# Determinants of transfusion decisions in the ICU: haemoglobin concentration, what else? - a retrospective cohort study

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ORIGINAL PAPER

# Determinants of transfusion decisions in the ICU: haemoglobin concentration, what else? – a retrospective cohort study

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Vox Sanguinis

**Background and Objectives** The aim of this study was to assess potentially relevant clinical characteristics which influence the decision to transfuse red cells in critically ill patients with low haemoglobin concentrations (6.0–10.0 g/dl).

**Materials and Methods** This was a retrospective observational cohort study of patients admitted between November 2004 and May 2016 at the intensive care unit (ICU) of the Leiden University Medical Center, Netherlands. Haemoglobin measurements, clinical variables and the subsequent transfusion decision were extracted from the electronic health records. Clinical variables were grouped by organ system. We first examined the association of each of the clinical variables with the decision to transfuse during the following 6 h after a haemoglobin measurement using generalized estimating equations. We then compared the predictive abilities of single variables within an organ system and the predictive ability of an organ system's combined variables using the change in Akaike information criterion (AIC).

**Results** A total of 83 394 haemoglobin measurements of 10 947 ICU admissions were included. Haemoglobin concentration was the most predictive for red cell transfusion. After the haemoglobin concentration, the combined variables for General Health, followed by the organ systems Cardiovascular and Pulmonary, were most predictive for red cell transfusion. Within these organ systems, the APACHE II score, referring department, APACHE admission diagnosis subgroup, troponin concentration, lactate concentration, respiratory rate, $PaO_2/FiO_2$ and ventilation mode had the highest predictive ability.

**Conclusion** Haemoglobin concentration is the dominant predictor for red cell transfusion. Other clinical characteristics are also predictive, though to a lesser extent.

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**Key words:** red cell transfusion, anaemia, ICU, predictors, clinical decision-making.

## INTRODUCTION

Anaemia is a common condition in critically ill patients. During an intensive care unit (ICU) admission, almost 60% of the patients develop a haemoglobin concentration below 9 g/dl on at least one occasion [1]. In the ICU, anaemia is often treated with red cell transfusions to help

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maintain adequate oxygen delivery. More than one-fourth of the patients in ICUs receive at least one red cell transfusion during their stay [2].

Despite an extensive number of red cell transfusions in ICUs worldwide and more than 60 years of research, indications for red blood cell (RBC) transfusion are still debated [3]. Previous research has established that a restrictive transfusion threshold of 7 g/dl is safe for stable nonbleeding critically ill patients compared to liberal transfusion thresholds [4,5]. However, uncertainty remains regarding the generalization of this restrictive trigger across heterogeneous critically ill patients.

As a result, it is still not exactly known who will benefit from red cell transfusion. Many trials will be needed to prove a restrictive trigger is safe in all subgroups of critically ill patients, a rather unfeasible task. Currently, transfusion guidelines do recommend to personalize the transfusion threshold based on the clinical condition of the patient with anaemia [6–8]. Often, the clinical condition is described in general terms such as 'acute illness-related factors', 'specific comorbidities' or 'overall clinical context'. These unclear recommendations regarding the clinical condition, together with the lack of evidence for specific patient subgroups, complicate the transfusion decision and lead to considerable practice variation [9].

ICU physicians frequently need to decide whether or not a transfusion might have an overall positive effect on each of their patient's outcomes. Certain patient characteristics, laboratory measurements and clinical parameters do influence this transfusion decision. These variables likely confound the observed effect of red cell transfusion on clinical outcome [10]. Previously, we tried to identify these variables by means of a questionnaire study using clinical scenarios [9]. However, answers of the respondents do not always correlate with their actual behaviour and clinical scenarios do not capture all detailed information readily available at the moment of transfusion decision-making [11]. Therefore, in the current study we used data that were readily available during transfusion decision-making to assess the additional importance of potentially relevant clinical characteristics with respect to predicting the decision to transfuse red cells in critically ill patients with low haemoglobin concentrations (6.0–10.0 g/dl).

## MATERIALS AND METHODS

### Setting

We performed a retrospective cohort study in a 29-bed tertiary university mixed (cardiothoracic, neuro-surgical and medical) ICU at the Leiden University Medical Center (LUMC), the Netherlands, using routinely collected data of critically ill patients. In the LUMC, the ICU is supervised by board-certified critical care physicians with different medical specialty backgrounds, together with a team of fellows and residents. Transfusion decision was only made by physicians, including fellows and resident. The local protocol for blood transfusion in critically ill patients, which had been in use since 2006, recommended to transfuse red cells when the haemoglobin concentration was lower or equal to approximately 7.2–8.0 g/dL (4.5–5 mmol/l) depending on the clinical condition of the patient. There was no computerized provider order entry or clinical decision support for transfusion practices.

