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Haemoglobin thresholds for transfusion: how are we doing in the era of Choosing Wisely? A retrospective cohort study

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Summary

INTRODUCTION: Clinical practice guidelines and the Choosing Wisely initiative launched in 2012 recommend a haemoglobin (Hb) threshold of 70–80 g/lfor red blood cell (RBC) transfusions in stable hospitalised patients. Data on transfusion practices and their trends in medical inpatients are limited. To address this gap, we investigated transfusion practices and their trends in general internal medicine and other clinics.

METHODS: This retrospective cohort study analysed data from all hospitalisations with RBC transfusions at a Swiss university hospital between 2012 and 2019. We included all first transfusion episodes if pretransfusion H b was available. The primary endpoint was mean pretransfusion Hb; secondary endpoints included potentially inadequate transfusions (i.e., transfusions at Hb ≥80 g/l) and receipt of a single RBC unit. Trends in mean pretransfusion Hb over time were estimated using generalised estimating equations, and risk factors for potentially inadequate transfusions were identified using multivariable adjusted generalised estimating equations models.

RESULTS: Of 14,598 hospitalisations with RBC transfusions, 1980 (13.6%) were discharged from general internal medicine. From 2012 to 2019, mean pretransfusion Hb decreased from 74.0 g/l to 68.8 g/l in general internal medicine (mean annual decrease –0.76 g/l, 95% confidence interval [CI] –0.51 to –1.02) and from 78.2 g/l to 72.7 g/l in other clinics (mean annual decrease –0.69, 95% CI –0.62 to –0.77; p for interaction 0.53). The overall proportion of potentially inadequate transfusions was 17.8%in general internal medicine and 24.1% in other clinics (p <0.001) and decreased over the study period from 26.9% to 5.5% in general internal medicine and from 37.0% to 15.2% in other clinics. In contrast, the proportion of cases receiving a single RBC unit increased (39.5% to 81.4% in general internal medicine, 42.7% to 66.1% in other clinics). Older age (adjusted odds ratio [aOR] 1.45, 95% CI 1.32–1.58 for ≥65 vs <65 years), having surgery (aOR 1.24, 95% CI 1.14–1.36), acute haemorrhage (aOR 1.16, 95% CI 1.02–1.33), chronic heart failure (aOR 1.17, 95% CI 1.04–1.32), ischaemic heart diseases (aOR 1.27, 95% CI 1.15–1.41), chronic pulmonary diseases (aOR 1.24, 95% CI 1.08–1.42), malignancy (aOR 1.11, 95% CI 1.01–1.21), and rheumatic disease (aOR 1.27, 95% CI 1.01–1.59) were risk factors for potentially inadequate transfusions.

CONCLUSIONS: More restrictive transfusion practices were adopted in general internal medicine and other clinics over time, suggesting that guideline recommendations and the Choosing Wisely initiative may have been increasingly followed. Interventions to reduce potentially inadequate transfusions should target providers who care for older patients and those with surgery or chronic cardiac and pulmonary diseases.

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Introduction

Red blood cell (RBC) transfusions are a common and potentially life-saving procedure to treat symptomatic anaemia or haemorrhage [1, 2]. Worldwide, 120 million units of blood are donated annually, with differing transfusion practices across regions [3]. Even though transfusion-related infection rates have decreased in past decades [4], a risk remains for adverse events, such as transfusion-associated circulatory overload or haemolytic transfusion reactions [4, 5]. Moreover, RBC transfusions are related to substantial costs, varying internationally from $500 to $1200 US per transfused unit [6, 7]. Therefore, providers should assess the risks and benefits before performing RBC transfusions.

Besides clinical evidence for acute bleeding, the absolute haemoglobin (Hb) value is the main trigger for RBC transfusions. Various studies have shown that a transfusion threshold of Hb <70 g/l (restrictive transfusion strategy) is not related to an increase in mortality and leads to lower use of transfusions compared with a threshold of Hb <100 g/l (liberal transfusion strategy) [8–11]. These findings have resulted in recommendations for a restrictive transfusion strategy by clinical practice guidelines as well as the Choosing Wisely® initiative launched in 2012 in the United States [12]: administration of RBC transfusions in hemodynamically stable, non-bleeding patients is not recommended if Hb is >70 g/l [1, 13]. Similarly, the Swiss Society for General Internal Medicine launched the Smarter

Medicine initiative in 2014, emphasising that only the minimum amount of RBCs should be transfused to treat symptomatic anaemia and providers should target a safe Hb level of 70 g/l in stable non-cardiac patients [14].

Most of the studies investigating transfusion trends in the era of Choosing Wisely® were conducted in intensive care units or surgical settings, and less is known about transfusion practices in the heterogeneous population of medical inpatients [15–17]. Thus, the overall goal of our study was to analyse transfusion practices and their trends over time in general internal medicine compared to other clinics.

Materials and methods

Study design and setting

We conducted a retrospective cohort study using data from a high-volume university hospital in Switzerland, which provides care for 44,000 inpatients annually. Clinical coverage is provided by post-graduate medical education trainees (i.e., resident physicians) under the supervision of attending physicians in most units [18]. Therefore, orders for laboratory tests and procedures, such as RBC transfusions, are made at the discretion of the attending physicians or their delegates. In 2014, following the publication of the Choosing Wisely® and the Swiss Smarter Medicine recommendations, the following systematic educational interventions were implemented in the general internal medicine department: resident training, smart cards used with computers during ward rounds, and skills training. Residents and attending training was repeated biannually or in case of adverse events related to transfusion. These trainings were not consistently conducted in all other departments.

Due to the nature of the study, it was exempted from ethical approval (Cantonal Ethics Committee Bern, Req-2020-01226). Anonymised data were used for this study, and informed consent was not necessary. This retrospective cohort study was not registered in a trial registry platform, and no study protocol has been published.

Study population

We included all hospitalisations of adults at the Bern University Hospital who received ≥1 RBC transfusion between January 2012 and December 2019. Patients <18 years of age and outpatients were excluded. Transfusions were identified from billing data with a Swiss Operations Classification (CHOP) code for RBC transfusion (99.04.xx). CHOP codes were originally based on procedure codes from the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) and modified to code medical procedures in Switzerland [19]. To identify the timing of RBC transfusions, we restricted the main analysis to patients who (in addition to the CHOP code) had a medication order with a time stamp for erythrocyte blood products (ATC code B05AX01) as identified from the electronic medical records. ATC codes were not available for transfusions administered in the emergency department, intensive care unit, or operating rooms, so these transfusions were not captured in our analysis.

