X*\text{Beta}$ for each individual, with X corresponding to the anemia-related variables and interactions. Given the model is inherently complex (containing many terms and interactions), the score must be calculated on the basis of the actual parameter estimates; this is in distinction to other commonly used scores, which usually require only simple conversion of the estimates to integers. The risk score was then applied in the validation cohort. Discrimination was assessed with c-statistics, and calibration was assessed by comparing observed versus predicted number of transfusions.

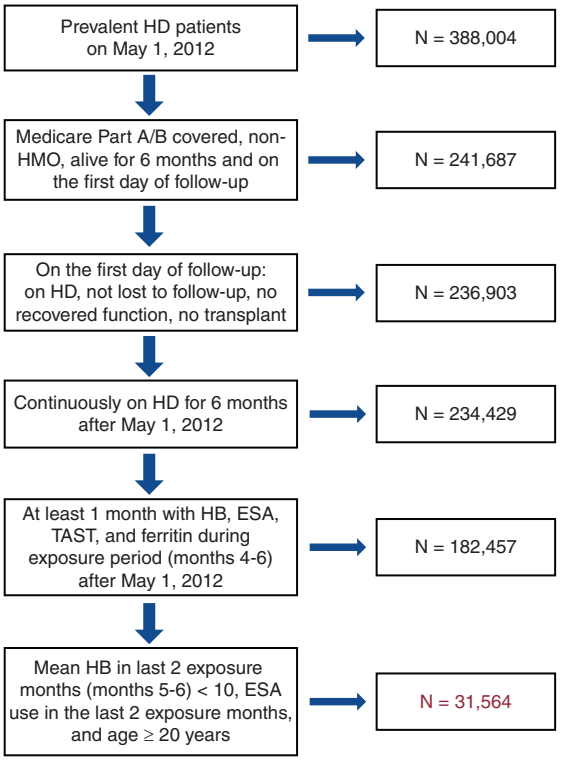

Figure 2. | **Selection of the study cohort (development).** HB, hemoglobin; HMO, health maintenance organization.

To assess the relationship between risk score and the separate outcomes of hospitalization or death, the distribution of risk scores was divided into five groups ranging from lower to higher risk of transfusion. Subsequently, Cox proportional hazard models were used to assess the relationship between the risk score and the outcomes of hospitalization and death within 12 months, adjusting for patient demographics and comorbid conditions. Outcomes within 6 and 12 months were investigated.

Institutional Review Board approval was obtained through the Hennepin Healthcare Research Institute, Office for Human Subjects Research. This manuscript has adhered to the tenets of the Declaration of Helsinki.

Results

After satisfying study selection criteria, 31,564 patients were available for analysis (Figure 2).

Baseline characteristics of the model development cohort are shown in Table 1. The mean age was 61.7 years, approximately half of patients were female, 51% were White, and 44% Black. Mean dialysis duration was 5.0 years. The

Table 1. Characteristics of the cohort used for model development

Characteristics	*n* (%)
Total patients	31,564 (100)
Mean age, years (SD)	61.73 (15)
Sex	
Men	15,847 (50)
Women	15,717 (50)
Race	
White	16,093 (51)
Black	13,763 (44)
Other	1708 (5)
Primary cause of ESKD	
Diabetes	14,100 (45)
Hypertension	9234 (29)
Glomerulonephritis	3715 (12)
Other	4515 (14)
Mean dialysis duration, years (SD)	5.04 (5)
Dialysis access type	
Catheter	6547 (21)
Fistula	25,017 (79)
Mean hospitalization days[a] (SD)	9.44 (16)
Mean weight, kg (SD)	76.28 (22)
Comorbid condition[a]	
Diabetes	20,184 (64)
ASHD	12,659 (40)
CHF	12,835 (41)
CVA/TIA	5052 (16)
PVD	10,888 (35)
Dysrhythmia	8912 (28)
Other cardiac	8814 (28)
COPD	7675 (24)
GI bleeding	3596 (11)
Liver disease	2316 (7)
Cancer	2686 (9)
Inflammatory conditions[a]	
Glomerulonephritis	2840 (9)
Chronic infections	1597 (5)
Crohn's disease	147 (0.5)
Ulcerative colitis	143 (0.5)
Hepatitis C	1291 (4)
Gout	2255 (7)
Rheumatoid arthritis	505 (2)

ASHD, atherosclerotic heart disease; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal.
[a]During 6-month baseline.

comorbidity burden was higher than in the general dialysis population; 64% had diabetes, 40% atherosclerotic heart disease, and 40% congestive heart failure. Overall, 10% received transfusions (3099 transfusions in 31,564 patients). Supplemental Table 2 shows the percentages of patients who received transfusions by patient characteristics. Mean hemoglobin was 9.4 g/dl (SD 0.59), mean monthly ESA dose was 83,160 units (SD 67,867), average TSAT was 29% (SD 13%), and average ferritin was 974 ng/ml (SD 2737) (Table 2). Patient characteristics and laboratory parameters for the validation cohort were similar.

