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 dialysis patients 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 (point prevalent hemodialysis patients on November 1, 2012) and a validation cohort (point prevalent hemodialysis patients 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 hemodialysis patients 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.
Introduction

Anemia is a near universal complication of advanced chronic kidney disease (CKD) and in patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis. Because anemia is associated with adverse outcomes, including hospitalization and mortality, in hemodialysis patients, 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. Therefore, avoiding transfusions is recommended in patients with CKD and ESRD, and is the main US Food and Drug Administration (FDA)-approved indication for ESA use in dialysis patients.

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 hemodialysis patients. 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 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 employed in a timely fashion.
Methods

Data sources

This study used data from the 2012-2013 United States Renal Data System (USRDS) ESRD database. This database contains information from the ESRD Medical Evidence Report (form Centers for Medicare & Medicaid Services [CMS]-2728), which includes patient demographic information, renal history, comorbid conditions, and selected information on pre-ESRD therapy (e.g., ESA use). The database also includes information from the ESRD Death Notification (form CMS-2746), 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 files (SAFs) 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). While the Medical Evidence Report and the Death Notification form are required for all ESRD patients, the SAFs and CROWNWeb data are available for ESRD patients with fee-for-service Medicare coverage, approximately two-thirds of all ESRD patients.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 prior to 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, who received ESAs, and who were aged 20 years or older. Individuals in both cohorts were followed for up to 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 ESRD (diabetes, hypertension, glomerulonephritis, other), time since dialysis initiation (dialysis
duration), and a broad range of comorbid conditions defined from form CMS-2728 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 disease, ulcerative colitis, hepatitis C, gout, and rheumatoid arthritis (Table S1). 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 analysis**

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 (LASSO) regression for variable selection to predict transfusion during the 3-month
follow-up period. LASSO regression is a method that performs variable reduction and shrinkage of parameter estimates to avoid overfitting. The risk score based on the final logistic regression model was created using the $\sum X \times Beta$ for each individual, with $X$ corresponding to the anemia-related variables and interactions. Given that the model is inherently complex (that is, containing many terms and interactions), the score must be calculated based on 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 vs. predicted number of transfusions.

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 comorbidity burden was higher than in the general dialysis population; 64% had diabetes, 40% atherosclerotic heart disease, and 40% congestive heart failure. Overall, 9.8% received transfusions (3099 transfusions in 31,564 patients). Table S2 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 Table S3. 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 vs. 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 Figure S1.

Over the 12 months of follow-up, 16,346 hospitalizations and 5,876 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. While 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,\textsuperscript{11-14} regulatory mandates,\textsuperscript{15} local policies, and provider preferences. At the bedside, benefits and risks of transfusions must be carefully considered. While 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 dialysis patients actually increased following introduction of the revised CMS Prospective Payment System (the “bundle”) in January 2011 and the FDA’s ESA label change in July 2011.\textsuperscript{16} Although transfusion rates have since decreased from the peak recorded circa 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 that need for transfusion may be a surrogate for adverse outcomes in the following year and as such should be scrutinized carefully by clinicians.

The present study is the first, to our knowledge, to attempt to develop and validate an RBC transfusion prediction model for hemodialysis patients, and to determine how the risk score derived from the prediction model was 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, as well as a number of interactions that included hemoglobin, ESA dose, TSAT, ferritin, and IV iron use.

While some work, described below, has investigated factors associated with RBC transfusions in the general population, most such work has focused only 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\textsuperscript{17} used a combination of administrative and electronic health record data to predict transfusion use among adult non-obstetric 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\textsuperscript{18} also found that hemoglobin was the strongest predictor, but sex, surgery type (re-operative or non-elective 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 hemodialysis patients. Whitman et al\textsuperscript{19} used a survey method to assess physician decision making regarding transfusion use in maintenance dialysis patients, 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, the present 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\textsuperscript{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.\textsuperscript{21} While 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 (as well as 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 that 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 that 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 that this was particularly true among individuals in the highest tertile of TSAT. This suggests that patients who are iron replete but also anemic (and who therefore are presumably being treated with high ESA doses) may have a functional iron block leading to ESA hypo-responsiveness, 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. Markers of comorbid conditions strongly characterized by inflammation such as Crohn disease, ulcerative colitis, hepatitis C, and rheumatoid arthritis emerged as important predictors of transfusion in the model. This suggests that physicians should be aware that patients with these conditions represent a subgroup of dialysis patients at especially high risk of requiring a transfusion.