Outcomes

The primary outcome was the transfusion threshold (i.e., the mean pretransfusion Hb value before the first RBC transfusion episode after hospital admission). Hb values and the time point of measurement were identified from electronic laboratory records. Secondary outcomes were the proportion of potentially inadequate transfusions (first defined as any RBC transfusion at Hb ≥80 g/l, and second using a more restrictive threshold of Hb ≥70 g/l) during the first transfusion episode of hospitalisation, the number of RBC units ordered during the first transfusion episode and the full hospitalisation, and the proportion of cases receiving a single RBC unit during the first transfusion episode. The first transfusion episode was defined as the period between the first administration of 1 RBC unit and the next Hb measurement. Additional secondary outcomes were the posttransfusion Hb value after the first transfusion and the minimal Hb during hospitalisation.

Covariates

For every hospitalisation, we collected information on patients' demographics, year and type (emergency vs elective) of hospital admission, comorbidities based on ICD-10 codes, transfer to intermediate or intensive care, length of hospital stay, and death during hospitalisation. We also calculated the Charlson comorbidity index, a validated measure to predict mortality in patients with multiple comorbidities [20]. For every hospitalisation, the department in charge (defined as the discharge unit) was identified and assigned to either the general internal medicine or other clinic group. For patients who were transferred between departments, the department in charge was defined as the department from which the patient was discharged.

Statistical analysis

Clinical characteristics and outcomes of cases discharged from general internal medicine and other clinics were compared using the Student's t-test, Wilcoxon rank sum test, or chi-squared test, as appropriate.

Unadjusted trends over time in mean pretransfusion Hb values, the proportion of potentially inadequate transfusions at Hb ≥80 g/l, and the proportion of cases receiving a single RBC unit were estimated using generalised estimating equations with an exchangeable correlation structure and robust standard errors. This analysis accounted for the within-patient correlation because a case can be hospitalised repeatedly. An interaction term between department (i.e., general internal medicine vs other clinics) and year was included to investigate whether trends differed between departments. Cases without measurement of Hb before the first transfusion were not considered for the primary outcome.

To investigate risk factors for potentially inappropriate transfusions (i.e., transfusions at Hb ≥80 g/l), we employed a multivariable regression model using generalised estimating equations (with a binomial distributional family, a logit link, an exchangeable correlation structure, and robust standard errors) to account for within-patient correlation. Age, sex, type of admission, discharge clinic (general internal medicine vs other clinics), surgical procedures,

and comorbidities (as listed in table 1) were included as predictors in the model.

We conducted sensitivity analyses broadly excluding cases to whom higher Hb thresholds for RBC transfusion may apply: patients with an ICD-10 diagnosis code for acute coronary syndrome and preexisting cardiovascular disease (defined as a history of myocardial infarction, peripheral vascular disease, or cerebrovascular disease), hypovolemic and traumatic shock, or those undergoing surgery [1, 11, 21]. Finally, we conducted a sensitivity analysis including all cases with a CHOP code for RBC transfusion irrespective of the presence of an ATC code to identify all hospitalised patients who received at least one RBC transfusion during the study period. For these cases, we analysed their minimal Hb during their hospital stay because identification of a pretransfusion Hb was not possible due to missing information on the timing of the RBC transfusion in patients without an ATC code.

Given the small proportion of missing data (i.e., data on the primary outcome were not available for 180 cases, representing 1.2% of the overall sample size), we performed complete case analyses. Two-sided p-values of 0.05 were considered statistically significant. All statistical analyses were conducted with Stata statistical software, release 16 (Stata Corporation, College Station, TX, USA).

Results

We included 14,598 hospitalisations with RBC transfusions, representing 10,609 unique patients (figure S1). Of all cases, 1980 (13.6%) were discharged from general internal medicine. Characteristics of cases are presented in table 1. The median age was 66 years (interquartile range [IQR] 55–75 years), and 44.7% were women. Compared to cases from other clinics, those discharged from general internal medicine were older (median age 72 vs 66 years, p <0.001) and more likely to be emergency admissions (76.4% vs 39.5%, p <0.001), whereas the proportion of intensive care unit admissions was lower (21.1% vs 28.7%, p <0.001). Patients from general internal medicine tended to have more comorbidities but were less likely to have surgical procedures than those from other clinics. The median length of stay was 12 days and in-hospital death occurred in 760 patients (5.2%) (table 1).

The first transfusion was administered a median of 72.5 hours after admission (IQR 28.1–166 hours), and the median time between Hb measurement and first transfusion was 3.9 hours (IQR 2.1–6.9 hours). Among the 14,418 (98.8%) cases with available data for Hb prior to the first RBC transfusion, the mean pretransfusion Hb was 74.9 g/l (standard deviation [SD] 9.1 g/l) and was lower in cases from general internal medicine compared to those from other clinics (72.6 g/l, SD 9.8 g/l vs 75.2 g/l, SD 9.0 g/l, p <0.001), as was the proportion of potentially inadequate

Table 1:
Characteristics of cases discharged from general internal medicine or other clinics. Numbers are presented in n (%) unless indicated otherwise. Characteristics were compared using the Wilcoxon rank sum test for continuous variables or the chi-squared test for categorical variables. Values were missing for the Charlson comorbidity index (n = 861).

		All cases	General internal medicine	Other clinics	p-value
		n = 14,598	n = 1980	n = 12,618	
Age in years, median (IQR)		66 (55–75)	72 (62–81)	66 (54–74)	<0.001
Female sex		6534 (44.7)	833 (42.1)	5701 (45.2)	0.010
Emergency admission		6496 (44.5)	1512 (76.4)	4984 (39.5)	<0.001
Intensive care unit admission*		4038 (27.7)	417 (21.1)	3621 (28.7)	<0.001
Surgical procedure		8756 (60.0)	634 (32.0)	8122 (64.4)	<0.001
Comorbidities	Acute haemorrhage**	2318 (15.9)	483 (24.4)	1835 (14.5)	<0.001
	Hypovolemic and traumatic shock	361 (2.5)	42 (2.1)	319 (2.5)	0.28
	Coagulation defects***	5320 (36.)	740 (37.4)	4520 (36.3)	0.36
	Peripheral vascular disease	2491 (17.1)	367 (18.5)	2124 (16.8)	0.061
	Cerebrovascular disease	845 (5.8)	185 (9.3)	660 (5.2)	<0.001
	Ischaemic heart disease	3353 (23.0)	524 (26.5)	2829 (22.4)	<0.001
	Chronic heart failure	2115 (14.5)	597 (30.2)	1518 (12)	<0.001
	Chronic pulmonary disease	1317 (9.0)	271 (13.7)	1046 (8.3)	<0.001
	Dementia	366 (2.5)	146 (7.4)	220 (1.7)	<0.001
	Diabetes mellitus	3074 (21.1)	503 (25.4)	2571 (20.4)	<0.001
	Peptic ulcer disease	340 (2.3)	76 (3.8)	264 (2.1)	<0.001
	Any malignancy	6088 (41.7)	613 (31.0)	5475 (43.4)	<0.001
	Liver disease	1220 (8.4)	241 (12.2)	979 (7.8)	<0.001
	Renal disease	4390 (30.1)	850 (42.9)	3540 (28.1)	<0.001
	Rheumatic disease	401 (2.8)	60 (3)	341 (2.7)	0.407
Charlson Comorbidity Index, median (IQR)****		5 (3–8)	6 (4–8)	5 (3–7)	<0.001
Length of stay in days, median (IQR)		12 (7–21.3)	10.9 (6.7–19.8)	12.1 (7–21.8)	<0.001
In-hospital death		760 (5.2)	154 (7.8)	606 (4.8)	<0.001

