Kidney360

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.

KIDNEY360 2: 948–954, 2021. doi: https://doi.org/10.34067/KID.0004512020

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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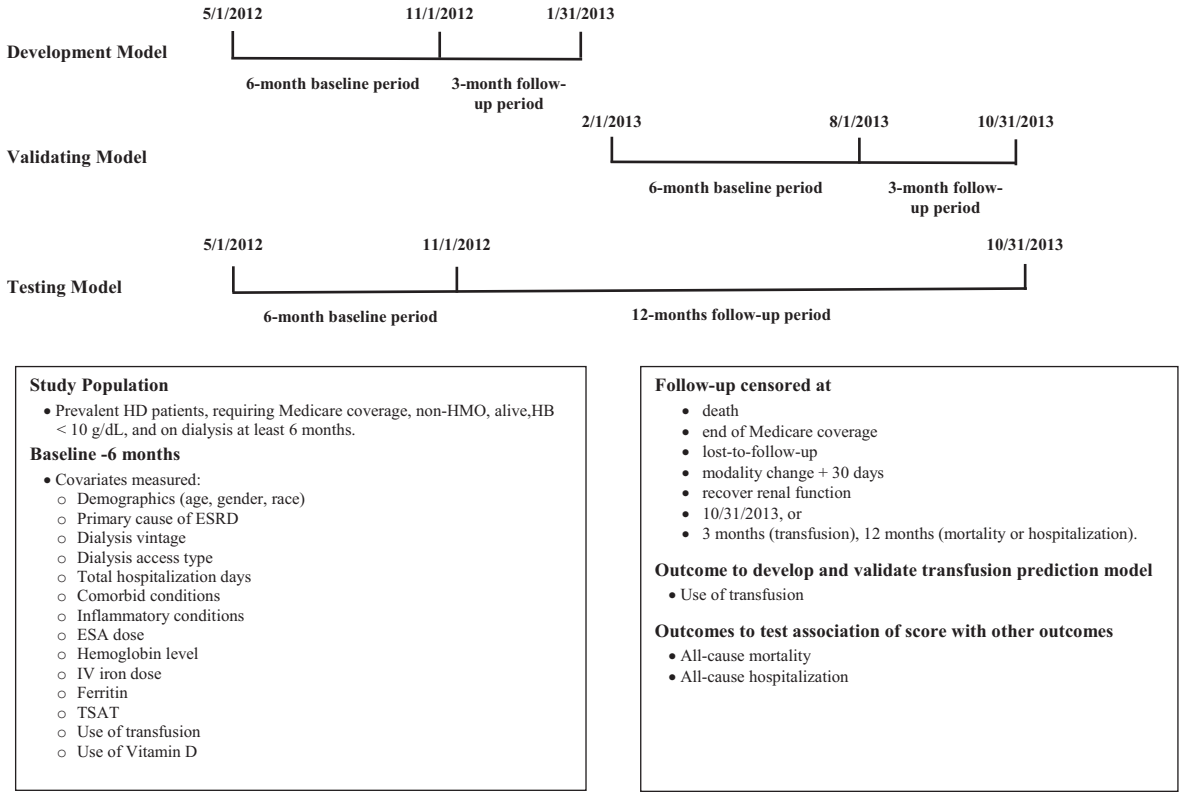

Figure 1. | **Study design.** ESA, erythropoiesis-stimulating agent; HD, hemodialysis; HMO, health maintenance organization; iv, intravenous; TSAT, transferrin saturation.

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.

