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Transfusion Probability as an Alternative Measure of Lab-Guided Medical Decision-Making

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ABSTRACT

Background. The clinical decision to transfuse is strongly influenced by laboratory results. Analysis of transfusion decision-making through pre-transfusion laboratory results (e.g. pre-transfusion haemoglobin) is a common yet misleading approach to study transfusion practice.

Study Design and Methods. We introduce "Transfusion Probability", an alternative method overcoming many limitations of pre-transfusion lab result analyses. Under this approach, we estimate the probability of transfusion after results at a specific value (e.g. haemoglobin 7.4 g/dL) or in a range of values (e.g. 7.0-7.9 g/dL) using the proportion of tests followed by transfusion. We provide comprehensive methodology for causal inference on the effect of patient characteristics and other variables of interest.

Results. Analyses using pre-transfusion and transfusion probability were compared through a retrospective cohort study of hospitalised patients (N=525,032). We found red blood cell transfusion probabilities of 76.2% in the 6.0-6.9 g/dL, 18.9% in the 7.0-7.9 g/dL, and 4.5% in the 8.0-8.9 g/dL haemoglobin ranges. After confounder adjustment, gastrointestinal bleeding patients were more likely to be transfused, with risk differences ranging from 6.6% in the 8.0-8.9 g/dL range to 13.8% in the 6.0-6.9 g/dL range. Pre-transfusion haemoglobin results showed minimal differences between gastrointestinal bleeding patients and other patients in unadjusted (0.00 g/dL) and adjusted analyses (-0.03 g/dL).

Discussion. In contrast to pre-transfusion result analysis, transfusion probability offers a nuanced account of transfusion practice and natural comparisons between patient groups. Wider use of our approach can provide actionable insights for clinical decision-making.

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BACKGROUND

Modern medical interventions are heavily influenced by laboratory results. Physicians use results to assess risk, diagnose disease, pick therapies, and monitor outcomes. Lab-guided management is especially prominent in transfusion medicine and laboratory results are the strongest predictors of whether a patient will receive a transfusion.[1] Specific values or ranges of values are widely used for eligibility, enrollment, intervention, and outcomes assessment in large randomised controlled trials of therapeutic interventions.[2 3] Laboratory thresholds also appear in transfusion guidelines, diagnostic algorithms, bundled ordersets, healthcare audits, educational materials, and medical lawsuits.[4 5 6] Despite their ubiquity, common approaches for measuring the effect of laboratory results on clinical transfusion behavior can be prone to errors in statistical design.

Traditional analyses of lab-guided transfusion rely predominantly on pre-transfusion test results, defined as the last available value within a given time interval preceding an order. For instance, large audits of red cell transfusion often rely on the last available haemoglobin result in the preceding 24 hours.[7 8] The popularity of these analyses may be partly due to convenience—pre-transfusion laboratory results are easily collected at the point of transfusion, widely familiar within the field, and readily visualised through histograms. Results are used to audit clinical practice across diverse hospital systems, monitor protocol adherence in clinical trials, and influence high-impact policy for disease management.[9 10 11] However, naïve use of pre-transfusion laboratory results has several limitations relating to confounding by indication, modeling assumptions, and misleading interpretation when used to predict and assess physician practice.

Some pitfalls of pre-transfusion lab-based analyses may be illustrated by considering pre-transfusion haemoglobin as a predictor of red cell transfusion. First, reporting only the frequency of a particular pre-transfusion haemoglobin result, e.g. 6.4 g/dL, disregards information provided by instances where a 6.4 g/dL value did not trigger a transfusion; as a result, such analyses do not truly reflect the effect of laboratory results (the exposure of interest) on transfusion behavior. Second, pre-transfusion haemoglobin does not naturally

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allow for granular comparisons between transfusion strategies in specific haemoglobin ranges of interest (e.g. 8.0 to 10.0 g/dL in cardiac disease patients). Third, pre-transfusion haemoglobin does not have an intuitive interpretation when used to predict patient outcomes in statistical models. By considering only haemoglobin values for those patients who received a transfusion, analyses using pre-transfusion haemoglobin introduce a selection bias in studying the effect of haemoglobin on transfusion practice. Fourth, when used as an outcome, pre-transfusion haemoglobin is only a proxy measure of transfusion decisions. This means that standard statistical methods to adjust for confounding may not work as intended (Appendix F). Additionally, pre-transfusion haemoglobin analyses may be misleading when comparing transfusion practice across patient subgroups with distinct haemoglobin distributions. Consider two physicians with identical thresholds for transfusion, where one treats general medical patients with gastrointestinal bleeding and a mean haemoglobin of 9.0 g/dL, while the other treats patients with leukemia and a mean haemoglobin of 7.0 g/dL. A naive comparison of their transfusion practice based on mean pre-transfusion haemoglobin could lead to the erroneous conclusion that the physician treating leukemia transfuses less aggressively, since a larger number of their transfusion decisions occur in a lower haemoglobin range (i.e. 6.0-6.5 g/dL).

Herein we introduce transfusion probability as an alternative measure which overcomes several limitations of pre-transfusion values for studying the effect of laboratory results on transfusion decisions. We begin by describing the mathematical calculation, conceptual framework, statistical usage, and clinical interpretation of transfusion probability for studies of transfusion decisions. We then illustrate the measure in a large multi-center dataset to explore the effect of haemoglobin results on red cell transfusion as a specific case, comparing results obtained using transfusion probability to results from pre-transfusion haemoglobin analysis. We conclude with a discussion of potential applications and important limitations of the method.