IQR: interquartile range; SD: standard deviation.

* stay at the intensive care or intermediate care unit at any time during the hospitalisation

** includes gastrointestinal haemorrhage, respiratory haemorrhage, traumatic haemorrhage, haemorrhagic shock and all other haemorrhage

*** defined as genetic coagulation disorders

**** the Charlson Comorbidity Index predicts the risk of death of comorbid disease. A score of 0 indicates a 1-year mortality of 12% and a score >5 indicates a 1-year mortality of 85% [20]

transfusions for both transfusion thresholds (table 2). The proportion of a first transfusion at Hb ≥80 g/l was 17.8% in general internal medicine and 24.1% in other clinics (p <0.001) and 65.8% vs 75.9%, respectively, at Hb ≥70 g/l (p <0.001). A median of 1 RBC unit was ordered during the first transfusion episode, and 54.2% of all transfused patients received a single RBC unit. The proportion of patients receiving a single RBC unit was higher in general internal medicine compared to other clinics (60.9% vs 53.1%, p <0.001) (table 2).

RBC transfusion practice over time

Over the observed period, the mean pretransfusion Hb decreased from 74.0 g/l to 68.8 g/l in general internal medicine (mean annual decrease –0.76 g/l, 95% confidence interval [CI] –0.51 to –1.02) and from 78.2 g/l to 72.7 g/l in other clinics (mean annual decrease –0.69, 95% CI –0.62 to –0.77) (figure 1).

The decrease was similar in general internal medicine and other clinics (p for interaction = 0.53). Similarly, the number of potentially inadequate transfusions at Hb ≥ 80 g/l decreased from 26.9% to 5.5% in general internal medicine (mean annual decrease = 3.0%, 95% CI 2.3–3.8) and from 37.0% to 15.2% in other clinics (mean annual decrease 3.3%, 95% CI 2.9–3.6) (figure 2 and S2).

The proportion of patients who received a single RBC unit during the first transfusion episode increased from 39.5% to 81.4% among general internal medicine patients (mean annual increase 5.8%, 95% CI 5.0–6.7) and from 42.7% to 66.1% among patients discharged from other clinics (mean annual increase 3.6%, 95% CI 3.2–4.1) (figure 3). Similarly, the proportion of patients receiving a single RBC unit during the overall hospitalisation increased from 22.2% in 2012 to 39.9% in 2019 (figure S3).

Risk factors for potentially inadequate transfusions

Several factors were associated with a higher risk of receiving potentially inadequate transfusions at Hb ≥80 g/l in multivariable analyses (table 3), including older age (adjusted odds ratio [aOR] 1.45, 95% CI 1.32–1.58 for ≥65 vs <65 years), having surgical procedures (aOR 1.24, 95% CI 1.14–1.36), acute haemorrhage (aOR 1.16, 95%CI 1.02–1.33), chronic heart failure (aOR 1.17, 95% CI 1.04–1.32), ischaemic heart diseases (aOR 1.27, 95% CI 1.15–1.41), chronic pulmonary diseases (aOR 1.24, 95%CI 1.08–1.42), any malignancy (aOR 1.11, 95% CI 1.01–1.21), and rheumatic disease (aOR 1.27, 95% CI 1.01–1.59). Conversely, a lower risk of potentially inadequate transfusions was associated with having a coagulation disorder (aOR 0.66, 05% CI 0.60–0.72), peripheral vascular disease (aOR 0.73, 95% CI 0.65–0.82), liver disease (aOR 0.66, 95% CI 0.56–0.79), and being discharged from general internal medicine compared to other clinics (aOR 0.68, 95% CI 0.60–0.78) (table 3).

Results from sensitivity analyses

In a sensitivity analysis of 3910 cases excluding patients for whom higher Hb thresholds for RBC transfusion may apply, the mean pretransfusion Hb was lower overall (73.0 g/l, SD 9.6 g/l) and remained lower in cases from general internal medicine compared to cases from other clinics (70.7 g/l, SD 10.6 g/l vs 73.7 g/l, SD 9.3 g/l, p <0.001) (table 2). Similarly, potentially inadequate first transfusions were lower at both thresholds when compared to the original sample (table 2).

Table 2:
Primary and secondary outcomes of cases discharged from general internal medicine and other clinics. Outcomes were compared using the Student's t-test or Wilcoxon rank sum test for continuous variables or the chi-squared test for categorical variables, as appropriate. Values were missing for pretransfusion Hb prior to the first transfusion in 180 cases, mean posttransfusion Hb after the first transfusion in 303 cases, potentially inadequate transfusions at Hb ≥80 g/l and Hb ≥70 g/l in 180 cases, RBC units ordered during 1st transfusion episode in 311 cases, RBC units transfused during hospitalisation in 3 cases, and transfusion of a single RBC unit during the first transfusion episode in 311 cases.