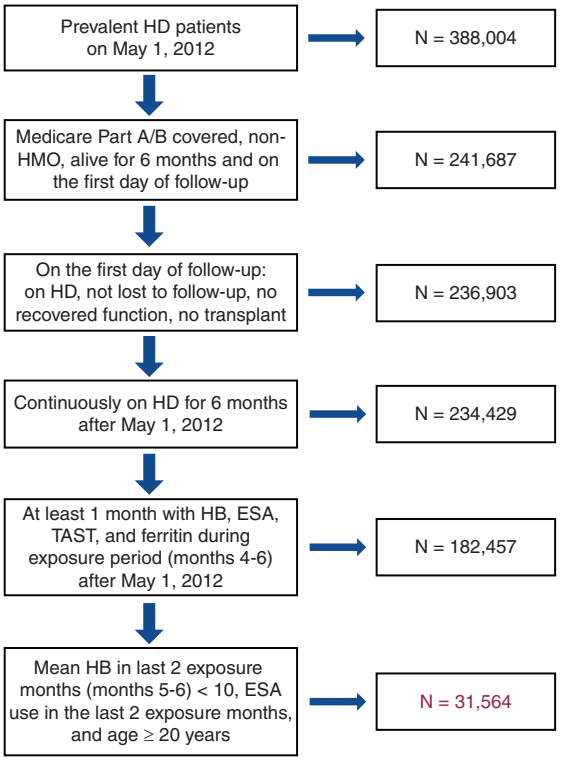

Figure 2. | **Selection of the study cohort (development).** HB, hemoglobin; HMO, health maintenance organization.

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.

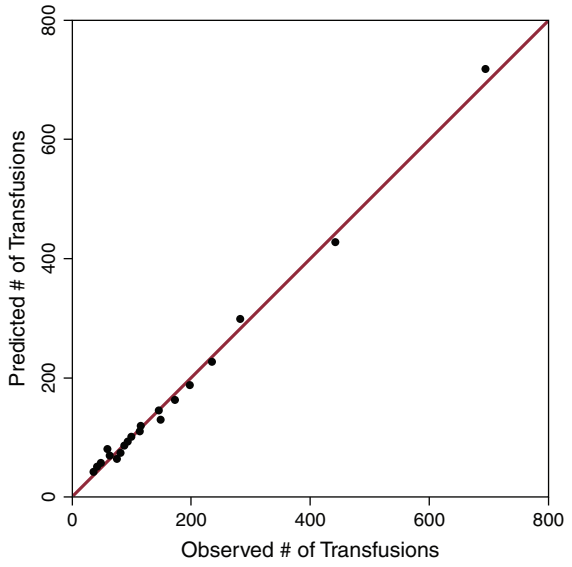

Figure 3. | Calibration plot, validation cohort.

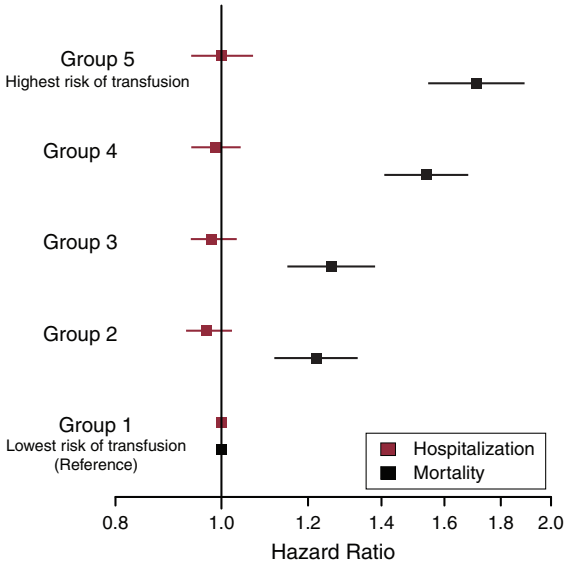

Figure 4. | Mortality and hospitalization hazard ratios.

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

D.T. Gilbertson reports having consultancy agreements with Amgen; reports receiving research funding from Acadia, Amgen, AstraZeneca, DaVita, Genentech, Gilead, Health Resources and Services Administration, Merck, the National Institutes of Health, and OPKO Renal. M. Sinsakul reports ownership interest in AstraZeneca. J.B. Wetmore reports *ad hoc* consulting for Bristol-Myers Squibb (BMS)-Pfizer Alliance; reports receiving research funding from Amgen, AstraZeneca, BMS-Pfizer, Genentech, Merck, and OPKO Health; reports receiving honoraria from BMS-Pfizer Alliance (for advisory board activities); and reports being a scientific advisor or member of BMS-Pfizer Alliance, with no standing relationships, but participating on occasion on *ad hoc* advisory boards. All remaining authors have nothing to disclose.

Funding

This study was supported by an AstraZeneca research grant.

Acknowledgments

The authors thank Chronic Disease Research Group colleagues Ms. Anne Shaw for manuscript preparation and Nan Booth, Master of Social Work, Editor in the Life Sciences, for manuscript editing.

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.

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Received: July 22, 2020 **Accepted:** April 2, 2021