METHODS

Pre-Transfusion Haemoglobin

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Based on past literature, we defined pre-transfusion haemoglobin as the last available haemoglobin result within 24 hours preceding red cell transfusion, using any test method.[12] Alternative definitions of pre-transfusion haemoglobin, such as extending the capture window to 1 week pre-transfusion or selecting the nadir haemoglobin, have been reported in literature but are not explored in this study.[13] [14] [15]

Transfusion Probability

Transfusion probability was defined as the proportion of haemoglobin results which were followed by a red cell transfusion in the subsequent 24 hours (the "exposure" window), out of all haemoglobin results at a specific value or range of values. The approach resembles traditional cohort analysis methods where the proportion of individuals with an outcome is calculated within each exposure group (e.g. treatment and control).[16] For instance, if a dataset contains 1,000 haemoglobin results with a value of 7.9 g/dL and 300 of these results were followed by a red cell transfusion, the transfusion probability would be 300/1,000, or 30% (Figure 1). Similarly, if a dataset contains 2500 haemoglobin results within the range of 8.0-9.0 g/dL and 500 of these are followed by a red cell transfusion, the transfusion probability in this range would be 500/2500 or 20%. Depending on the study question and amount of data available, this calculation can be repeated at each haemoglobin value or ranges of values, and the results plotted to generate transfusion probability curves which reflect the clinical propensity for transfusion across the range of interest (Figure 2 depicts an example of visualization at each haemoglobin level). Transfusion probability curves can also be generated for different subgroups of interest and analyzed either visually or through rigorous statistical methods for comparison of transfusion practice.

Exposure Window

Although our analysis will calculate transfusion probability over a 24-hour exposure window following a test result, the method can also be generalized to accommodate alternate exposure windows. The window may be defined in different ways depending on the study question, data availability, need for precision, and clinical validity. For instance, in our analysis, we chose a 24-hour fixed exposure window based on a few

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considerations. Setting the exposure window to be too large can be misleading, as very distant haemoglobin results are unlikely to influence clinical decisions. In the extreme example, a last-available haemoglobin value of 12.0 g/dL from three years ago is unlikely to influence transfusion strategy for an acutely exsanguinating patient. Another approach might be to split clinical time into intervals between haemoglobin results, yielding several exposure windows defined by consecutive haemoglobin results. This might lead to shorter exposure windows, which requires controlling for length of exposure window and might discount the impact of earlier haemoglobin results when tests are ordered in close succession (e.g. when four tests are ordered within an hour). Our approach of selecting a fixed exposure window has the advantage of simpler analysis and clinical interpretation and incorporates the influence of multiple results obtained in close succession. However, it can introduce additional noise due to overlap of exposure windows between nearby test results. Although we favored a fixed-time interval approach in the current study, other definitions of the exposure window may be desirable depending on the question of interest.

Statistical Analyses using Transfusion Probability

In this section we provide a rigorous statistical description of transfusion probability analysis. Let $X_1, \ldots, X_n$ be a set of haemoglobin measurements (including multiple measurements per patient). Let $Y_1, \ldots, Y_n$ represent a binary indicator for the decision to transfuse where $Y_i = 1$ if a transfusion occurred within a given time interval (e.g. 24 hours) and $Y_i = 0$ if no transfusion occurred.

We can estimate transfusion probability at a specific haemoglobin value x (e.g. 6.9 g/dL), represented by the conditional probability $P(Y_i = 1 | X_i = x)$, as follows:

$$\widehat{p_x} = \frac{\sum_{i=1}^{n} Y_i I(X_i = x)}{\sum_{i=1}^{n} I(X_i = x)} \quad (1)$$

where $I(X_i = x)$ is an indicator function which takes value 1 only if X_i takes exactly value x and is otherwise 0.

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If we assume that the observations are independent and identically distributed (IID), and that there are no confounding factors, we can estimate the variance of $\hat{p}$ using the variance of a binomial random variable:

$$\widehat{Var}(\hat{p}) = \frac{\hat{p}(1-\hat{p})}{\sum_{i=1}^{n} I(X_i = x)}$$

The assumption of IID data does not necessarily hold for measurements from similar medical contexts (e.g. same patient, physician, or hospital), and we discuss potential extensions to deal with this issue in Appendix B. After estimating variance, we can then construct a confidence interval and compare transfusion probabilities at different haemoglobin values or between groups of patients. A caveat relating to analysis at individual haemoglobin values is the need to adjust for multiple testing, as comparison at each level would be considered a separate test.

We can also estimate transfusion probability in a range of haemoglobin values given by x_1-x_2 (e.g. 7.0-8.0 g/dL). This may be desirable if the number of results at individual haemoglobin values is limited due to small sample size or infrequent testing. For haemoglobin ranges, transfusion probability can be calculated as follows:

$$\hat{p} = \frac{\sum_{i=1}^{n} Y_i I(x_1 \leq X_i \leq x_2)}{\sum_{i=1}^{n} I(x_1 \leq X_i \leq x_2)}$$

This approach has a natural interpretation and effectively captures the broad patterns of transfusion behavior while smoothing out some of the noise associated with any finite sample size.

Covariate Adjustment for Transfusion Probability

In many cases, researchers are interested in assessing the impact of a particular characteristic (physician, hospital, or patient-level) on transfusion probability. For

observational studies, this often requires adjusting for confounding due to a variety of patient characteristics including age, condition, and presence of bleeding.

To model this scenario, each haemoglobin measurement X_i can be said to be associated with a binary variable of interest A_i (e.g., gastrointestinal bleeding), and a set of potential confounders $\boldsymbol{Z_i} = (Z_{1i}, \ldots, Z_{qi})$ (e.g. age, gender for each patient). For analysis, the dataset can be restricted to consider only those haemoglobin measurements within a range of interest, e.g. 7.0-8.0 g/dL. This allows us to fit a logistic regression controlling for confounders, haemoglobin value, and variable of interest as follows:

$$g(P(Y_i = 1|X_i, A_i, \boldsymbol{Z_i})) = \boldsymbol{\alpha^T Z_i} + \sum_{j=70}^{80} \beta_j I(X_i = j) \; + \gamma A_i$$

where g is a chosen *link function* (such as logit-link). We adjust for haemoglobin value X_i as a categorical variable because treatment and control groups may have different haemoglobin distributions even within the range of interest. This modeling approach allows calculation of a predicted odds ratio ($e^{\widehat{\gamma}}$) with a natural interpretation e.g. "compared to patients with no bleeding, gastrointestinal bleeding was associated with an odds ratio of 1.2 for transfusion within 24 hours among patients with haemoglobin 7.0-8.0 g/dL". For interested readers, an alternate approach using spline regression to model transfusion probability is discussed in Appendix C.