	All cases	General internal medicine	Other clinics	p-value
	n = 14,598	n = 1980	n = 12,618	
Primary outcome				
Pretransfusion Hb (g/l) prior to 1st transfusion, mean (SD)	74.9 (9.1)	72.6 (9.8)	75.2 (9.0)	<0.001
Secondary outcomes				
Posttransfusion Hb (g/l) after 1st transfusion, mean (SD)	86.9 (12.5)	84.5 (13.0)	87.3 (12.4)	<0.001
Potentially inadequate transfusions at Hb ≥80 g/l, n (%)	3358 (23.3)	347 (17.8)	3011 (24.1)	<0.001
Potentially inadequate transfusions at Hb ≥70 g/l, n (%)	10,743 (74.5)	1284 (65.8)	9459 (75.9)	<0.001
RBC units ordered during 1st transfusion episode, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	<0.001
RBC units transfused during hospitalisation, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	<0.001
Cases with transfusion of a single RBC unit during the first transfusion episode, n (%)	7742 (54.2)	1177 (60.9)	6565 (53.1)	<0.001
Sensitivity analysis excluding cases in whom higher Hb thresholds may apply*	**n = 3910**	**n = 812**	**n = 3098**	
Pretransfusion Hb (g/l) prior to 1st transfusion, mean (SD)	73.0 (9.6)	70.7 (10.6)	73.7 (9.3)	<0.001
Potentially inadequate transfusions at Hb ≥80 g/l, n (%)	705 (18.0)	101 (12.4)	604 (19.5)	<0.001
Potentially inadequate transfusions at Hb ≥70 g/l, n (%)	2581 (66.0)	566 (57.4)	2115 (68.3)	<0.001
Sensitivity analysis including all cases with a CHOP code for RBC transfusion	**n = 28,150**	**n = 2790**	**n = 25,360**	
Minimal Hb during hospitalisation (g/l), mean (SD)	73.2 (10.7)	69.7 (10.7)	73.6 (10.6)	<0.001

CHOP: Swiss Operations Classification; Hb: haemoglobin, IQR: interquartile range; SD: standard deviation.

* exclusion of cases with an IDC-10 code related to the following conditions: acute coronary syndrome and preexisting cardiovascular disease, hypovolemic and traumatic shock, or those undergoing surgery

In a second sensitivity analysis including all 28,150 cases (representing 21,241 unique patients; characteristics in table S1) who received at least one RBC unit transfusion during the study period irrespective of the presence of an ATC code and had at least one Hb measurement available, mean minimal Hb during their hospitalisation was 73.2 g/l (SD 10.7 g/l) (table 2). The mean minimal Hb was lower in cases discharged from general internal medicine compared to those from other clinics (69.7 g/l, SD 10.7 vs 73.6 g/l, SD 10.6, p <0.001) (table 2). From 2012 to 2019, the minimal Hb decreased from 71.5 g/l to 66.9 g/l in general internal medicine (mean annual decrease 0.67 g/l, 95%CI 0.50–0.85), and from 75.9 g/l to 70.9 g/l in other clinics (mean annual decrease 0.62 g/l, 95% CI 0.56–0.68) (figure S4).

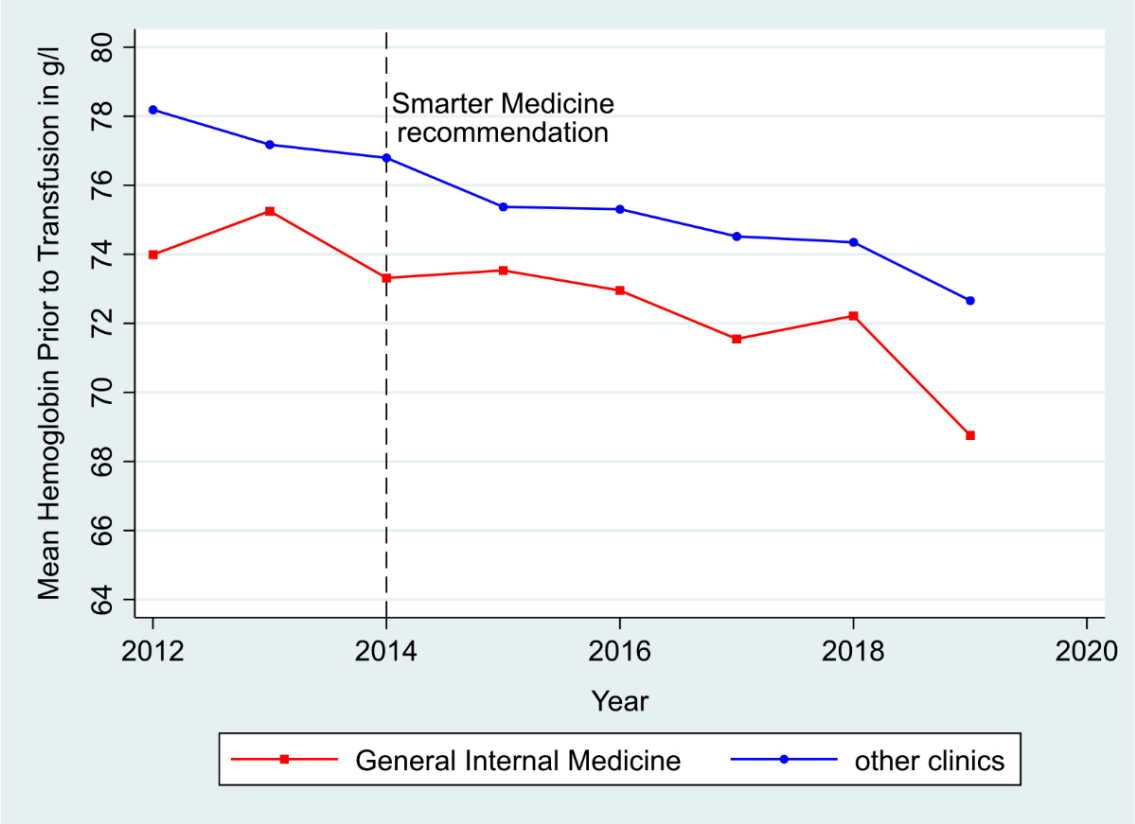
Discussion

In this study, we observed an almost linear decrease in the transfusion threshold over 7 years in all departments, which may indicate an increased awareness of the Choosing Wisely® recommendations and improved adherence to national and international guidelines across the board. However, the transfusion threshold and the proportion of potentially inadequate transfusions in general internal medicine wards remained significantly lower compared to other clinics over the study period, suggesting an impact of the efforts to systematically promote the Choosing Wisely® recommendations. Although the number of potentially inadequate transfusions and the number of transfused RBC units during the first transfusion episode decreased during the study period, potentially inadequate RBC transfusions were observed in up to one-fifth of all cases, particularly in older patients, those with surgery, chronic pulmonary, or ischaemic heart disease.

Randomised trials found no increase in mortality and morbidity with a restrictive transfusion threshold (Hb = 70–80 g/l) compared to a more liberal threshold (Hb = 90–100 g/l) [10, 11, 22]. Based on these findings, guidelines from the American Association of Blood Banks (AABB) and the European Society of Intensive Care Medicine (ESICM) recommend a restrictive transfusion strategy with Hb thresholds of 70 g/l in stable, hospitalised patients [1, 23, 24]. Initiatives to reduce low-value care, such as Choosing Wisely® or the Swiss equivalent Smarter Medicine, endorse not transfusing above an Hb level of 70–80 g/l in hemodynamically stable, non-bleeding patients without signs of inadequate tissue oxygenation, and advise administering a single RBC unit as the standard in such patients [12, 14].