### Study population

Our research questions pertained to anaemic adult, critically ill patients without significant acute bleeding. The study population therefore comprised consecutive patients with at least one haemoglobin concentration equal to or less than 10 g/dl during their ICU stay between November 2004 and May 2016. This concentration was based on the most liberal transfusion trigger recommended in the most recent guideline on red cell transfusion in critically ill patients [8]. We excluded all patients that received at least five red cell transfusions within a period of 24 h at the ICU, assuming those would be the patients with significant acute bleeding. Additionally, we excluded Jehovah's Witnesses who were likely to refuse blood transfusions. These were identified via free text searches in the electronic medical health records. Patients with no data in the Mediscore database were also excluded from the analysis.

### Data retrieval

Electronic routine care data were available since the introduction of the electronic medical record system in 2004 which was in use in all ICU units by 2006. Data on patient characteristics, medical history, admission diagnosis, clinical parameters, laboratory measurements and treatment were extracted from electronic health records. In addition, we also retrieved institutional data from the Mediscore database. This database encompasses patient data that are registered for the purpose of the National Intensive Care Evaluation (NICE) registration, a co-operation of Dutch intensive care units which registers information of all consecutive admitted critically ill patients to improve the quality of health care [12]. Patient information was de-identified prior to analysis.

### Study variables

We compared the clinical characteristics of the decision moments that did result in red cell transfusion with the clinical characteristics of the decision moments that did

not result in red cell transfusion, stratified by haemoglobin concentration. To do this, we selected variables for inclusion in our analysis. This selection was based on physiological reasoning and previous literature regarding red blood cell transfusion practice. The selected variables can be divided into fixed variables and time-varying variables (Table 1). The fixed variables included demographic characteristics, the medical history and comorbidities, admission characteristics like APACHE admission diagnosis subgroups, and risk assessment scores such as APACHE II (range 0–71). Time-varying variables consisted of variables that varied in time during the ICU stay. The primary time-varying variable was the haemoglobin concentration. Each Hb measurement was considered to be a 'decision moment for red blood cell transfusion'. We documented information on all other potentially relevant transfusion indications before or during these 'decision moments'. This information included time-varying variables such as all hemodynamic and respiratory vital signs, mechanical ventilator settings, use of other medical assist devices and use of certain medication (type and dose). Furthermore, we selected the latest laboratory results of interest up to 48 h before each decision moment. For each RBC transfusion, date and time of the transfusion was recorded. The main outcome was RBC transfusion defined as transfusion of one or more units of red cells at the ICU in the period between a haemoglobin measurement and six hours thereafter. When a patient was discharged or died within 6 h following a haemoglobin measurement, we were not able to assess the outcome. Therefore, these decision moments were also discarded from our analysis.

### Statistical analyses

In our analysis, we only included decision moments where the haemoglobin was between 6 g/dl and 10 g/dl. This was to avoid exceptional reasons for transfusion or no transfusion. In addition, decisions below 6 g/dl are mainly based on the haemoglobin concentration itself, making examination of the relation of those haemoglobin concentrations with other possible determinants of transfusion futile. Variables were grouped based on whether they were indicators of general health or of the functioning of one of the organ systems (cardiovascular, pulmonary, renal, haemostasis and bleeding, liver, immune system and other). The General Health group included patient characteristics, admission characteristics and measurements related to the haemoglobin measurement.

First, generalized estimating equations (GEE) were used to examine the association of each clinical variable with the administration of red blood cells during the following 6 h after each haemoglobin measurement. This univariable analysis was stratified and tested for interactions by haemoglobin concentration. The GEE approach is an extension of logistic regression that accounts for correlated observations within patients [13]. The unit of analysis was a haemoglobin measurement.

Secondly, for each organ system we constructed a multivariable model including the variables of that organ system (see Table 1). These models were adjusted for current haemoglobin concentration and previous haemoglobin concentration. The Akaike information criterion (AIC) was calculated as relative measure of the quality of each model. To assess the independent predictive ability of a single predictor, the difference between the AIC of the multivariable model without the predictor and the model with the predictor was calculated (ΔAIC). A higher ΔAIC value indicates better predictive ability (see Box ) [14]. Thirdly, to determine which of the organ systems was most predictive of blood transfusion, we compared the AIC of the model with only current haemoglobin concentration and previous haemoglobin concentration as covariables to a model that included current haemoglobin concentration, previous haemoglobin concentration and all variables of a specific organ system. The organ system that created the greatest change in AIC added most to the current haemoglobin concentration and previous haemoglobin concentration in predicting blood transfusion. Additionally, we calculated the change in area under the curve (ΔAUC) to assess the discriminative ability of the models [15].