Inverse Propensity Weighting (IPW) for Transfusion Probability

A natural approach to adjust for confounding when estimating transfusion probability is the use inverse propensity weighting (IPW). Under this approach, we build a model for the probability of having a condition of interest (A_i, e.g. gastrointestinal bleeding) based on the observed confounders, and use the predicted probabilities to weight treatment ($A_i = 1$) and control ($A_i = 0$) observations, such that we achieve covariate balance in the weighted sample. This allows inference on the effect of our covariate of interest by conducting weighted logistic regression including only A_i. This approach has a few useful features. Firstly, it can be much easier to specify the propensity score model

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compared to the outcome model because the covariate of interest (e.g. cardiac disease, physician gender) is unlikely to depend in a highly non-linear fashion on the confounders, haemoglobin, and associated interactions in the same way as transfusion probability. Secondly, we can use our weights to produce adjusted curves of transfusion probability that account for differences between groups. This allows for informative data visualisation of transfusion probability after covariate adjustment, much in the same way as the established IPW Kaplan-Meier methodology.[17] Thirdly, we can blend the IPW and outcome regression approaches using the augmented inverse probability weighting (AIPW) method. This method is double robust, meaning it only requires one of the two models to be correct. For example, if we failed to account for a non-linear effect of a confounder in our outcome model, our estimates remain statistically valid as long as the propensity score model is correct because the reweighting ensures that treatment groups will be balanced.[18 19] Additional details, including combination with outcome regression, causal inference on the treatment effect, and uncertainty quantification, are discussed in Appendix D.

Taken together, the suite of statistical methods described above can generate practical, rigorous, and straightforwardly interpretable analysis of transfusion behavior. We demonstrate the usage of these methods in the following sections, and our code is shared in the supplementary material. All statistical analyses were conducted using R version 4.1.3.

Transfusion Probability Analysis using Real-World Data

We analysed clinical data for all adults (aged 18 years or older) available in the GEMINI database, a multicenter collaborative which captures clinical information for hospitalised patients admitted to medical wards and intensive care units across 32 hospitals. GEMINI covers approximately 50% of all inpatient admissions across Ontario, which is Canada's largest province with a population of 14.6 million.[20] Patient-level data are reported separately by individual hospitals, encrypted through a standard security protocol, and validated in past research. Laboratory and transfusion data are collected from electronic health records. Data on primary diagnosis and comorbidities are recorded using ICD-10

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codes and collected through a standardised and validated abstract of admission details. Blood products in Ontario are supplied free of charge by Canadian Blood Services, funded by the Ontario Health Insurance Plan, and administered through hospital transfusion services. Provincial red cell transfusion guidelines are standardized across the province and captured in the Bloody Easy Handbook published by the Ontario Regional Blood Coordinating Network.[21]

Red cell transfusion data were available for 24 out of 32 hospitals was included in the primary analysis (Appendix E) and details included product order and issue time. Laboratory data included haemoglobin results. Pre-transfusion haemoglobin was defined as the last available haemoglobin result before red cell transfusion within 24 hours. Transfusion probability analysis included all patients and selected patient subgroups (sickle cell disease, gastrointestinal bleeding, and cardiac disease) to illustrate conditions with known differences in transfusion practice.[22]

Statistical Analysis

Comparison of Transfusion Probability and Pre-Transfusion Haemoglobin, Unadjusted Analysis

We compared transfusion probability to traditional analysis using pre-transfusion haemoglobin in a side-by-side comparison for all patients and selected subgroups. Transfusion probability analysis was performed for pre-transfusion intervals of 6.0-6.9, 7.0-7.9, and 8.0-8.9 g/dL. We chose specific haemoglobin decile intervals due to relatively stable transfusion probabilities within deciles and their use in large trials of red cell transfusion.[23] [22] Pre-transfusion haemoglobin-based analysis reported typical measures of centrality (mean, median) and spread (standard deviation, SD, and interquartile range, IQR). Sample sizes and red cell transfusions per admission were reported for all groups. For visualization, we plotted transfusion probability at individual haemoglobin levels for the full cohort and selected subgroups—similar curves can be visualized for decile-level analysis, although would be less graphically informative.

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Comparison of Transfusion Probability and Pre-Transfusion Haemoglobin, Adjusted Analysis

We also compared transfusion probability to pre-transfusion haemoglobin for performing adjusted analyses, focusing specifically on the impact of gastrointestinal bleeding on transfusion probability. To represent the traditional approach, we used augmented inverse probability weighting (AIPW) with pre-transfusion haemoglobin as the dependent variable and gastrointestinal bleeding as the independent variable, adjusted for age, gender, Charlson Comorbidity Index, and cardiac disease. Patient characteristics were defined based on ICD-10 codes or the Ontario discharge abstract database, where applicable.

Our approach of using transfusion probability analysis was again performed for pre-transfusion intervals of 6.0-6.9, 7.0-7.9, and 8.0-8.9 g/dL, this time using the AIPW approach to adjust for the aforementioned covariates and haemoglobin level within the range. We reported the average treatment effect (ATE = difference in probability), and adjusted probabilities for the gastrointestinal bleeding and control groups.

RESULTS

Overview

The available data captured 525,032 inpatient admissions from 24 hospitals between December 2016 and June 2022, representing 4,912,147 inpatient days. Of these, 100,518 (19.1%) had cardiac disease, 35,291 (6.7%) had gastrointestinal bleeding, and 1,710 (0.3%) had sickle cell disease (Table 1).

Pre-Transfusion Haemoglobin Analysis

The mean haemoglobin across the entire patient cohort was 10.7 g/dL (SD 2.4 g/dL) and median was 10.6 g/dL (IQR 8.8-12.5 g/dL). Compared with pre-transfusion haemoglobin for all patients (6.76, 95% CI 6.76-6.76), sickle cell disease patients were transfused at lower haemoglobin levels (6.34 g/dL, 95% CI 6.34-6.35), cardiac disease patients with higher haemoglobin (6.90 g/dL, 95% CI 6.89-6.90), and gastrointestinal bleeding patients with comparable haemoglobin (6.76 g/dL, 95% CI 6.75-6.77). Mean pre-transfusion

haemoglobin values for sickle cell and cardiac disease patients were significantly different from the general population of patients in t-test comparisons (Table 2).