Previous studies have analysed RBC transfusion practices and their trends over time [25–28]. Similar to our results, the pretransfusion Hb value among 468 patients hospitalised in 2012 and 2013 in internal medicine wards of a Swiss regional hospital was 73.0 g/l with higher thresholds observed in surgical units [26]. In another small regional hospital in Switzerland, 63% of 400 RBC transfusions in acutely ill inpatients were administered at an Hb level <70 g/l and 9.7% at a level >80 g/l in 2016. The investigators identified several targets to improve patient

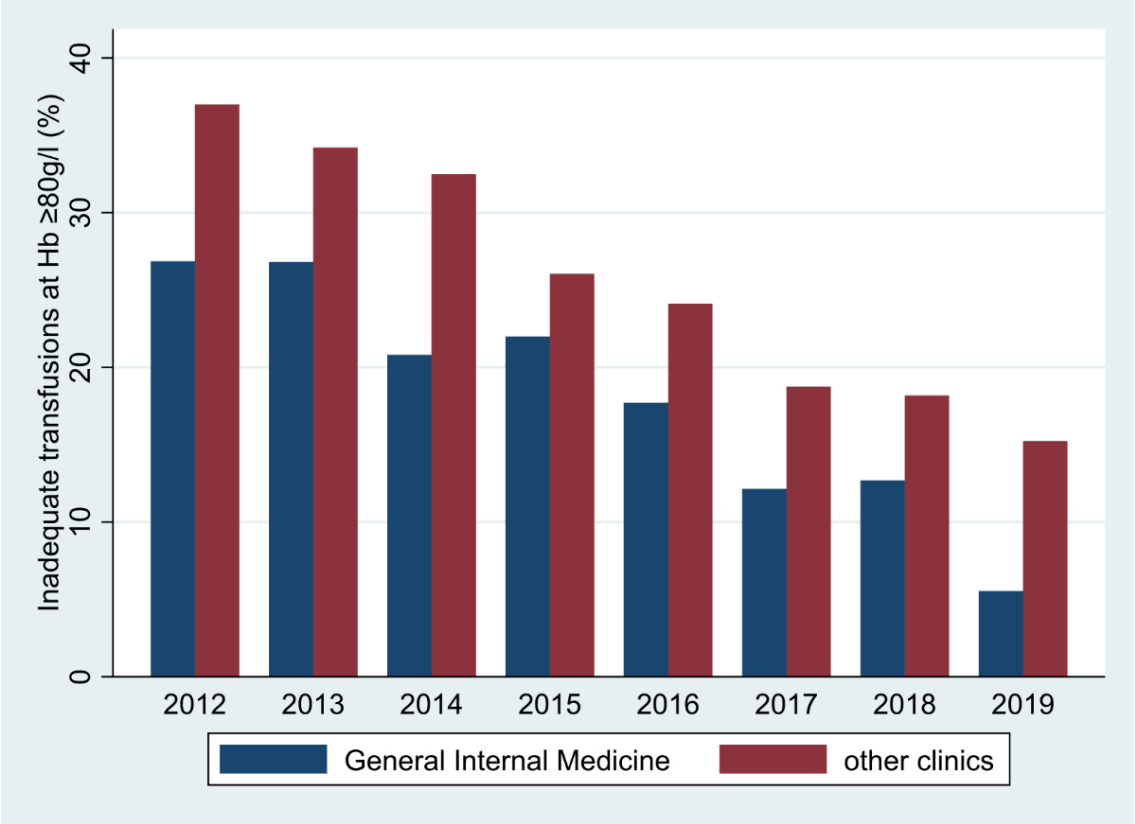
Figure 1: Mean haemoglobin value prior to transfusion over time in cases discharged from general internal medicine compared to those discharged from other clinics. The Smarter Medicine recommendations endorsing a more restrictive haemoglobin threshold of 70 g/l in the majority of non-cardiac patients were published in 2014. Data on haemoglobin prior to the first transfusion were missing in 180 (1.2%) cases (general internal medicine n = 53, other clinics n = 127).



blood management, including the implementation of local transfusion guidelines and systematic training of medical trainees regarding a patient-centred restrictive transfusion policy, especially in the surgery department [29]. As a result of educational and quality improvement projects, a significant decline in mean pretransfusion Hb levels over time was observed in a large retrospective cohort of >60,000 inpatients at Kaiser Permanente Northern California hospitals between 2009 and 2013 [30]. Similar to our study, pretransfusion Hb thresholds were slightly lower in medical compared to surgical inpatients. Given that this study was conducted in a private nonprofit healthcare organisation in the United States, the data may not be directly comparable to ours (e.g., because economic pressure may play a more important role in private hospitals or patient care is organised differently). A nationwide study in the United States showed that the proportion of hospitalised patients receiving at least one RBC transfusion decreased from 2011 to 2014 [27], and the 2020 Swiss hemovigilance report demonstrated a reduction in the absolute number of RBC transfusions administered in Switzerland since 2015 [31]. Even though physicians and educators continue to struggle with how to implement Choosing Wisely® recommendations to reduce low-value care worldwide [32], the overall body of evidence indicates that a more restrictive RBC transfusion strategy has been slowly adopted over the last decade in various clinical settings, similar to our institution [30]. This trend may reflect not only the growing awareness of the recommendations and the solid body of evidence on the safety of restrictive transfusion thresholds but may also result from the development and spread of dedicated quality improvement initiatives and patient blood management programmes [33, 34].