We have chosen to use the AIC as the performance measure for our study, because the AIC is more sensitive to the addition of new important variables. In contrast, the AUC changes very little after inclusion of a variable with good predictive ability. Furthermore, the AIC is adjusted for the statistical complexity of the model fit [16].

Missing values in the time-varying variables were imputed using linear interpolation, the last observation carried forward method or the first observation carried backward method. The percentage of imputed values and the remaining missing values for all included haemoglobin measurements when none of these methods were feasible can be found in the supplemental material. Several measurements were only performed in specific situations, namely cardiac index, central venous oxygen saturation, mean central venous pressure, $PaO_2/FiO_2$ ratio, bilirubin, Glasgow Coma Scale (GCS), albumin, creatine kinase and troponin level. For those instances, dummy variables were created, indicating that a certain parameter was not measured.

## RESULTS

### Population

During the study period, the total number of ICU admissions was 22 817 of 19 315 patients. In 13 304 (58.3%)

**Table 1** List of studied variables

| Fixed variables | Time-varying variables |
|---|---|
| *General health variables* | |
| Age (years) | Time to previous Hb measurement (h) |
| Gender | Number of Hb measurement |
| Weight (kg) | Routine Hb measurement |
| Height (m) | SOFA score |
| BMI | Body temperature |
| Type of admission | |
| Referring facility | |
| APACHE II score | |
| APACHE II admission diagnosis subgroup | |
| *Cardiovascular variables* | |
| Cerebrovascular disease at admission | Lactate concentration (mmol/l) |
| Thrombolytic therapy after acute MI at admission | Cardiac index (l/min/$m^2$) |
| Cardiopulmonary resuscitation at admission | Creatinine kinase (U/l) |
| Myocardial infarction before CABG at admission | Troponin (ug/l) |
| Dysrhythmia at admission | Furosemide total per 24 h (mg) |
| Diabetes (chronic diagnosis) | Noradrenalin (ugr/kg/min) |
| Cardiovascular insufficiency (chronic diagnosis) | Dobutamine (ugr/kg/min) |
| | Treated with Amiodarone |
| | Mean heart rate (bpm) |
| | Mean systolic pressure (mm Hg) |
| | Mean diastolic pressure (mm Hg) |
| | Mean arterial pressure (mm Hg) |
| | Mean central venous pressure (mm Hg) |
| *Pulmonary variables* | |
| COPD (chronic diagnosis) | Mechanical ventilation mode |
| Respiratory insufficiency (chronic diagnosis) | Mechanically ventilated |
| Mechanically ventilated within 24 h after admission | $PaO_2/FiO_2$ ratio |
| | Central venous oxygen saturation monitored |
| | Mean respiratory rate (breaths/min) |
| | Arterial pH |
| | Arterial $pO_2$ (kPa) |
| | Arterial $pCO_2$ (kPa) |
| | Arterial base excess (mmol/l) |
| | Arterial alkaline reserve (mmol/l) |
| | Arterial oxygen saturation (%) |
| *Renal variables* | |
| Dialysis (chronic diagnosis) | Diuresis (ml/h) |
| Chronic renal insufficiency (chronic diagnosis) | Creatinine (μmol/l) |
| Acute renal failure at admission | CVVH |
| Haemostasis and bleeding variables | |
| Gastrointestinal blood loss at admission | Thrombocytes (x$10^9$/l) |
| | Prothrombin time (s) |
| | Activated partial thromboplastin time (s) |
| | INR |
| *Liver variables* | |
| Cirrhosis (chronic diagnosis) | Bilirubin (μmol/l) |
| | Albumin (g/l) |
| *Immune system variables* | |
| AIDS (chronic diagnosis) | Leucocytes (x$10^9$/l) |
| Immunologic insufficiency (chronic diagnosis) | |
| Confirmed infection at admission | |
| *Other variables* | |
| Metastasized neoplasm (chronic diagnosis) | Glasgow Coma Scale |
| Haematological malignancy (chronic diagnosis) | |
| Intracranial mass at admission | |
| Burns at admission | |

BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVVH, continuous venovenous haemodialysis; FiO2, fraction of inspired oxygen; Hb, haemoglobin concentration; MI, myocardial infarction; paO2, arterial partial pressure of oxygen; pCO2, partial pressure of carbon dioxide; INR, international normalized ratio; SOFA, sepsis-related organ failure assessment score.
Cardiovascular insufficiency is defined as NYHA IV.
Respiratory insufficiency is defined as chronic hypoxia or secondary polycythemia of severe pulmonary hypertension.
Only patients with metastasized neoplasms were identifiable in our dataset.