While 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, i.e., hemodialysis patients, and may not be generalizable to all
ESRD patients, or to non-dialysis-dependent CKD patients. 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 that the performance characteristics in a completely independent validation cohort might differ from those reported here. Finally, we recognize that, in order to leverage our score’s full clinical utility, a practical bedside calculator must be developed based on 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 hemodialysis patients at risk of RBC transfusion. The model also predicts mortality, suggesting that anemic patients 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 that 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. Gilbertson reports Consultancy Agreements: Amgen; Research Funding: NIH, HRSA, Amgen, DaVita, AstraZeneca, Acadia, Gilead, Opko Renal, Genentech, Merck. J. Wetmore reports Consultancy Agreements: Ad hoc consulting for BMS-Pfizer Alliance; Research Funding: AstraZeneca; OPKO Health; Merck; Genentech, Amgen, BMS/Pfizer; Honoraria: BMS-Pfizer Alliance (for advisory board activities, as noted below); Scientific Advisor or Membership: BMS-Pfizer Alliance: No standing relationships, but I participate on occasion on ad hoc advisory boards. M. Sinsakul reports Ownership Interest: AstraZeneca. All remaining authors have nothing to disclose.

Funding

This study was supported by a research grant from AstraZeneca, Gaithersburg, Maryland.

Acknowledgments

The authors thank Chronic Disease Research Group colleagues Anne Shaw for manuscript preparation and Nan Booth, MSW, MPH, ELS, for manuscript editing.

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H Xu: Conceptualization; Formal analysis; Writing - review and editing
M Sinsakul: Conceptualization; Formal analysis; Writing - review and editing
Y Peng: Conceptualization; Formal analysis; Methodology; Writing - review and editing
J Wetmore: Conceptualization; Formal analysis; Writing - review and editing
J Liu: Conceptualization; Formal analysis; Methodology; Writing - review and editing
S Li: Conceptualization; Formal analysis; Methodology; Writing - review and editing.

Supplementary Material

Table S1. ICD-9-CM diagnosis codes used to identify baseline comorbid conditions
Table S2. Percentages of patients who received transfusions by patient characteristics
Table S3. Parameter estimates from a logistic regression using 2012 training data
Figure S1. Percentages of patients receiving transfusions by risk score
Reference List


(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


Table 1. Characteristics of the Cohort Used for Model Development

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Total patients</td>
<td>31,564 (100.0)</td>
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<tr>
<td>Mean age, years (SD)</td>
<td>61.73 (14.88)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Men</td>
<td>15,847 (50.2)</td>
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<tr>
<td>Women</td>
<td>15,717 (49.8)</td>
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<td>White</td>
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<td>Black</td>
<td>13,763 (43.6)</td>
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<td>Other</td>
<td>1708 (5.4)</td>
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<td>Primary cause of ESRD</td>
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<tr>
<td>Diabetes</td>
<td>14,100 (44.7)</td>
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<tr>
<td>Hypertension</td>
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<td>Glomerulonephritis</td>
<td>3715 (11.8)</td>
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<td>Other</td>
<td>4515 (14.3)</td>
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<td>Mean dialysis duration, years (SD)</td>
<td>5.04 (4.97)</td>
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<td>Catheter</td>
<td>6547 (20.7)</td>
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<td>Fistula</td>
<td>25,017 (79.3)</td>
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<td>Mean hospitalization days* (SD)</td>
<td>9.44 (15.88)</td>
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<td>Mean weight, kg (SD)</td>
<td>76.28 (22.07)</td>
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<td>CHF</td>
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<tr>
<td>CVA/TIA</td>
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<td>PVD</td>
<td>10,888 (34.5)</td>
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<td>Other cardiac</td>
<td>8814 (27.9)</td>
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<td>COPD</td>
<td>7675 (24.3)</td>
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<td>GI bleeding</td>
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<td>Liver disease</td>
<td>2316 (7.3)</td>
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<tr>
<td>Cancer</td>
<td>2686 (8.5)</td>
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<td>Inflammatory conditions*</td>
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<td>Glomerulonephritis</td>
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<td>Ulcerative colitis</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>505 (1.6)</td>
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</table>