Despite the trend towards more restrictive transfusions practices, up to 60% of transfusions are administered above the recommended Hb level of 70–80 g/l [6, 35, 36]. The substantially lower proportion of potentially inadequate transfusions in general internal medicine compared to other clinics in our study may be due to differences in the patient population (e.g. fewer critically ill patients). However, it may also indicate that systematic education of the Choosing Wisely® recommendations as performed in our general internal medicine department and peer behaviour influence clinical practice, although the Choosing Wisely® and Smarter Medicine initiatives may have had only a minor effect on the overall decrease of the transfusion threshold as also observed in other clinics. Even though restrictive transfusion thresholds may not be adequate in all clinical situations, such as major bleeding or acute ischaemic events [1, 21], these exceptions apply to a minority of patients in our cohort, suggesting that there remains room for improvement in transfusion behaviour. This is particularly true for transfusion decisions in older individuals, surgical patients, and those with chronic cardiovascular and pulmonary disease or malignancy, as these factors predict transfusions at inappropriately high Hb levels of >80 g/l as found in our study as well as others [6, 15, 37]. These findings may reflect the uncertainty of physicians regarding recommendations in these subgroups and particularly for transfusions in the range of Hb levels between 70 g/l and 90 g/l. The Hb threshold for transfu-

Figure 2: Potentially inadequate transfusions over time. Potentially inadequate transfusions were defined as red blood cell transfusions at haemoglobin (Hb) ≥80 g/l. Data on potentially inadequate transfusions were missing in 180 (1.2%) cases (general internal medicine n = 53, other clinics n = 127).



sion in patients with preexisting cardiovascular disease and those undergoing orthopaedic or cardiac surgery as recommended by the American Association of Blood Banks guidelines is 80 g/l, and thus higher than the threshold of 70 g/l in hospitalised patients without these characteristics [1]. In patients with cancer and haematological malignancy, anaemia due to factors such as bone marrow infiltration, inflammation, or treatment side effects is particularly common [38]. However, transfusion recommendations do not differ for this particular population [1, 23, 38],

Figure 3: Transfusion of a single red blood cell (RBC) unit during the first transfusion episode over time. A transfusion episode was defined as the time period between the first administration of 1 RBC unit and the next haemoglobin measurement. Data on the number of RBC units transfused during the first transfusion episode were missing in 311 (2.1%) cases (general internal medicine n = 47, other clinics n = 264).

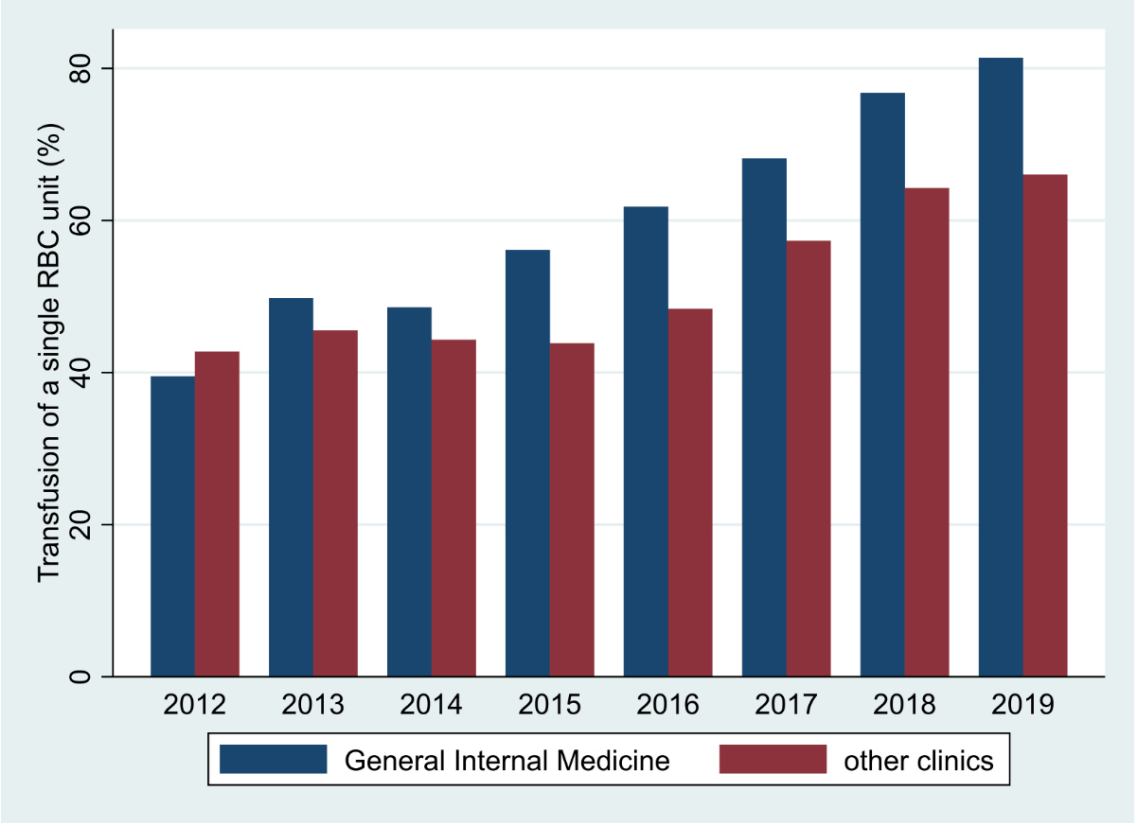


Table 3:
Risk factors for potentially inadequate transfusions at haemoglobin values of ≥80 g/l.

Of the study population, 180 cases had missing values on pretransfusion Hb and were excluded from this analysis. All variables shown in this table were included in the model.

	Multivariable adjusted analysis		
Characteristic	**Adjusted odds ratio**	**95% confidence interval**	**p-value**
Age ≥65 years	1.45	1.32–1.58	<0.001
Female sex	1.02	0.93–1.11	0.62
Emergency admission	0.93	0.85–1.01	<0.08
Discharge from general internal medicine	0.69	0.60–0.78	<0.001
Surgical procedure	1.24	1.14–1.36	<0.001
Acute haemorrhage	1.16	1.02–1.33	0.021
Hypovolemic/traumatic shock	0.89	0.67–1.18	0.41
Coagulation disorders	0.66	0.60–0.72	<0.001
Peripheral vascular disease	0.73	0.65–0.82	<0.001
Cerebrovascular disease	0.97	0.82–1.15	0.74
Chronic heart failure	1.17	1.04–1.32	0.011
Ischaemic heart disease	1.27	1.15–1.41	<0.001
Chronic pulmonary disease	1.24	1.08–1.42	0.002
Dementia	1.21	0.95–1.54	0.13
Diabetes mellitus	1.01	0.91–1.12	0.82
Peptic ulcer disease	0.92	0.69–1.22	0.56
Any malignancy	1.11	1.01–1.21	0.023
Liver disease	0.66	0.56–0.79	<0.001
Renal disease	0.94	0.85–1.03	0.20
Rheumatic disease	1.27	1.01–1.59	0.038

as there is insufficient evidence demonstrating a potential benefit of a more liberal transfusion strategy for patients with malignancy compared to those without [11]. Continuing efforts are needed to support practising physicians by adhering to current guideline recommendations [39]. For example, computerised decision support using a smartphone app with the provision of evidence-based recommendations can improve adherence to transfusion guidelines [40]. Other interventions that can reduce the overuse of RBC transfusions among inpatients include education, combined with alerts in the electronic health record system [41, 42], and audit and feedback [43], mostly implemented in multifaceted interventions [44, 45]. In addition, the impact of current restrictive transfusions policies on patient-centred outcomes and length of stay should be further investigated.