of the ICU admissions, the haemoglobin concentration was 10 g/dl or less on at least one occasion. A total of 721 admissions were excluded due to severe bleeding, and 23 admissions were excluded because the patients were Jehovah Witnesses. The final cohort for the present analysis consisted of 9542 critically ill patients that represented 10 947 ICU admissions in total (Fig. 1). Of these admissions, a total of 83 394 haemoglobin measurements were included in the analysis. Table 2 presents the characteristics of the patients and admissions. The median age of the included patients was 66 years, and 59% of the patients were male. On admission, the median APACHE II score was 17 (interquartile range 13–21). The most common diagnosis subgroups were cardiovascular (54.3%), respiratory (14.0%) and gastrointestinal (11.6%). In 72.3%

**Box 1.**

**Akaike's information criterion (AIC)** is a measure of the quality of a model. It reflects the trade-off between goodness of fit, that is how well the model 'fits' the data, and the complexity of the model, that is the number of variables included in the model. The AIC is often used for variable selection of models, a lower AIC indicates a better model. The value of the AIC itself has no meaning; therefore, often differences (deltas) between AIC scores are presented. In our study, the delta AIC for a specific predictor or set of predictors was defined as the AIC of a model without the predictor(s) minus the AIC of the model with the specific predictor(s). A higher positive delta AIC then indicates better predictive ability.

The **area under the curve (AUC)** is a measure which indicates how well a prediction model can discriminate between two different outcomes (e.g. transfusion or no transfusion). In other words, it is a measure of the model's ability to separate decision moments with transfusion from those without transfusion. An AUC of 0·5 means no separation, whereas perfect separation of the outcome leads to an AUC of 1.

**Generalised estimating equation (GEE)** procedure is an extension of standard regression methods. It accounts for correlated observations or repeated measurements, such as the correlation of haemoglobin measurements of the same patient.

of the admissions, the patient was referred from the ward and 49.8% of the admissions were medical ICU admissions.

### Anaemia and RBC transfusion

At ICU admission, the mean haemoglobin concentration of all included admissions was 9.8 g/dl (standard deviation 1.6). During 61.9% of the admissions, the patient had at least one haemoglobin level less than 9 g/dl and in 11.5% of the admission at least one haemoglobin level less than 7 g/dl. In 39.5% of the admissions, the patient received one or more RBC transfusions.

### Predictors of RBC transfusion

Of the total 83 394 measurements, 10 327 (12.4%) resulted in transfusion of one or more units of red blood cells during the following 6 h after the haemoglobin measurement. (Fig. ]). As expected, transfusion was given more frequently when the haemoglobin concentration was lower. The association between many of the clinical variables and the decision to transfuse red cells depended often on the haemoglobin concentration, that is the higher the haemoglobin concentration, the more other clinical factors co-determined the decision to transfuse and the lower the haemoglobin, the less other clinical factors did. This is demonstrated by the attenuation (towards no association) of the estimated measure of association (odds ratio) as the haemoglobin concentration declines. For example, for high lactate concentrations (>2.2 mmol/l) compared to normal lactate concentrations, the odds ratio of transfusion decreases from 2.93 (95% CI: 2.53–3.39) to 1.78 (95% CI 1.40–2.25) by declining haemoglobin levels (test for interaction, $P < 0.001$). The same was found for emergency surgical and elective surgical admissions, APACHE II admission diagnosis subgroup cardiovascular, low mean systolic blood pressure, acidosis and diuresis less than 30 ml/h (tests for interaction, $P < 0.001$). These and other noteworthy interactions with haemoglobin concentrations can be found in the Supplemental material.

Fig. 2 shows the predictive ability of single predictors belonging to an organ system with ΔAICs >100. The haemoglobin concentration had the highest predictive ability (ΔAICs ranging from 8109 to 10 910) together with the previous haemoglobin concentration (ΔAICs ranging from 346 to 7302 within each organ system). Additionally, in the category General Health, time to previous haemoglobin measurement, number of haemoglobin measurement, non-routine haemoglobin measurement (not scheduled), referring department, APACHE II score and APACHE submission diagnosis subgroup were most predictive for transfusion. In the category Cardiovascular, lactate concentration and troponin concentration had the highest predictive value. The ventilation mode, $PaO_2/FiO_2$ ratio and respiratory rate had the highest predictive ability in the Pulmonary category. In the remaining categories, diuresis, creatinine concentration, thrombocyte concentration and bilirubin concentration had the highest ΔAICs (Fig. 2 & Table S1). The ΔAICs and odds ratios of the multivariable logistic model of all variables within each category can be found in the online Supplemental material (Tables S3 & S43). In terms of organ systems, the combined variables of the categories General Health, Cardiovascular and Pulmonary had most predictive ability compared to the other categories of organ systems as shown by the higher ΔAIC and the higher ΔAUC (Table 3).