*During 6-month baseline.
ASHD, atherosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; GI, gastrointestinal; PVD, peripheral vascular disease, SD, standard deviation.
Table 2. Distributions of laboratory parameters, IV iron, vitamin D, and prior transfusion

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
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<tr>
<td>Total patients, ( n )</td>
<td>31,564</td>
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<tr>
<td>Hemoglobin, ( \text{g/dL} ), mean (SD)</td>
<td>9.37 (0.59)</td>
</tr>
<tr>
<td>Monthly ESA, ( \text{units} ), mean (SD)</td>
<td>83,160 (67,867)</td>
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<td>TSAT, ( % ), mean (SD)</td>
<td>29 (13)</td>
</tr>
<tr>
<td>Ferritin, ( \text{ng/mL} ), mean (SD)</td>
<td>974 (2737)</td>
</tr>
<tr>
<td>IV iron use, ( % )</td>
<td>80.1</td>
</tr>
<tr>
<td>IV vitamin D use, ( % )</td>
<td>80.6</td>
</tr>
<tr>
<td>RBC transfusion use, ( % )</td>
<td>12.4</td>
</tr>
</tbody>
</table>

*Mean value of last 2 months.

†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 Legends

Figure 1. Study design. ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; HD, hemodialysis; HMO, health maintenance organization; IV, intravenous; TSAT, transferrin saturation.

Figure 2. Selection of the study cohort (development). ESA, erythropoiesis-stimulating agent; HB, hemoglobin; HD, hemodialysis; HMO, health maintenance organization; TSAT, transferrin saturation.

Figure 3. Calibration plot, validation cohort.

Figure 4. Mortality and hospitalization hazard ratios.
Study Population
- Prevalent HD patients, requiring Medicare coverage, non-HMO, alive, HB < 10 g/dL, and on dialysis at least 6 months.

Baseline - 6 months
- Covariates measured:
  - Demographics (age, gender, race)
  - Primary cause of ESRD
  - Dialysis vintage
  - Dialysis access type
  - Total hospitalization days
  - Comorbid conditions
  - Inflammatory conditions
  - ESA dose
  - Hemoglobin level
  - IV iron dose
  - Ferritin
  - TSAT
  - Use of transfusion
  - Use of Vitamin D

Follow-up censored at
- death
- end of Medicare coverage
- lost-to-follow-up
- modality change + 30 days
- recover renal function
- 10/31/2013, or
- 3 months (transfusion), 12 months (mortality or hospitalization)

Outcome to develop and validate transfusion prediction model
- Use of transfusion

Outcomes to test association of score with other outcomes
- All-cause mortality
- All-cause hospitalization
Figure 2.

Prevalent HD patients on May 1, 2012

N = 388,004

Medicare Part A/B covered, non-HMO, alive for 6 months and on the first day of follow-up

N = 241,687

On the first day of follow-up: on HD, not lost to follow-up, no recovered function, no transplant

N = 236,903

Continuously on HD for 6 months after May 1, 2012

N = 234,429

At least 1 month with HB, ESA, TSAT, and ferritin during exposure period (months 4-6) after May 1, 2012

N = 182,457

Mean HB in last 2 exposure months (months 5-6) < 10, ESA use in the last 2 exposure months, and age ≥ 20 years

N = 31,564
Figure 3.
Figure 4.

Group 5
Highest risk of transfusion

Group 4

Group 3

Group 2

Group 1
Lowest risk of transfusion
(Reference)

Hazard Ratio

- Hospitalization
- Mortality