A strength of this study was its large sample size and the variety of cases from various departments. We only analysed the first RBC transfusion episode of each hospitalisation because subsequent transfusions thresholds may be influenced by the response to transfusions in each case. Notably, generalised estimating equations is a population average model, and thus the results (e.g., change in mean pretransfusion haemoglobin per year) can be interpreted across all patients observed. Compared to random effect (or mixed) models, population average models are less prone to biased estimates because they do not require untestable assumptions on the underlying data-generating distribution [46]. However, the study has some limitations. First, due to the use of retrospective data from electronic health records, we did not have complete information on the patient's clinical status. Thus, we cannot make definite judgements about the appropriateness of the pretransfusion Hb thresholds in individual cases. Second, we did not have data on the timing of RBC transfusions and pretransfusion Hb for all cases in our hospital because data from the emergency department, intensive care unit, or operating rooms are captured in separate systems. Consequently, our findings are not generalisable to these settings. Third, we compared patients discharged from general internal medicine vs other clinics, although this may not have been the place where the RBC transfusions occurred. However, most in-hospital transfers occur between either the emergency department, operating rooms, or the intensive care units and the wards (rather than between wards), so it is unlikely that a relevant proportion of RBC transfusions investigated in this study were administered outside of the discharge clinic. Fourth, our results arise from a single-centred study conducted at a university hospital. Thus, our findings and conclusions may not represent the transfusion practices from other regions or smaller non-university hospitals, as differences in the availability of resources and patient populations among different healthcare settings can influence transfusion practices. Finally, we did not explore the outcomes of the transfused patients; therefore, the effect of transfusions at various Hb thresholds on patient-relevant endpoints is unknown. However, while transfusion thresholds decreased over the study period, in-hospital mortality in our institution did not increase.

Conclusion

Pretransfusion Hb thresholds have decreased and the proportion of patients receiving only one RBC unit during their first transfusion episode has increased over the last decade in general internal medicine and other clinics in our institution. Significantly lower Hb thresholds and a lower proportion of potentially inadequate transfusion in general internal medicine wards compared to other wards may suggest that continuous education on Choosing Wisely® recommendations influences clinical practice, although other factors such as economic pressure may play a role. Potentially inadequate RBC transfusions in up to one-fifth of cases indicate room for improvement. Risk factors for transfusions at Hb levels of >80 g/l included older age, surgery, chronic pulmonary and ischaemic heart disease, and malignancy. Thus, interventions to further improve adherence with transfusion recommendations should primarily target physicians caring for these patient populations. While the focus of this study was primarily on transfusion thresholds and the number of RBC units transfused, individualised medicine remains important; this is also reflected by recommendations to consider individual symptoms of anaemia when deciding on RBC transfusions [14].

Open science

The data analysed for the current study are not publicly available because this study was exempted from ethical approval. Data may be shared with researchers for reasonable scientific purposes on request if an ethical committee has approved the use. For data access and requests for the analytical code, external researchers can contact the corresponding author.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix: Supplementary table and figures

Table S1:
Characteristics of all cases with an RBC transfusion in the study period (irrespective of the presence of an ATC code for RBC transfusions). Numbers are presented in n (%), unless indicated otherwise. Characteristics were compared using the Wilcoxon rank sum test for continuous variables or the chi-squared test for categorical variables.

		All patients	**General internal medicine**	**Other clinics**	**p-value**
		n = 28,150	**n = 2790**	**n = 25,360**	
Age in years, median (IQR)		67 (56–76)	73 (62–81)	67 (55–75)	<0.001
Female sex		12,313 (43.7)	1215 (43.6)	11,098 (48.8)	0.829
Emergency admission		12,034 (42.8)	2124 (76.1)	9910 (39.1)	<0.001
Intensive care unit admission*		12,534 (44.5)	848 (30.4)	11,686 (46.1)	<0.001
Surgical procedure		20,175 (71.7)	1029 (36.9)	19,146 (75.5)	<0.001
Comorbidities	Acute haemorrhage**	4632 (16.5)	698 (25)	3934 (15.5)	<0.001
	Hypovolemic and traumatic shock	1277 (4.5)	101 (3.6)	1176 (4.6)	0.014
	Coagulation defects***	9690 (34.4)	1048 (37.6)	8642 (34.1)	<0.001
	Peripheral vascular disease	5926 (21.1)	537 (19.3)	5389 (21.3)	0.014
	Cerebrovascular disease	2595 (9.2)	325 (11.7)	2270 (9)	<0.001
	Ischaemic heart disease	8616 (30.6)	773 (27.7)	7843 (30.9)	<0.001
	Chronic heart failure	5046 (17.93)	833 (29.9)	4213 (16.6)	<0.001
	Chronic pulmonary disease	2671 (9.5)	378 (13.6)	2293 (9)	<0.001
	Dementia	671 (2.4)	208 (7.5)	463 (1.8)	<0.001
	Diabetes mellitus	5848 (20.8)	709 (25.4)	5139 (20.3)	<0.001
	Peptic ulcer disease	653 (2.3)	121 (4.3)	532 (2.1)	<0.001
	Any malignancy	8323 (29.6)	777 (27.9)	7546 (29.8)	0.036
	Liver disease	2177 (7.7)	330 (11.8)	1847 (7.3)	<0.001
	Renal disease	7976 (28.3)	1164 (41.7)	6812 (26.9)	<0.001
	Rheumatic disease	698 (2.5)	78 (2.8)	620 (2.4)	0.258
Charlson Comorbidity Index, median (IQR)****		5 (3–7)	6 (4–8)	5 (3–7)	<0.001
Length of stay in days, median (IQR)		11 (6.8–19)	10.6 (6.1–19)	11 (6.9–19)	0.037
In-hospital death		2272 (8.1)	345 (12.4)	1927 (7.6)	<0.001

IQR: interquartile range; RBC: red blood cell; SD: standard deviation.