## DISCUSSION

This study indicates that current haemoglobin concentration and previous haemoglobin concentration are,

**Table 2** Baseline characteristics

| Patient characteristics | Total unique patients ($n$ = 9542) |
|---|---|
| Age (years) - median (IQR) | 66 (55–74) |
| Gender - no. (%) male | 5629 (59.0) |
| Weight (kg) - median (IQR) | 76 (67-86) |
| Height (m) - mean (SD) | 1.73 (0.10) |
| BMI - mean (SD) | 26 (5) |
| Number of admissions - no. (%) | |
| 1 | 8460 (88.7) |
| 2 | 847 (8.9) |
| 3 | 173 (1.8) |
| 4 | 43 (0.5) |
| 5 | 14 (0.2) |
| 6 | 3 (0.0) |
| 7 | 2 (0.0) |
| Chronic diagnosis - no. (%) | |
| Diabetes | 1080 (11.3) |
| Cardiovascular insufficiency | 342 (3.6) |
| COPD | 351 (3.7) |
| Chronic respiratory insufficiency | 210 (2.2) |
| Chronic dialysis | 235 (2.5) |
| Chronic renal insufficiency | 683 (7.2) |
| Cirrhosis | 288 (3.0) |
| AIDS | 17 (0.2) |
| Immunologic insufficiency | 610 (6.4) |
| Metastasized neoplasm | 323 (3.4) |
| Haematological malignancy | 396 (4.2) |
| *Admission characteristics* | **Total admissions ($n$ = 10 947)** |
| Admissions with red cell transfusion - no. (%) | 4578 (41.8) |
| Type of admission - no. (%) | |
| Medical | 5456 (49.8) |
| Emergency surgery | 4355 (39.8) |
| Elective surgery | 1136 (10.4) |
| Referring facility - no. (%) | |
| Ward | 7919 (72.3) |
| Emergency room | 1677 (15.3) |
| High care department | 720 (6.6) |
| Other hospital, ICU | 417 (3.8) |
| Other hospital, ward | 171 (1.6) |
| Other | 16 (0.2) |
| APACHE II score - median (IQR) | 17 (13-21) |
| APACHE II admission subgroup diagnosis - no. (%) | |
| Cardiovascular | 5949 (54.3) |
| Respiratory | 1533 (14.0 |
| Gastrointestinal | 1269 (11.6)) |
| Neurological | 1095 (10.0) |
| Sepsis | 513 (4.7) |
| Renal | 308 (2.8) |
| Metabolic | 100 (0.9) |
| Haematological | 87 (0.8) |
| Diagnosis at admission - no. (%) | |
| Mechanically ventilated within 24 h | 8,296 (75.8) |
| Confirmed infection | 937 (8.6) |
| Acute renal failure | 731 (6.7) |
| Cardiopulmonary resuscitation | 540 (4.9) |
| Myocardial infarction before CABG | 470 (4.3) |
| Dysrhythmia | 379 (3.5) |
| Intracranial mass | 326 (3.0) |
| Cerebrovascular disease | 312 (2.9) |
| Gastrointestinal blood loss | 170 (1.6) |
| Thrombolytic therapy after acute MI | 25 (0.2) |
| Burns | 8 (0.1) |
| *Haemoglobin measurements* | **Total measurements ($n$ = 83 394)** |
| 6–7 g/dl | 2194 (2.6) |
| 7–8 g/dl | 14 908 (17.9) |
| 8–9 g/dl | 33 846 (40.6) |
| 9–10 g/dl | 32 446 (38.9) |

BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation; MI, myocardial infarction.
Only valid measurements presented, therefore percentages do not add up to 100%. Data on missing values can be found in the supplemental material.
Patients could have multiple diagnoses.

obviously, the most important predictors for red cell transfusion. Additionally, we were able to identify and quantify other clinical predictors for transfusion: that is the variables belonging to the group General Health, followed by the variables in the groups Cardiovascular and Pulmonary, had the highest additional predictive values for red cell transfusion. Within these categories, the APACHE II score, referring facility, APACHE admission diagnosis subgroup, troponin concentration, lactate concentration, respiratory rate, $PaO_2/FiO_2$ and ventilation mode were relatively more important in the indication for red cell transfusion, besides the haemoglobin concentration.

What we further showed is that the dominance of haemoglobin concentration as predictor for transfusion decreases in patients with mild anaemia, that is with increasing haemoglobin levels other clinical factors also influence the critical care physician in his decision to administer red blood cells. This is shown by the interaction tests, and the relative importance of many variables differed between the strata of haemoglobin concentration. It suggests that at lower haemoglobin concentrations, the relative importance of other clinical variables with respect to the decision to transfuse decreases.