Results from the logistic model used to develop the transfusion risk score are shown in Supplemental Table 3. This complex model, which included many interaction terms, demonstrated that key clinical variables predictive of transfusion included prior transfusion, ferritin (but not TSAT), more hospitalization days during baseline, higher comorbidity burden (particularly gastrointestinal bleeding), hemoglobin, and key interactions (hemoglobin, ESA dose, TSAT, ferritin, and iv iron use). Figure 3 shows a calibration plot applying the risk score from the development model to the validation cohort, showing observed versus predicted number of transfusions, and suggesting good calibration. The corresponding c-statistic in the validation cohort was 0.741. Percentages of patients receiving transfusions by the risk score are shown in Supplemental Figure 1.

Over the 12 months of follow-up, 16,346 hospitalizations and 5876 deaths occurred. Figure 4 shows results from the Cox proportional hazard models that assessed the association between the transfusion risk score with the outcomes of mortality and hospitalization within 12 months. The lowest group (lowest risk of transfusion) was the reference group, and increasing risk groups were compared with the lowest group. Although hazard ratios for death increased monotonically with increasing risk score (1.0, 1.22, 1.26, 1.54, 1.71 across the lowest to highest risk score), there was no relationship with hospitalization. Results for 6 months were similar (not shown).

Discussion

Use of transfusions to manage anemia is influenced by findings from clinical trials and observational studies (11–14), regulatory mandates (15), local policies, and provider preferences. At the bedside, benefits and risks of transfusions must be carefully considered. Although transfusion use in the general population appears to have decreased in recent years, with most hospitals enacting more restrictive procedures relative to decades past, RBC transfusion use in patients on dialysis increased after the introduction of the revised CMS Prospective Payment System (the "bundle") in January 2011 and the FDA's ESA label change in July 2011 (16). Although transfusion rates have since decreased from the peak recorded around 2012, avoiding transfusions is still preferable in most clinical scenarios. As such, we developed a transfusion risk score designed to predict the need for RBC transfusion in individual patients and to determine the strength of association between need for transfusion and potential risks of hospitalization and mortality. Our score, which demonstrated good performance characteristics, could be further developed into a useful bedside application (such as on a smartphone) for use by clinicians seeking to predict patient-level risk of future transfusions. Successful implementation of a transfusion risk score might permit clinicians at the bedside to invoke strategies to avoid transfusions. The fact that the score was also associated with mortality suggests the need for transfusion may be a surrogate for adverse outcomes in the following year and, as such, should be scrutinized carefully by clinicians.

This study is the first, to our knowledge, to attempt to develop and validate an RBC transfusion prediction model for patients on hemodialysis, and to determine how the risk score derived from the prediction model was

Table 2. Distributions of laboratory parameters, intravenous iron, vitamin D, and prior transfusion

Parameters	Values
Total patients, *n*	31,564
Hemoglobin,[a] g/dl, mean (SD)	9.37 (0.59)
Monthly ESA,[a] units, mean (SD)	83,160 (67,867)
TSAT,[b] %, mean (SD)	29 (13)
Ferritin,[b] ng/ml, mean (SD)	974 (2737)
iv iron use, %	80.1
iv vitamin D use, %	80.6
RBC transfusion use, %	12.4

ESA, erythropoiesis-stimulating agent; TSAT, transferrin saturation; iv, intravenous; RBC, red blood cell.
[a]Mean value of last 2 months.
[b]Mean value calculated in the order: (1) mean of last 2 months; (2) mean of any other 2 months; (3) value if there is only one measure.