In the adjusted analysis, gastrointestinal bleeding was associated with lower average pre-transfusion haemoglobin compared to no gastrointestinal bleeding with a difference of -0.03 g/dL (95% CI: [-0.04, -0.01]) after adjustment for age, gender, Charlson Comorbidity Index and cardiac disease (Table 3).

Transfusion Probability Analysis

Across the full patient cohort, the probability of a transfusion by haemoglobin range was 76.2% (95% CI 75.9-76.5) in the 6.0-6.9 g/dL, 18.9% (95% CI 18.8-19.0) in the 7.0-7.9 g/dL, and 4.5% (95% CI 4.5-4.6) in the 8.0-8.9 g/dL range. The 7.0 g/dL threshold played a substantial role in transfusion practice in the general patient population (Figure 2). Compared with all patients, sickle cell disease patients had a lower probability of transfusion at haemoglobin 6.0-6.9 g/dL (17.3% vs. 76.2%, 95% CI 15.6-19.1%) and 7.0-7.9 g/dL (9.2% vs. 18.9%, 95% CI 8.1-10.4%) range (Table 2). Cardiac disease patients had a higher transfusion probability in the 6.0-6.9 g/dL (69.0%, 95% CI 68.9-69.0) and 7.0-7.9 g/dL (78.1%, 95% CI 77.5-78.7%), and similar in the 8.0-8.9 g/dL range. Gastrointestinal bleeding patients had a higher transfusion probability in all three haemoglobin deciles (Figure 3). The result for gastrointestinal bleeding was tested and persisted in adjusted analyses (Table 3), with higher covariate-adjusted transfusion probability for gastrointestinal bleeding patients compared to other patients at all levels of haemoglobin (Figure 4).

DISCUSSION

We propose transfusion probability as an alternative to pre-transfusion hemoglobin analysis for measuring the effect of diagnostic test results on the decision to transfuse, develop a rigorous statistical approach for analysis and causal inference, and demonstrate its use in a large dataset of hospitalised patients. In our cohort, transfusion probability analysis revealed substantial differences in practice across different haemoglobin ranges

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and medical conditions. In contrast, comparable pre-transfusion haemoglobin-based analysis, although informative, underrepresented or masked clinically important trends in transfusion behavior. For example, comparison of patients with and without gastrointestinal bleeding performed using unadjusted and adjusted pre-transfusion haemoglobin analysis indicated no clinically significant difference in transfusion practice, whereas transfusion probability analyses showed substantially higher rates of transfusion for patients with gastrointestinal bleeding. Overall, our findings highlight potential pitfalls of pre-transfusion haemoglobin analyses for causal inference and group comparisons. Conversely, for some research questions, transfusion probability may provide a statistically sound alternative.

The analysis of transfusion probability has several strengths over pre-transfusion result based analysis (Table 4). By including all haemoglobin results and associated exposure intervals, transfusion probability gives a more direct measure of transfusion practice patterns. Transfusion probability also provides a more granular account of transfusion practice across the entire range of diagnostic test results without distortion from relative frequency of test results across the range (e.g. haemoglobin of 7.1 g/dL being more frequent than 6.8 g/dL). For causal inference, the measure has an intuitive interpretation because covariate effects can be expressed as risk differences (e.g. 5% higher risk of transfusion), whereas differences in pre-transfusion haemoglobin are difficult to interpret clinically. We provide an example for hemoglobin-guided red cell transfusion, however our methods can be readily adapted to study other diagnostic tests and blood products (e.g. international normalized ratio-guided plasma transfusion). Although similar measures have been proposed previously in transfusion literature, we provide an extended statistical approach for confounder adjusted visualisation and causal inference with reproducible code for analysis.[24]

An appealing feature of transfusion probability analysis is that results can be easily plotted to create highly informative visualizations of transfusion practice. For example, visual inspection of Figure 4 shows a comparison of transfusion practice for patients with and without gastrointestinal bleeding across the haemoglobin range 5.0-10.0 g/dL. As

might be expected, transfusion probability appears higher for patients with gastrointestinal bleeding across the entire haemoglobin range. Examining different parts of the curve shows transfusion probability is relatively low at haemoglobin values above 8.0 g/dL, rises sharply near the 7.0 g/dL threshold, and remains consistently high below this threshold. This trend is consistent with our regional transfusion guidelines, which recommend a threshold of 7.0 g/dL for this population of patients unless there are clinical signs (e.g. active bleeding) or patient considerations (e.g. patient refusal) which provoke or prevent transfusion at higher or lower haemoglobin levels. Similarly, visual inspection of Figure 3 shows that transfusion practice for patients with sickle cell disease is distinct from other groups, with a smaller inflection point at 7.0 g/dL and a lower transfusion probability below this threshold. Transfusion probability curves may provide valuable insights for scientific modeling, descriptive audits, and clinical trials of transfusion practice.

Limitations

Transfusion probability has important limitations. Calculation requires comprehensive laboratory data including all haemoglobin results regardless of transfusion status which may necessitate additional ethics review and data infrastructure. Depending on the interval of analysis chosen (e.g. testing individual haemoglobin values rather than deciles), transfusion probability may require larger sample size which precludes calculation in some clinically important ranges of laboratory results (e.g. in our dataset, haemoglobin values below 3.0 g/dL were too infrequent for analysis). Transfusion probability analysis may be unfamiliar for clinicians accustomed to pre-transfusion haemoglobin analysis and warrant additional explanation. Comparisons of transfusion probability between subgroups, although superior to comparisons using pre-transfusion haemoglobin, are still affected by large differences in unmeasured patient characteristics. Our approach of counting every individual haemoglobin value as a separate exposure ensures equal decision interval length but has the drawback of potentially misattributing some transfusions when multiple tests are performed within 24 hours.