Most transfusion decisions are made shortly after a haemoglobin measurement. In our study, we assessed

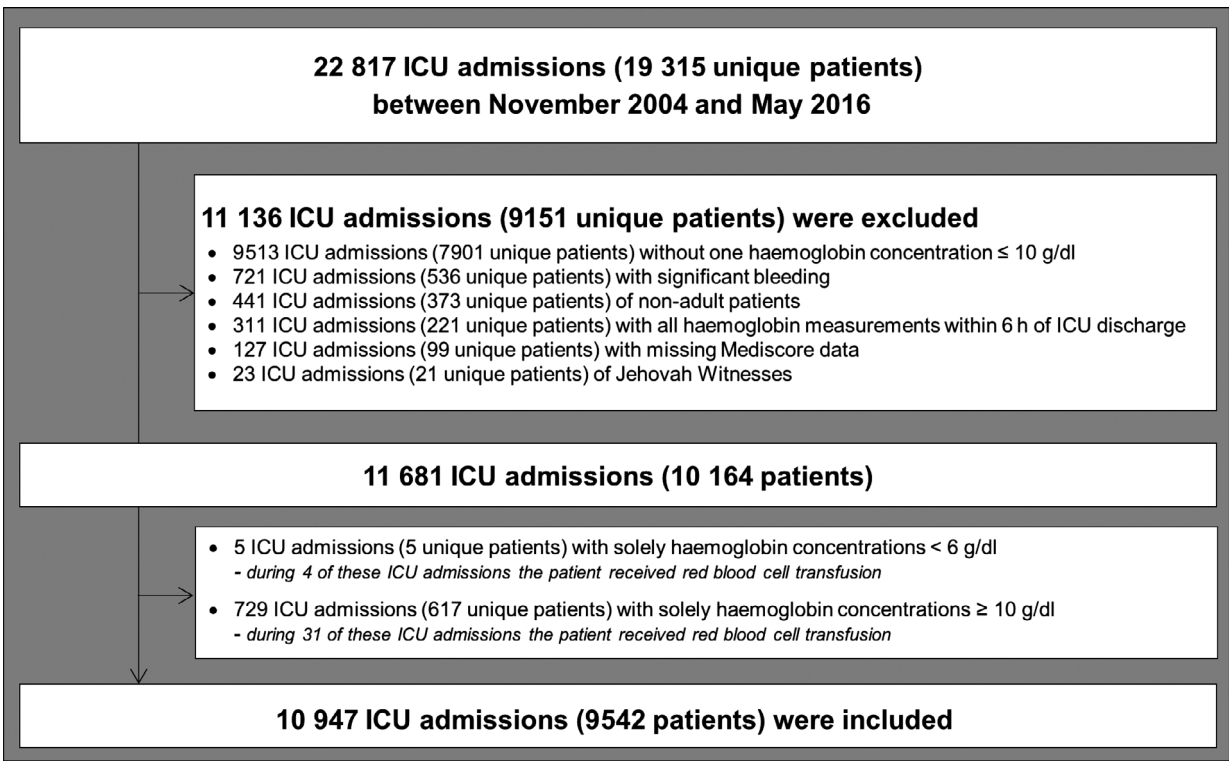


**Fig. 1** Derivation of analysis set of decision moments.

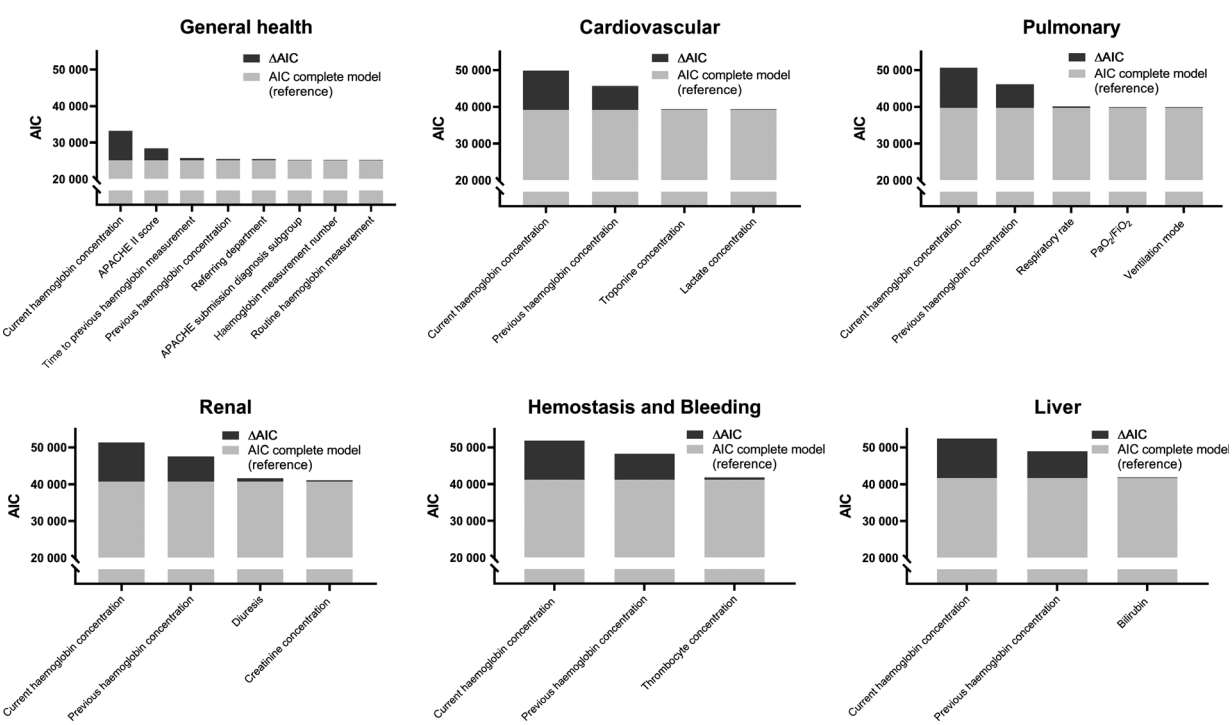


**Fig. 2** Change in Akaike information criterion after excluding the single predictor from the multivariable model containing all variables of the organ system[a]. Only variables with ΔAIC>100 are presented.

which clinical characteristics that were present at the time of haemoglobin measurement, also influenced the decision to transfuse. As far as we are aware, no other studies assessed other clinical factors with respect to their ability to predict red blood cell transfusion in critically ill patients in this extent. In previous studies, the investigators only accounted for admission variables to predict red blood cell transfusion during the admission or after the admission [17,18]. Previously, haemoglobin concentration, age, female sex, emergent surgery, renal function and peripheral vascular disease were identified as factors associated with increased transfusion rates in patients undergoing coronary artery bypass surgery [19]. In contrast to this study's finding, we did not identify female sex as predictor, despite the lower reference limit for haemoglobin concentration in women and the higher risk for alloimmunization for female recipients [20]. In our study, this finding probably reflects that recommended transfusion triggers are not dependent on the sex of the patient. In addition, we adjusted for haemoglobin and age, which are suggested by the authors as potential explanation for their finding.

Another study evaluated the role of patient comorbidities and severity of illness in predicting red blood cell transfusion in hospitalized patients. The authors found that the haemoglobin concentration was superior to other parameters in predicting red blood cell transfusion [18]. Our findings are consistent with this result, as the haemoglobin concentration had the highest predictive ability in all our models.