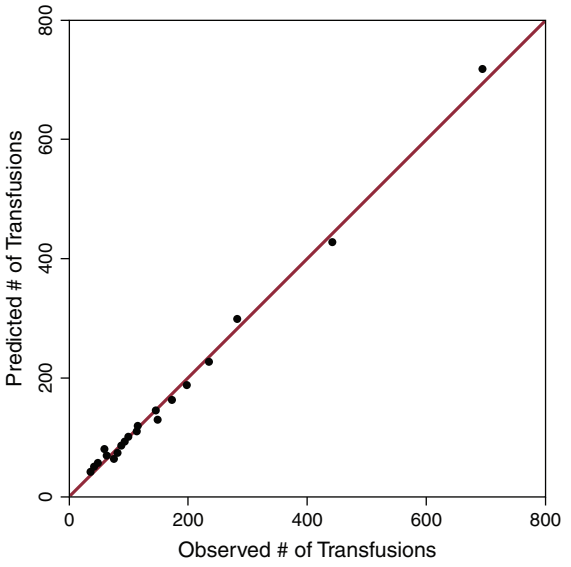

Figure 3. | Calibration plot, validation cohort.

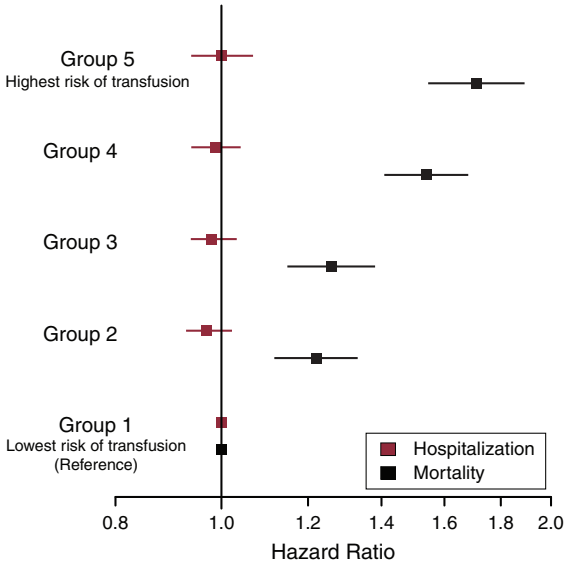

Figure 4. | Mortality and hospitalization hazard ratios.

associated with risks of mortality and hospitalization over the ensuing year. Although our model was not designed to highlight associations between specific risk factors and transfusions *per se*, variables predictive of transfusion included prior transfusion, ferritin, more hospitalization days during baseline, higher comorbidity burden (particularly history of gastrointestinal bleeding), and hemoglobin, and a number of interactions that included hemoglobin, ESA dose, TSAT, ferritin, and iv iron use.

Although some work, described below, has investigated factors associated with RBC transfusions in the general population, most has focused on the short-term need for future transfusions and has not emphasized the longer-term predictive implications of transfusions for morbidity or mortality. For example, Roubinian *et al*. (17) used a combination of administrative and electronic health record data to predict transfusion use among adult nonobstetric hospitalized patients. They found, not surprisingly, that hemoglobin at admission was the strongest predictor; perhaps unexpectedly, severity of illness and prior transfusion added little predictive power. In contrast, our study found a strong relationship between prior and subsequent transfusion, increasing the face validity of our findings. Alghamdi *et al*. (18) also found that hemoglobin was the strongest predictor, but sex, surgery type (reoperative or nonelective surgeries), kidney function, and weight also contributed. However, their score was developed in a very specific situation, namely risk stratification for patients undergoing cardiac surgery according to likelihood of requiring a near-term transfusion, and could not be expected to provide insights regarding maintenance patients on hemodialysis. Whitman *et al*. (19) used a survey method to assess physician decision making regarding transfusion use in patients on maintenance dialysis, finding that hemoglobin level, followed by functional status and comorbid conditions, most strongly influenced the decision to transfuse. This is generally concordant with our finding that increasing comorbidity burden was associated with increased risk of transfusion.

In addition, this study helps fill knowledge gaps in the kidney disease population, given that little previous work has focused on transfusion risk in the CKD population with anemia or in the dialysis population. Gill *et al*. (20) assessed transfusion use and predictors of transfusion in patients with CKD; they found hemoglobin and previous transfusion to be important predictors of future transfusion, as were comorbid heart failure and diabetes. Our group previously developed a standardized transfusion ratio to assess dialysis facility-level performance in avoiding transfusions (21). Although useful in gauging how units perform with regard to meeting quality measures, that study was not designed to predict transfusions at the level of the individual patient, nor did it examine longer-term implications of transfusion.

As with some other studies, previous transfusion was the strongest predictor of future transfusion in our study.