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An important further caveat with using transfusion probability is that multiple comparisons across individual hemoglobin values may lead to false positives, while analysis using large datasets may show statistically significant but clinically trivial differences. We recommend careful pre-specification of thresholds of statistical and clinical significance and correction for multiple testing where warranted. Our analysis showed several differences in transfusion practice using transfusion probability analysis (e.g. gastrointestinal bleeding) which were not apparent in pre-transfusion haemoglobin analyses. However, we cannot comment on the validity of previously published findings using pre-transfusion haemoglobin, as this would depend on the study question, risk of confounding, and re-analysis of original datasets. Several factors other than laboratory results can influence transfusion decisions such as local practice norms, quality improvement interventions, blood availability, and concurrent medical therapies. Transfusion probability analysis provides a tool for quantitative comparison of practice across different levels of such factors if they are known, however cannot account for their effect when they are unmeasured (e.g. haemoglobin not checked) or unavailable.

Future Directions

There are several potential applications of transfusion probability. As we demonstrate, the method can be informative for comparing transfusion practice across a range of test results and subgroups (e.g. red cell transfusion in sickle cell disease). The analysis might be applied in initiatives seeking to compare physician behavior before and after quality improvement interventions. The method can be used to isolate the influence of patient variables (e.g. active cardiac ischemia) on transfusion practice while controlling for the effect of test results (e.g. haemoglobin value). Ease of interpretation means transfusion probability results can be directly quoted in conversations about patient blood management and provide direct information about the risk of requiring transfusion. The analysis may also be used to characterize transfusion practice during different phases of medical care such as emergency resuscitation, hospital admission, intraoperative settings, and outpatient care. The calculation can be naturally included in machine learning models for predicting the probability of transfusion to forecast blood utilization. Furthermore, the general methodology can be extended to study treatment guided by clinical scores, allele

frequencies, and radiological measurements, or in other contexts where numerical ranges or thresholds guide medical interventions. Given that physician behavior is heavily influenced by diagnostic test results, a more robust measure of this tendency ultimately allows for clear thinking and shared decision-making to guide treatments and study outcomes.

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DECLARATION OF INTERESTS

The authors have declared that no conflict of interest exists.

DATA SHARING

Access to GEMINI is not available without approval. Requests for data access can be directed to GEMINI.Data@unityhealth.to.

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Table 1. Summary statistics for transfusion practice and haemoglobin test results across conditions

		All Patients	**Cardiac Disease**	**GI Bleeding**	**Sickle Cell Disease**
Sample	Patients	525,032	100,518	35,291	1,710
	Test Results	3,345,641	803,791	398,367	10,967
	Transfusion Episodes	131,508	30,440	50,611	761
Haemoglobin	Mean (SD)	10.7 (2.4)	10.6 (2.3)	9.2 (2.1)	7.9 (1.9)
	Median (IQR)	10.6 (8.8-12.5)	10.3 (8.7-12.2)	8.8 (7.8-10.3)	7.8 (6.7-9.1)
Red cell transfusions per admission	Mean (SD)	0.28 (1.34)	0.33 (1.44)	1.62 (3.09)	0.73 (2.14)
	Median (IQR)	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-0)

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Table 2. Comparison of all haemoglobin-based (Hb) transfusion between all patients and specific patient subgroups using pre-transfusion haemoglobin and transfusion probability

Measure		**All Patients**	**Cardiac Disease**	**GI Bleeding**	**Sickle Cell Disease**
Sample	Patients with a test result*	121,474	27,848	22,862	1,229
	Test Results**	880,625	228,840	208,294	6,600
	Patients with a transfusion episode	51,480	11,737	17,421	400
	Transfusion Episodes	131,508	14,561	50,611	761
Mean Pre-transfusion Hb (mean g/dL, 95% CI)		6.76 (6.76, 6.77)	6.90 (6.89, 6.90)	6.76 (6.75, 6.77)	6.34 (6.34, 6.35)
Transfusion Probability (%, 95% CI)	6.0-6.9 g/dL	76.2 (75.9, 76.5)	78.1 (77.5, 78.7)	86.9 (86.4, 87.3)	17.3 (15.6, 19.1)
	7.0-7.9 g/dL	18.9 (18.8, 19.0)	18.4 (18.1, 18.7)	29.4 (29.1, 29.7)	9.2 (8.1, 10.4)
	8.0-8.9 g/dL	4.5 (4.5, 4.6)	4.4 (4.3, 4.5)	10.0 (9.8, 10.2)	4.5 (3.6, 5.4)

* patient counts restricted to those with at least one haemoglobin between 5.9 and 9.0 g/dL

** test results between 5.9 and 9.0 g/dL

Table 3. Comparison of all haemoglobin-based transfusion between patients with and without gastrointestinal (GI) bleeding, first using pre-transfusion haemoglobin, and then using transfusion probability. Covariate-adjusted estimates using AIPW for age, gender, Charlson Comorbidity Index, and cardiac disease. Abbrevs: AIPW, Augmented Inverse Propensity Weighting; ATE, Average Treatment Effect.

	n	GI Bleeding	No GI Bleeding	ATE
Pre-Transfusion Haemoglobin (Mean g/dL, 95% CI)	51,451**	6.76 (6.75, 6.77)	6.76 (6.76, 6.77)	0.00 (-0.01, 0.01)
Covariate-Adjusted Pre-Transfusion Haemoglobin (Mean g/dL, 95% CI)	51,451**	6.74 (6.73, 6.75)	6.77 (6.76, 6.78)	-0.03 (-0.04, -0.01)*
Unadjusted Transfusion Probability (%, 95% CI)				
6.0-6.9 g/dL	35,696	86.9% (86.4, 87.3)	71.9% (71.5, 72.2)	15.0% (14.4, 15.6)*
7.0-7.9 g/dL	71,161	29.4% (29.1, 29.7)	15.3% (15.2, 15.4)	14.1% (13.8, 14.5)*
8.0-8.9 g/dL	110,437	10.0% (9.8, 10.2)	3.0% (3.0, 3.1)	7.0% (6.8, 7.2)*
Covariate-Adjusted Transfusion Probability (%, 95% CI)				
6.0-6.9 g/dL	35,696	86.1% (85.6, 86.6)	72.3% (71.9, 72.6)	13.8% (13.2, 14.4)*
7.0-7.9 g/dL	71,161	28.7% (28.4, 29.0)	15.4% (15.3, 15.6)	13.3% (12.9, 13.6)*
8.0-8.9 g/dL	110,437	9.7% (9.5, 9.9)	3.1% (3.0, 3.1)	6.6% (6.4, 6.8)*