The aim of red blood cell transfusion is to increase the haemoglobin level with the intention to increase oxygen delivery ($DO_2$) at the tissue level [2,3]. This increase of oxygen delivery after transfusion is caused by increasing oxygen-carrying capacity as well as by increasing intravascular volume and improving the hemodynamic status. It is therefore not surprising that many variables identified as important predictors for transfusion are related to the physiology of oxygen transport and consumption. Other variables, such as the APACHE score, admission diagnosis subgroup, time to previous haemoglobin measurement and total number of haemoglobin measurements, are more likely to be proxy variables for the patients' severity of illness.

The major strengths of our study are the sample size and the high granularity of our routinely collected data. Instead of baseline characteristics, we also assessed multiple variables which were repeatedly measured during the ICU admission. Hereby, we also consider changes in clinical parameters over time that can influence the transfusion decision and possibly modify the effect of red cell transfusion.

Our study has some limitations. Firstly, we could only retrieve data that were stored in the electronic medical record of the ICU. Therefore, we could not analyse pre-ICU admission data, data regarding the prescriber characteristics or results of pre-transfusion testing which might also have influenced the transfusion decisions. Secondly, due to the design of our study we had to deal with missing data. For most of the missing data, we assumed these were missing at random, allowing us to use imputation methods without introducing bias. However, this assumption could have been wrong. Thirdly, in the current study, we identified predictors of the outcome of the transfusion decision based on data of a single institution. Although it is likely that the clinical decision-making will be comparable in other institutions, our results need to be validated in another population of critically ill patients to improve generalizability. In other institutions, transfusion decision