However, our inclusion of iron parameters, such as ferritin and TSAT (and interactions of these variables with other markers of anemia and anemia management), led to improved model performance as evidenced by an increase in the c-statistic. Although unsurprising, our results confirmed these routinely assessed laboratory values play a role in anemia and anemia management, increasing the face validity of our analysis. In addition to the factors listed above, we also considered ESA use (a factor not explicitly considered in most other studies). ESA dose and its interactions with TSAT are important factors to model when attempting to predict transfusions. We found the risk of transfusion increased as ESA dose increased (specifically, the highest tertile of ESA dose was associated with the highest likelihood of transfusion), and this was particularly true among individuals in the highest tertile of TSAT. This suggests patients who are iron replete and anemic (and therefore presumably being treated with high ESA doses) may have a functional iron block, leading to ESA hyporesponsiveness, which puts them at particular risk of requiring a transfusion.

Inflammation appears to be an important determinant of the need for transfusion, possibly *via* the hepcidin pathway (22). Markers of comorbid conditions strongly characterized by inflammation such as Crohn's disease, ulcerative colitis, hepatitis C, and rheumatoid arthritis emerged as important predictors of transfusion in the model. This suggests physicians should be aware that patients with these conditions represent a subgroup of patients on dialysis at especially high risk of requiring a transfusion.

Although the results of our exploratory analyses investigating the association between the transfusion risk score and mortality have intuitive appeal, the nature of the association between transfusion risk score and hospitalization may be less straightforward. Because most transfusions are administered during a hospitalization, we hypothesized that risks for transfusion and hospitalization would be concordant. Possibly, because the overall risk of transfusion during a given hospitalization is low, no clear signal is present. One hypothesis may involve competing risks: patients who are at higher risk of transfusion are also at particularly high risk of unexpected death outside the hospital or in the emergency department, but without a temporally antecedent hospitalization.

These results should be considered in light of the following limitations. First, results are limited to the study population, that is, patients on hemodialysis, and may not be generalizable to all patients with ESKD, or to patients with CKD who are not dialysis dependent. Second, this is an observational study using Medicare ESRD claims data, and except for TSAT and ferritin, laboratory data were not available, including actual biomarkers of inflammation, such as C-reactive protein. Third, as with any observational study, any associations of modeled factors with transfusions, and of transfusion score and risk of outcomes, cannot be considered causal relationships. Fourth, our study design and resultant complex modeling approach required a large sample size, necessitating the use of point-prevalent, rather than incident, cohorts. As such, some patients appeared in both the development and validation cohorts. It is possible the performance characteristics in a completely independent validation cohort might differ from those reported here. Finally, we recognize that, to leverage our score's full clinical utility, a practical bedside calculator must be developed on the basis of the model parameter estimates; however, this would not be difficult to do.

In summary, we developed and validated a novel, patient-level transfusion prediction model that demonstrated good overall performance in identifying patients on hemodialysis at risk of RBC transfusion. The model also predicts mortality, suggesting that patients who are anemic and at risk of receiving a transfusion are also at risk of death, and heightening the importance of close attention to anemia and its appropriate management. Given patients at increasing risk of transfusion are also at elevated risk of death, our model, if further developed into a clinically useful bedside application, could prove informative for clinicians in the comprehensive management of anemia. Risk stratifying patients for RBC transfusions might therefore guide use of transfusion-avoidance drugs, such as those designed to raise hemoglobin levels and iron, in patients receiving dialysis, but more work is required.

Disclosures

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Author Contributions

D. Gilbertson was responsible for the investigation and project administration, provided supervision, and wrote the original draft; S. Li, J. Liu, Y. Peng, M. Sinsakul, J. Wetmore, and H. Xu reviewed and edited the manuscript; and all authors conceptualized the study and were responsible for formal analysis and methodology.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0004512020/-/DCSupplemental.

Supplemental Table 1. ICD-9-CM diagnosis codes used to identify baseline comorbid conditions.

Supplemental Table 2. Percentages of patients who received transfusions by patient characteristics.

Supplemental Table 3. Parameter estimates from a logistic regression using 2012 training data.

Supplemental Figure 1. Percentages of patients receiving transfusions by risk score.