* $p<0.001$

**excluding 29 patients with transfusion episodes with no associated haemoglobin

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Table 4. Comparison of Features of Pre-Transfusion Laboratory Result and Transfusion Probability for Analysis of Transfusion

Measure	Definition	Advantages	Limitations
Pre-transfusion Laboratory Result	Last available laboratory result before a transfusion	Requires less data Used widely in literature Easily analyzed with summary statistics	Underestimates or masks differences in transfusion behavior across haemoglobin ranges Discards the majority of test results Discounts underlying distribution of laboratory results Neglects transfusion behavior at extremes of laboratory values May lead to confounding by indication when included in multivariable models
Transfusion Probability	Proportion of measured value occurrences which are followed by a transfusion	Includes all test results for all patients (transfused and non-transfused) Measures propensity for transfusion Accounts for variation in testing frequency and distribution of results Intuitive interpretation Allows direct comparison of transfusion across subgroups with differing utilization Superior for analysing haemoglobin ranges for diseases which deviate	Requires comprehensive laboratory data Involves a relatively novel analysis method within the field of transfusion Analysis may not be possible at extremes of laboratory results due to insufficient sample size

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		from population distributions Easier inter group comparisons	

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Appendix: Transfusion Probability as a Novel Measure for Lab-Guided Medical Decision-Making

This appendix is intended to provide readers with additional information statistical methods and cohort creation.

Appendix A. Correlation between Transfusion Decisions

Hemoglobin measurements and associated transfusion decisions will typically take the form of longitudinal data with multiple observations per patient. This means that individual transfusion decisions are unlikely to be truly independent of one another, particularly if they concern the same patient, or are made by the same doctor. This is a limitation of our proposed methodology and a potential avenue for future work. Substantial progress in this area could be made by applying statistical work on longitudinal mobile health data[25] or SMART (sequential multiple assignment randomized trial designs) clinical trials[26] to the transfusion setting. Observational transfusion data is a particularly difficult correlated data problem as it involves irregular Hb measurements subject to informative measurement bias, sequential treatment decisions confounded by underlying patient characteristics, and a multi-level correlation structure (within-patient, within-physician, and within-hospital).

Appendix B. The Spline Approach

The approach of dividing hemoglobin measurements into discreet ranges is somewhat ad-hoc, so we might prefer building a flexible logistic regression model where we assume that transfusion probability is a smooth function of hemoglobin value:

$$g(P(Y_i = 1|X_i)) = \beta_0 + \beta_1 B_1(X_i) + \cdots + \beta_p B_p(X_i)$$

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Here g is a chosen *link function* (typically we would choose the logit-link) and $B_1(X_i), \ldots, B_p(X_i)$ are a set of *spline basis functions*[27], typically defined via polynomial transformations of the continuous variable of interest, in this case hemoglobin. We could then use our regression model to construct a curve of predicted transfusion probability, smoothing out some of the random fluctuations associated with any finite sample size. This approach is appealing, although in cases of a very large sample size the non-parametric approach of considering each hemoglobin value individually or considering small ranges might be more flexible.

For analysis of a particular covariate, say that each hemoglobin measurement X_i is associated with a binary variable of interest A_i (for example, gastrointestinal bleeding), and a set of potential confounders $\boldsymbol{Z_i} = \left(Z_{1i}, \ldots, Z_{qi}\right)$ (e.g. age, gender for each patient). We could include these variables into our spline regression model:

$$g(P(Y_i = 1|X_i, A_i, \boldsymbol{Z_i})) = \boldsymbol{\alpha^T Z_i} + \boldsymbol{\beta^T B}(\boldsymbol{X_i}) + \gamma A_i$$

The main issue with this approach is that hemoglobin has a highly non-linear effect on transfusion probability, and this effect can be very different depending on underlying patient conditions. For example, sickle cell patients might look similar to other patients above 80 g/L where transfusions only occur for compelling reasons independent of hemoglobin, but very different below 70 g/L where physicians are dramatically less willing to transfuse them due to the potential for adverse reactions. This means should include some kind of interaction term in our model, which would be easy if we were assuming a simple linear association for hemoglobin and transfusion probability:

$$g(P(Y_i = 1|X_i, A_i, \boldsymbol{Z_i})) = \boldsymbol{\alpha^T Z_i} + \beta X_i + \gamma A_i + \eta X_i A_i$$

However, such a model does not adequately capture the non-linear effect of hemoglobin value. Adding an interaction term into our spline model is going to be more difficult and cause issues with interpretation, requiring a high degree of statistical and subject-matter

expertise. This is why we prefer the simpler strategy of dividing the dataset into discrete ranges of hemoglobin values and fitting separate models.

Appendix C. Augmented Inverse Probability Weighting (AIPW)

Fitting a propensity score model also allows us to combine IPW with outcome regression using augmented inverse probability weighting (AIPW), which is an increasingly popular method in causal inference.[28] Assume that we have restricted ourselves to hemoglobin values in a particular range (e.g. $70 \leq X_i \leq 79$), and are interested in the effect of a characteristic A_i on probability of 24-hour transfusion Y_i in the presence of confounders $\boldsymbol{Z_i}$. The AIPW estimator of the average treatment effect (ATE) would then be given by:

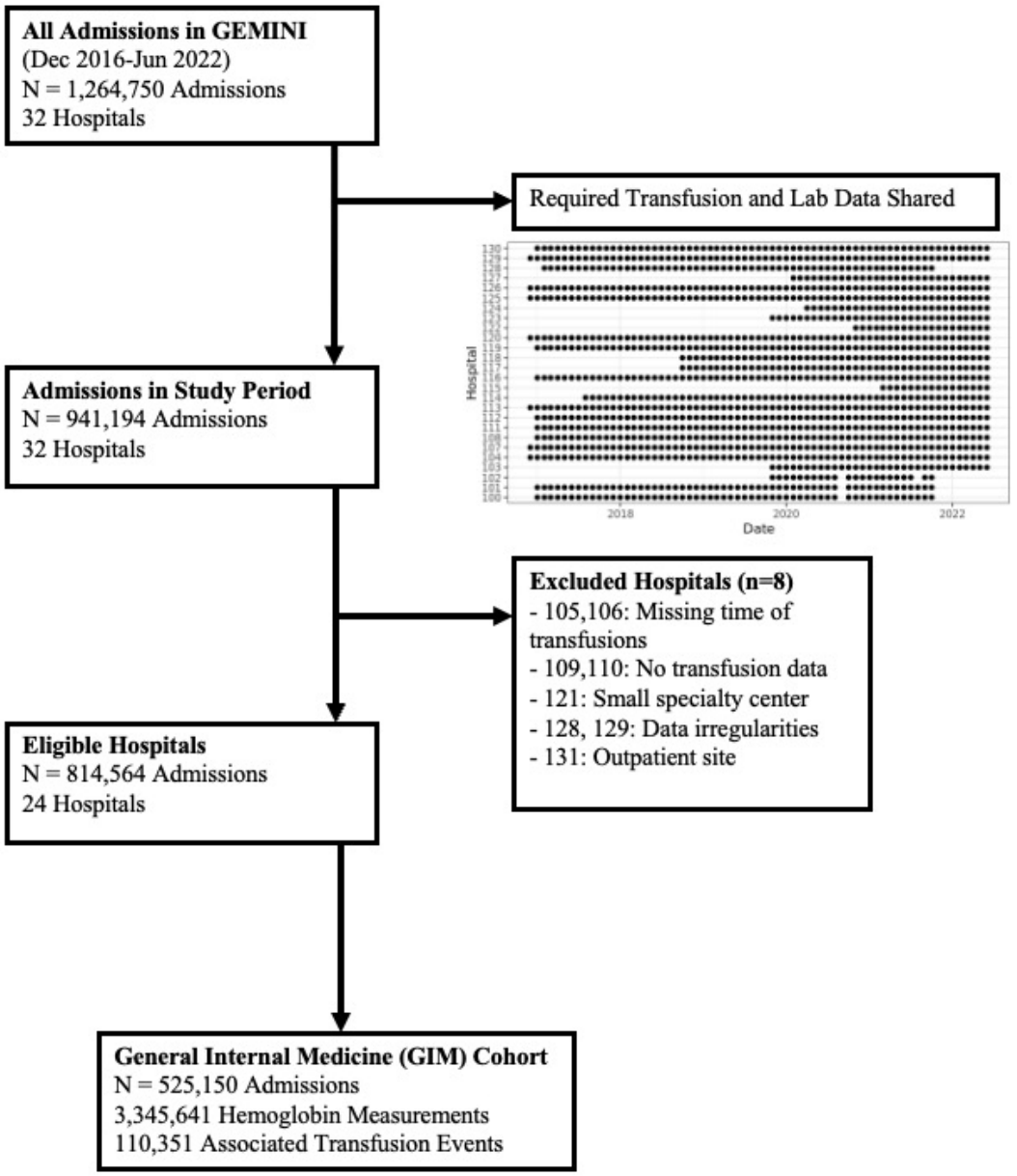
$$\widehat{ATE_{AIPW}} = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{A_i Y_i}{\hat{p}(\boldsymbol{Z_i}, X_i)} - \frac{(1-A_i)}{1-\hat{p}(\boldsymbol{Z_i}, X_i)}\right] - \frac{A_i - \hat{p}(\boldsymbol{Z_i}, X_i)}{\hat{p}(\boldsymbol{Z_i}, X_i)\left(1-\hat{p}(\boldsymbol{Z_i}, X_i)\right)}\left[\left(1-\hat{p}(\boldsymbol{Z_i}, X_i)\right)\hat{e}(Y_i|A_i = 1, \boldsymbol{Z_i}, X_i\right) + \hat{p}(\boldsymbol{Z_i}, X_i)\,\hat{e}(Y_i|A_i = 0, \boldsymbol{Z_i}, X_i)]$$

Here $\hat{p}(\boldsymbol{Z_i}, X_i)$ comes from the propensity score model and is the predicted probability of having the characteristic A_i given the confounders and hemoglobin, whereas $\hat{e}(Y_i|A_i = a, \boldsymbol{Z_i}, X_i)$ comes from the outcome model and is the predicted probability of transfusion given the confounders, hemoglobin, and setting $A_i = a$ (regardless of the true value for patient i). The key benefit of AIPW is that you only need to get one model right; as long as either the propensity score or outcome model is correct, we will have consistent estimation of the true ATE of characteristic A on probability of transfusion in our range of interest. The ATE represents the average difference in transfusion probability between a hypothetical world where everyone had the characteristic of interest ($A_i = 1$) and one where nobody had the characteristic ($A_i = 0$). This statistic has the benefit of being on the risk difference scale, which is often more interpretable than the odds ratio scale. We can estimate the variance of the ATE using either bootstrap or the more computationally

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efficient stacked score method[29], allowing for confidence intervals and p-values for testing a null hypothesis of no treatment effect.