**Table 3** Additional predictive ability of the combined variables per organ system category compared to the model with only haemoglobin concentration and previous haemoglobin concentration

| Category | AIC | ΔAIC | ΔAIC | AUC | ΔAUC |
|---|---|---|---|---|---|
| Current haemoglobin concentration (g/dl) and previous haemoglobin concentration (g/dl) | 42 017 | ref | 100% | 0.8318 | ref |
| General health | 25 083 | 16 935 | 40% | 0.8776 | 0.0458 |
| Cardiovascular | 39 158 | 2859 | 7% | 0.8589 | 0.0271 |
| Pulmonary | 39 720 | 2297 | 5% | 0.8556 | 0.0238 |
| Renal | 40 657 | 1360 | 3% | 0.8398 | 0.0080 |
| Haemostasis and Bleeding | 41 171 | 847 | 2% | 0.8405 | 0.0087 |
| Liver | 41 662 | 355 | 1% | 0.8363 | 0.0045 |
| Immune system | 41 870 | 147 | 0% | 0.8337 | 0.0019 |
| Other | 41 898 | | | | |
| | 119 | 0% | 0.8330 | | |
| | 0.0012 | | | | |

*AIC* Akaike information criterion (lower is better fit of the model) Δ*AIC* change in Akaike information criterion (higher is better additional predictive ability) *AUC* area under the receiver operating curve (higher is better).

could be made in a different way due to differences in training, local protocols and logistics.

## Conclusion

Just like many other treatments in the ICU, red cell transfusion is a titrated treatment mostly influenced by haemoglobin concentration. Within certain ranges of the Hb concentration, we assume that other clinical factors are not only important in the physicians' decision to transfuse red blood cells but also can modify the effect of transfusion. Only a few, but not all, clinical characteristics that influence the indication for red blood cell transfusion are known and explicitly stated in the guidelines. In this study, we identified multiple possible effect modifiers of red blood cell transfusion. Further research is needed to quantify the joint effects of different combinations of these effect modifiers in order to personalize transfusion strategies in future critically ill patients with anaemia.

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## Conflicts of interests

The authors declare no conflicts of interest.

## Author contributions

Floris J Kranenburg designed research, performed research, collected data, analysed and interpreted data, performed statistical analysis, and revised the manuscript. Saskia le Cessie interpreted data, performed statistical analysis and revised the manuscript. Camila Caram-Deelder analysed and interpreted data and revised the manuscript. M. Sesmu Arbous designed research, interpreted data and revised the manuscript. Johanna G. van der Bom designed research, interpreted data and revised the manuscript.

## Ethics approval and consent to participate

The study was approved by the Medical Ethical Committee of the LUMC, which waived the need for requesting patient's informed consent.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Change in Akaike Information Criterion after excluding the single predictor from the multivariable model containing all variables of the organ system.
**Table S2.** Remaining missing values in final dataset ($N$ = 83 394) for which missing data methods were insufficient
**Table S3a.** Association between clinical variables and red cell transfusion per stratum of hemoglobin concentration: General health variables
**Table S3b.** Association between clinical variables and red cell transfusion per stratum of hemoglobin concentration: Cardiovascular variables
**Table S3c.** Association between clinical variables and red cell transfusion per stratum of hemoglobin concentration: Pulmonary variables
**Table S3d.** Association between clinical variables and red cell transfusion per stratum of hemoglobin concentration: Renal variables
**Table S3e.** Association between clinical variables and red cell transfusion per stratum of hemoglobin concentration: Hemostasis and bleeding variables
**Table S3f.** Association between clinical variables and red cell transfusion per stratum of hemoglobin concentration: Liver variables
**Table S3g.** Association between clinical variables and red cell transfusion per stratum of hemoglobin concentration: Immune system variables
**Table S3h.** Association between clinical variables and red cell transfusion per stratum of hemoglobin concentration: Other variables
**Table S4a.** Change in Akaike Information Criterion for each single predictor and multivariable model for red cell transfusion per organ system: General health variables
**Table S4b.** Change in Akaike Information Criterion for each single predictor and multivariable model for red cell transfusion per organ system: Cardiovascular variables
**Table S4c.** Change in Akaike Information Criterion for each single predictor and multivariable model for red cell transfusion per organ system: Pulmonary variables
**Table S4d.** Change in Akaike Information Criterion for each single predictor and multivariable model for red cell transfusion per organ system: Renal variables
**Table S4e.** Change in Akaike Information Criterion for each single predictor and multivariable model for red cell transfusion per organ system: Hemostasis and Bleeding variables
**Table S4f.** Change in Akaike Information Criterion for each single predictor and multivariable model for red cell transfusion per organ system: Liver variables
**Table S4g.** Change in Akaike Information Criterion for each single predictor and multivariable model for red cell transfusion per organ system: Immune system variables
**Table S4h.** Change in Akaike Information Criterion for each single predictor and multivariable model for red cell transfusion per organ system: Other variables.