References

1. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J: Association of kidney function with anemia: The Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med* 162: 1401–1408, 2002 https://doi.org/10.1001/archinte.162.12.1401
2. Collins AJ, Li S, St Peter W, Ebben J, Roberts T, Ma JZ, Manning W: Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol* 12: 2465–2473, 2001
3. Locatelli F, Pisoni RL, Combe C, Bommer J, Andreucci VE, Piera L, Greenwood R, Feldman HI, Port FK, Held PJ: Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 19: 121–132, 2004 https://doi.org/10.1093/ndt/gfg458
4. Li S, Collins AJ: Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients. *Kidney Int* 65: 626–633, 2004 https://doi.org/10.1111/j.1523-1755.2004.00425.x
5. Robinson BM, Joffe MM, Berns JS, Pisoni RL, Port FK, Feldman HI: Anemia and mortality in hemodialysis patients: Accounting for morbidity and treatment variables updated over time. *Kidney Int* 68: 2323–2330, 2005 https://doi.org/10.1111/j.1523-1755.2005.00693.x
6. Wolfe RA, Hulbert-Shearon TE, Ashby VB, Mahadevan S, Port FK: Improvements in dialysis patient mortality are associated with improvements in urea reduction ratio and hematocrit, 1999 to 2002. *Am J Kidney Dis* 45: 127–135, 2005 https://doi.org/10.1053/j.ajkd.2004.09.023
7. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K: Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 17: 1181–1191, 2006 https://doi.org/10.1681/ASN.2005090997
8. Franchini M, Marano G, Mengoli C, Pupella S, Vaglio S, Muñoz M, Liumbruno GM: Red blood cell transfusion policy: A critical literature review. *Blood Transfus* 15: 307–317, 2017
9. Amgen Inc: Epogen® and PROCRIT® (epoetin alfa) injection. Highlights of prescribing information. 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103234Orig1s5166_103234Orig1s5266lbl.pdf. Accessed May 4, 2020
10. United States Renal Data System: 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. 2018 Available at: https://www.usrds.org/adr.aspx. Accessed May 4, 2020
11. Ma JZ, Ebben J, Xia H, Collins AJ: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 10: 610–619, 1999
12. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339: 584–590, 1998 https://doi.org/10.1056/NEJM199808273390903
13. Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P: Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: A meta-analysis. *Clin J Am Soc Nephrol* 4: 755–762, 2009 https://doi.org/10.2215/CJN.02730608
14. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R; TREAT Investigators: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 361: 2019–2032, 2009 https://doi.org/10.1056/NEJMoa0907845
15. U.S. Food and Drug Administration: FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease. 2011 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm. Accessed May 4, 2020
16. Hirth RA, Turenne MN, Wilk AS, Wheeler JR, Sleeman KK, Zhang W, Paul MA, Nahra TA, Messana JM: Blood transfusion practices in dialysis patients in a dynamic regulatory environment. *Am J Kidney Dis* 64: 616–621, 2014 https://doi.org/10.1053/j.ajkd.2014.01.011
17. Roubinian NH, Murphy EL, Swain BE, Gardner MN, Liu V, Escobar GJ; NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)Northern California Kaiser Permanente DOR Systems Research Initiative: Predicting red blood cell transfusion in hospitalized patients: Role of hemoglobin level, comorbidities, and illness severity. *BMC Health Serv Res* 14: 213, 2014 https://doi.org/10.1186/1472-6963-14-213
18. Alghamdi AA, Davis A, Brister S, Corey P, Logan A: Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. *Transfusion* 46: 1120–1129, 2006 https://doi.org/10.1111/j.1537-2995.2006.00860.x
19. Whitman CB, Shreay S, Gitlin M, van Oijen MG, Spiegel BM: Clinical factors and the decision to transfuse chronic dialysis patients. *Clin J Am Soc Nephrol* 8: 1942–1951, 2013 https://doi.org/10.2215/CJN.00160113
20. Gill KS, Muntner P, Lafayette RA, Petersen J, Fink JC, Gilbertson DT, Bradbury BD: Red blood cell transfusion use in patients with chronic kidney disease. *Nephrol Dial Transplant* 28: 1504–1515, 2013 https://doi.org/10.1093/ndt/gfs580
21. Liu J, Li S, Gilbertson DT, Monda KL, Bradbury BD, Collins AJ: Development of a standardized transfusion ratio as a metric for evaluating dialysis facility anemia management practices. *Am J Kidney Dis* 64: 608–615, 2014 https://doi.org/10.1053/j.ajkd.2014.04.012
22. Young B, Zaritsky J: Hepcidin for clinicians. *Clin J Am Soc Nephrol* 4: 1384–1387, 2009 https://doi.org/10.2215/CJN.02190309