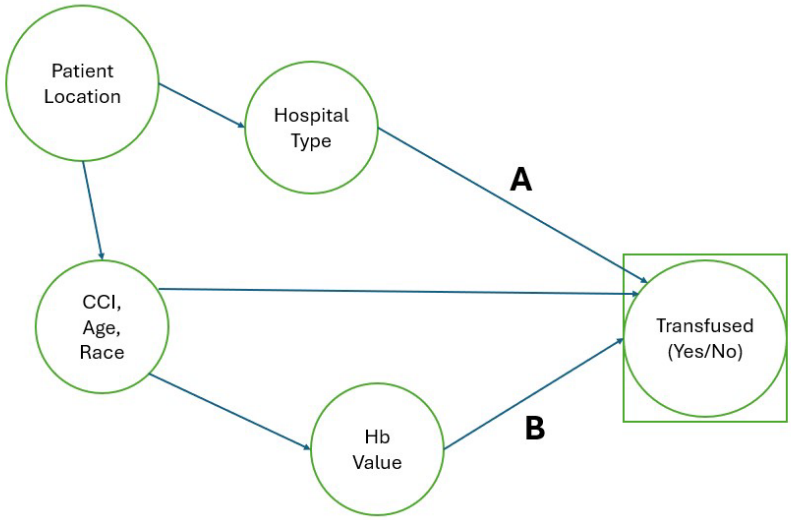
Appendix D. Patient Flow Diagram



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Appendix E. Causal Problems with Pre-Transfusion Hemoglobin



Say that we are interested in the effect of hospital type (e.g. teaching vs. non-teaching) on transfusion practice. For example, we might want to answer the basic question of whether transfusion practices are more or less restrictive at teaching hospitals compared to non-teaching hospitals. In the above DAG, this means we are interested in the arrow A, the direct effect of hospital type on how likely a patient is to receive transfusion. Transfusion probability analysis will directly take hospital type as the exposure, transfusion (yes/no) as the outcome, and treat patient characteristics, including observed hemoglobin value, as confounders. This is a straightforward causal inference task; we isolate arrow A by blocking all backdoor pathways to the outcome.

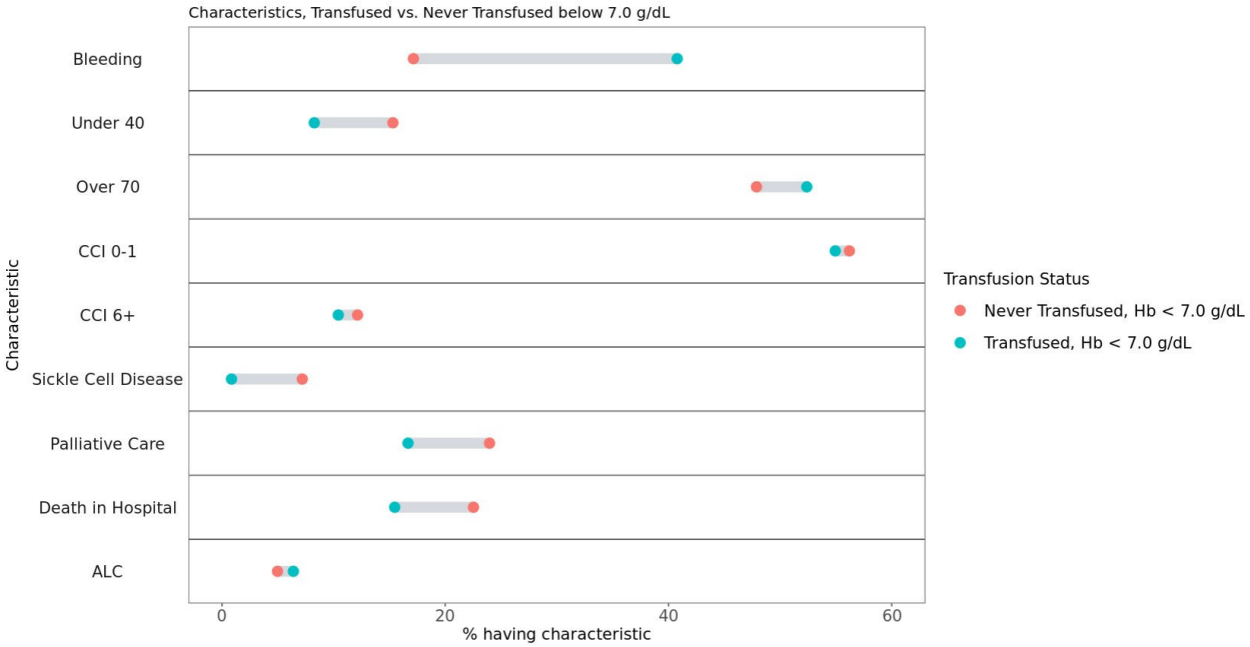
Pre-transfusion hemoglobin has a far less straightforward causal interpretation. By selecting only transfused patients, we condition on transfusion status (represented by the box in the above DAG), thus inducing a relationship between hospital type and hemoglobin value by conditioning on a collider (transfusion status). We assume that if the relationship A is positive, we drag higher hemoglobin values into the transfused group, and hence infer that a higher mean pre-transfusion hemoglobin implies more aggressive transfusion practice. However, this approach of conditioning on a collider to

construct a proxy variable does not fit into any established causal inference framework. In particular, we do not know how to address potential confounding through patient characteristics and our final result will be strongly impacted by the shape of relationship B, which should be totally orthogonal to our main interest (arrow A). There is no reason to expose ourselves to these potential pitfalls of causal inference when a more straightforward and well-established approach is available.

Perhaps even more importantly, questions in transfusion medicine frequently center around the role of hemoglobin as an effect modifier of the relationship between another variable and transfusion. For example, we might want to know whether cardiac surgery patients are being transfused more aggressively than other patients in the 7.0-7.9 g/dL range due to differing guidelines. By immediately conditioning on transfusion status in the pre-transfusion hemoglobin approach, we have distorted the hemoglobin variable via selection bias, and hence precluded any opportunity to study it as an effect modifier. In contrast, transfusion probability analysis means that we can use any established causal inference method for studying interaction to study hemoglobin as an effect modifier.

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Appendix F. Patients without a transfusion below 7.0 g/dL

Due to guidelines, we would expect most patients with a hemoglobin value under 7.0 g/dL to be transfused within 24 hours or at least at some point during their stay. However, transfusion probability tends to plateau at around 80% under 7.0 g/dL, and even decreases a bit in very low hemoglobin ranges. The above figure compares patients who had at least one hemoglobin value under 7.0 g/dL and no transfusion during their hospital stay to patients who had a hemoglobin value under 7.0 g/dL and at least one transfusion. According to this figure the major factors that characterize these patients are younger age, no bleeding, and elevated rates of sickle cell disease, palliative care, and death in hospital.

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