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Supplementary Material

Table S1. ICD-9-CM diagnosis codes used to identify baseline comorbid conditions

Conditions	ICD-9-CM Diagnosis Codes/HCPCS	ICD-9-CM V codes
Comorbid conditions		
ASHD	410-414	V45.81; V45.82
CHF	398.91;422; 425; 428; 402.X1; 404.x1; 404.x3	V42.1
CVA/TIA	430-438	
PVD	440-444; 447; 451-453; 557	
Cardiac (other)	420-421;423-424; 429; 785.0-785.3	V42.2;V43.3
COPD	491-494; 496; 510	
GI bleeding	456.0-456.2; 530.7; 531-534; 569.84; 569.85; 578	
Liver disease	570; 571; 572.1; 572.4; 573.1-573.3	V42.7
Dysrhythmia	426-427	V45.0; V53.3
Cancer	140-172; 174-208; 230-231; 233-234	
Diabetes	250; 357.2; 362.0x; 366.41	
Inflammatory conditions		
Glomerulonephritis	582.9, 582.1, 583.1, 583.2, 583.81, 583.89, 583.4, 580.0, 582.0	
Chronic infections	Osteomyelitis (730.1), endocarditis (424.90), HIV (042), tuberculosis (010-018), systemic fungal infections: (Cryptococcosis [117.5], coccidioidomycosis [114], aspergillosis [117.3], pneumocystis pneumonia [136.3])	
Crohn disease	555	
Ulcerative colitis	556	
Hepatitis C	070.41, 070.44, 070.51, 070.54, 070.70, 070.71	
Gout	274	V77.5
Rheumatoid arthritis	714.0	

ASHD, atherosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; GI, gastrointestinal; HCPCS, Healthcare Common Procedure Coding System; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PVD, peripheral vascular disease.

Table S2. Percentages of patients who received transfusions by risk score

Score group	Transfusion rate (%)
score<=-1.3720000	3.8
-1.3720000 <score<=-1.2386100	3.94
-1.2386100<score<= -1.1129000	5.04
-1.1129000<score<=-1.0242000	5.9
-1.0242000 <score<=-0.9186000	5.98
-0.9186000 <score<=-0.8198000	6.63
-0.8198000 <score<=-0.5483800	8.24
-0.5483800 <score<=-0.3750800	10.91
-0.3750800 <score<=0.2766000	14.83
0.2766000<score	32.75

Table S3. Percentages of patients who received transfusions by risk score

Score group	Transfusion rate (%)
score<=-1.2386100	3.88
-1.2386100<score<=-0.9186000	5.64
-0.9186000 <score<=-0.5483800	7.42
-0.5483800<score<=0.2766000	12.91
0.2766000<score	32.75

Table S4. Percentages of patients who received transfusions by patient characteristics

	N	Percent Transfused
All	31,564	9.8
Age groups		
20-44	4,455	10.2
45-64	13,189	9.4
65-79	10,390	10.2
80+	3,530	9.6
Gender		
Male	15,847	9.7
Female	15,717	9.9
Race		
White	16,093	10.3
Black	13,763	9.4
Other	1,708	8.8
Primary cause of ESRD		
diabetes	14,100	9.6
hypertension	9,234	9.1
glomerulonephritis	3,715	9.7
Other	4,515	12.1
Dialysis vintage		
< 1 year	4,557	11.1
1-<2 years	4,470	9.8
2-<3 years	4,176	9.2
3-<5 years	6,926	9.6
5+ years	11,435	9.7
Dialysis access type		
Catheter	6,547	12.1
Fistula/Graft	25,017	9.2
Total length of hospitalization during 6 months baseline		
0 days	13,896	6.1
1-10 days	8,874	10.1
>10 days	8,794	15.5
Weight (kilogram)		
< 60.9	7,892	9.7
60.9 -< 72.4	7,917	9.6
72.4 -< 87.5	7,878	10.0
87.5+	7,877	9.9
Comorbid conditions during 6 months baseline		
Diabetes	20,184	10.1
ASHD	12,659	11.9
CHF	12,835	12.5
CVA/TIA	5,052	12.1
PVD	10,888	12.5
Dysrhythmia	8,912	13.2
Cardiac (other)	8,814	13.2
COPD	7,675	13.1
GI	3,596	19.0
Liver disease	2,316	14.9
Cancer	2,686	14.6
Inflammatory conditions during 6 months baseline		
Glomerulonephritis	2,840	13.0
Chronic infections	1,597	12.7
Crohn's disease	147	18.4
Ulcerative colitis	143	18.9
Hepatitis C	1,291	15.3
Gout	2,255	12.5
Rheumatoid arthritis	505	10.7
Hemoglobin (measured by mean value of last 2 months)		
< 8.5	2,398	21.9
>= 8.5 and < 9.5	11,676	11.3
>= 9.5	17,490	7.2
Monthly ESA (measured by mean value of last 2 months)		
<= 42000	10,345	6.4
> 42000 and < 112000	13,028	8.1
>= 112000	8,191	16.8
TSAT		
< 20	6,493	11.6
>= 20 and <= 40	20,203	8.7
> 40	4,868	12.0
Ferritin		
<= 600	7,328	11.7
> 600 and < 1000	11,672	7.8
>= 1000	12,564	10.6
IV iron use in exposure period		
No	6294	11.9
Yes	25270	9.3
IV vitamin D use in exposure period		
No	6132	10.9
Yes	25432	9.6
RBC Transfusion use in exposure period		
No	27645	7.0
Yes	3919	30.0

Table S5. Parameter estimates from a logistic regression using 2012 training data

Variables			Estimate	Standard Error	Chi-Square	*P*
Intercept			-1.821	0.313	33.896	< 0.0001
Age groups, years						
45-64			-0.116	0.064	3.290	0.0697
65-79			-0.021	0.069	0.093	0.7604
≥ 80			-0.028	0.086	0.106	0.7448
Female			0.077	0.041	3.549	0.0596
Race groups						
Black			-0.096	0.044	4.806	0.0284
Other			-0.001	0.094	0.000	0.9888
Primary cause of ESRD						
Hypertension			0.002	0.057	0.002	0.9684
Glomerulonephritis			-0.018	0.076	0.053	0.8176
Other			0.155	0.067	5.332	0.0209
Fistula/graft			-0.103	0.048	4.690	0.0303
Total length of hospitalization during 6-month baseline, days						
1-10			0.120	0.057	4.407	0.0358
> 10			0.230	0.064	12.840	0.0003
Comorbid and inflammatory conditions						
Diabetes			0.045	0.055	0.675	0.4114
ASHD			0.036	0.048	0.573	0.4489
CHF			0.083	0.048	3.032	0.0816
PVD			0.083	0.045	3.409	0.0649
Dysrhythmia			0.049	0.047	1.061	0.3031
COPD			0.091	0.047	3.768	0.0522
GI bleeding			0.245	0.055	19.770	<.0001
Liver disease			0.120	0.070	2.936	0.0866
Cancer			0.183	0.064	8.225	0.0041
Crohn disease			0.467	0.229	4.135	0.042
Ulcerative colitis			0.441	0.232	3.630	0.0568
Hepatitis C			0.170	0.090	3.565	0.059
Rheumatoid arthritis			-0.274	0.156	3.073	0.0796
Parameters and interactions	Groups					
HB	2		-0.798	0.246	10.516	0.0012
HB	3		-1.268	0.245	26.743	<.0001
ESA	2		-0.063	0.246	0.065	0.7992
ESA	3		0.405	0.230	3.107	0.078
TSAT	2		-0.136	0.193	0.497	0.4808
TSAT	3		0.101	0.243	0.172	0.6783
Ferritin	2		-0.716	0.230	9.707	0.0018
Ferritin	3		-0.131	0.197	0.443	0.5057
IV iron	yes		-0.285	0.228	1.569	0.2103
HB*ESA	2	2	0.050	0.212	0.055	0.8144
HB*ESA	2	3	-0.003	0.193	0.000	0.9877
HB*ESA	3	2	0.572	0.208	7.547	0.006

HB*ESA	3	3	0.393	0.194	4.106	0.0427
ESA*TSAT	2	2	0.008	0.149	0.003	0.9571
ESA*TSAT	2	3	0.001	0.185	0.000	0.9969
ESA*TSAT	3	2	0.215	0.145	2.189	0.139
ESA*TSAT	3	3	0.553	0.179	9.594	0.002
HB*Ferritin	2	2	0.309	0.171	3.272	0.0705
HB*Ferritin	2	3	0.162	0.159	1.039	0.308
HB*Ferritin	3	2	0.239	0.171	1.957	0.1618
HB*Ferritin	3	3	0.176	0.159	1.221	0.2692
TSAT*Ferritin	2	2	0.141	0.122	1.336	0.2478
TSAT*Ferritin	2	3	0.046	0.122	0.140	0.7087
TSAT*Ferritin	3	2	0.381	0.194	3.856	0.0496
TSAT*Ferritin	3	3	0.323	0.183	3.110	0.0778
IV iron*HB	yes	2	0.532	0.153	12.024	0.0005
IV iron*HB	yes	3	0.513	0.158	10.622	0.0011
IV iron*ESA	yes	2	-0.197	0.129	2.339	0.1262
IV iron*ESA	yes	3	-0.176	0.133	1.757	0.1851
IV iron*TSAT	yes	2	-0.005	0.142	0.001	0.973
IV iron*TSAT	yes	3	-0.513	0.162	10.061	0.0015
IV iron*Ferritin	yes	2	0.114	0.173	0.435	0.5094
IV iron*Ferritin	yes	3	-0.196	0.145	1.829	0.1762
Use of vitamin D	yes		-0.058	0.050	1.369	0.2419
Prior transfusion	yes		1.301	0.048	745.500	<.0001

ASHD, atherosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESA, erythropoiesis-stimulating agent; GI, gastrointestinal; HB, hemoglobin; IV, intravenous; PVD, peripheral vascular disease; TSAT, transferrin saturation.

Table S6. Development cohort (2012) and the validation cohort (2013). Characteristics were similar between the cohorts.

	2012 Cohort		2013 Cohort	
	N	%	N	%
Total patients	31,564	100.0	34,890	100.0
Mean age (SD)	61.73 (14.88)		62.26 (14.95)	
Age group				
20-44	4,455	14.1	4,745	13.6
45-64	13,189	41.8	14,162	40.6
65-79	10,390	32.9	11,762	33.7
80+	3,530	11.2	4,221	12.1
Gender				
Male	15,847	50.2	17,598	50.4
Female	15,717	49.8	17,292	49.6
Race				
White	16,093	51.0	17,851	51.2
Black	13,763	43.6	14,995	43.0
Other	1,708	5.4	2,044	5.9
Primary cause of ESRD				
Diabetes	14,100	44.7	15,597	44.7
Hypertension	9,234	29.3	10,381	29.8
Glomerulonephritis	3,715	11.8	4,026	11.5
Other	4,515	14.3	4,886	14.0
Mean dialysis vintage (SD)	5.04 (4.97)		5.31 (5.00)	
Dialysis vintage				
<1 year	4,557	14.4	3,870	11.1
1-<2 years	4,470	14.2	4,863	13.9
2-<3 years	4,176	13.2	4,635	13.3
3-<5 years	6,926	21.9	7,995	22.9
5+ years	11,435	36.2	13,527	38.8
Dialysis access type				
Catheter	6,547	20.7	7,574	21.7
Fistula/Graft	25,017	79.3	27,316	78.3
Mean days of total hospitalizations (SD) during baseline	9.44 (15.88)		9.14 (15.26)	
Length of total hospitalizations in days during baseline				
0 days	13,896	44.0	15,693	45.0
1-10 days	8,874	28.1	9,602	27.5
>10 days	8,794	27.9	9,595	27.5
Mean weight	76.28 (22.07)		76.65 (22.15)	
Weight (kilogram)				
< 60.9	7,892	25.0	8,728	25.0
60.9 -< 72.4	7,917	25.1	8,727	25.0
72.4 -< 87.5	7,878	25.0	8,731	25.0

87.5+	7,877	25.0	8,704	25.0
Comorbid conditions during 6 months baseline				
Diabetes	20,184	64.0	22,414	64.2
ASHD	12,659	40.1	13,881	39.8
CHF	12,835	40.7	14,269	40.9
CVA/TIA	5,052	16.0	5,652	16.2
PVD	10,888	34.5	12,038	34.5
Dysrhythmia	8,912	28.2	9,910	28.4
Cardiac (other)	8,814	27.9	9,713	27.8
COPD	7,675	24.3	8,697	24.9
GI	3,596	11.4	3,906	11.2
Liver Disease	2,316	7.3	2,683	7.7
Cancer	2,686	8.5	2,807	8.1
Inflammatory conditions during 6-month baseline period				
Glomerulonephritis	2,840	9.0	3,234	9.3
Chronic infections	1,597	5.1	1,774	5.1
Crohn disease	147	0.5	141	0.4
Ulcerative colitis	143	0.5	100	0.3
Hepatitis C	1,291	4.1	1,463	4.2
Gout	2,255	7.1	2,572	7.4
Rheumatoid arthritis	505	1.6	588	1.7

Figure S1. Percentages of patients receiving transfusions by risk score