* stay at the intensive care or intermediate care unit at any time during the hospitalisation

** includes gastrointestinal haemorrhage, respiratory haemorrhage, traumatic haemorrhage, haemorrhagic shock and all other haemorrhage

*** defined as genetic coagulation disorders

**** the Charlson Comorbidity Index predicts the risk of death of comorbid disease. A score of 0 indicates a 1-year mortality of 12% and a score >5 indicates a 1-year mortality of 85% [20]

Figure S1: Flow chart. ATC codes were not available for transfusions administered in the emergency department, intensive care unit, or operating rooms. ATC: anatomical therapeutical chemical; CHOP: Swiss Operations Classification; RBC: red blood cell

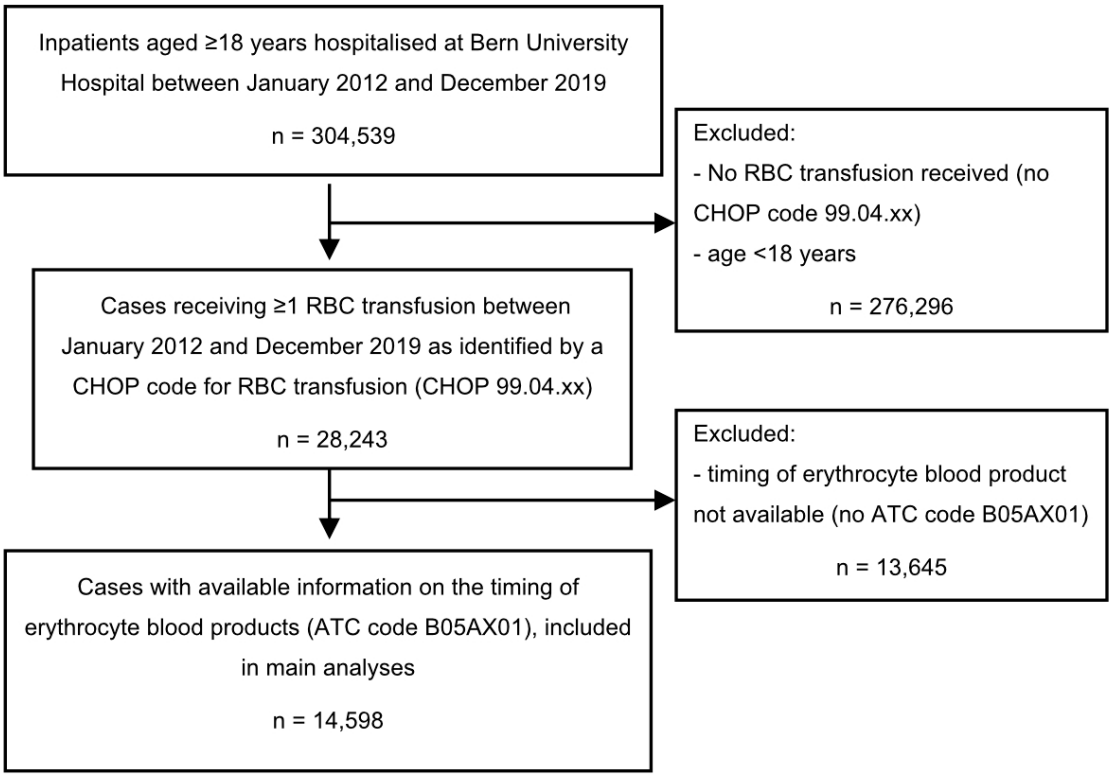

Figure S2: Proportion of red blood cell transfusions at different haemoglobin (Hb) thresholds. Data on haemoglobin thresholds were missing in 180 (1.2%) cases (general internal medicine n = 53, other clinics n = 127).

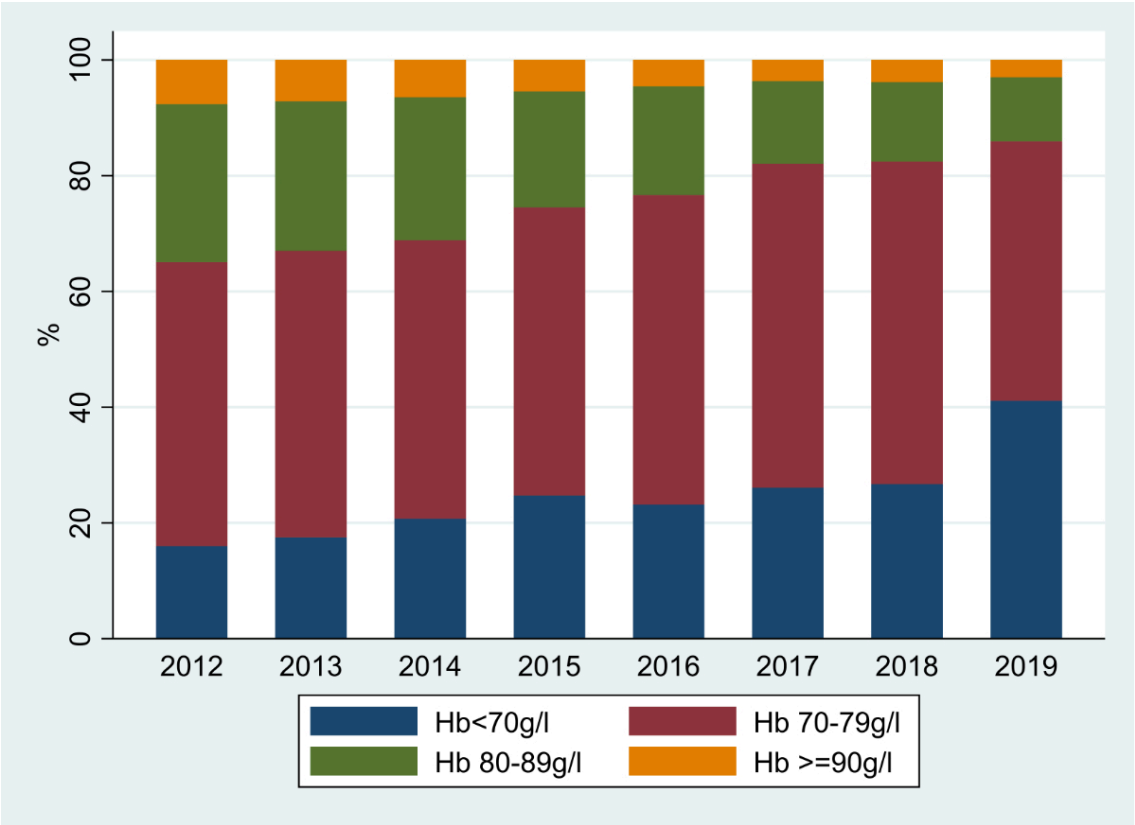

Figure S3: Number of red blood cell units during hospitalisation over time among all cases receiving a red blood cell transfusion. Data were missing in 3 cases (general internal medicine n = 0, other clinics n = 3).

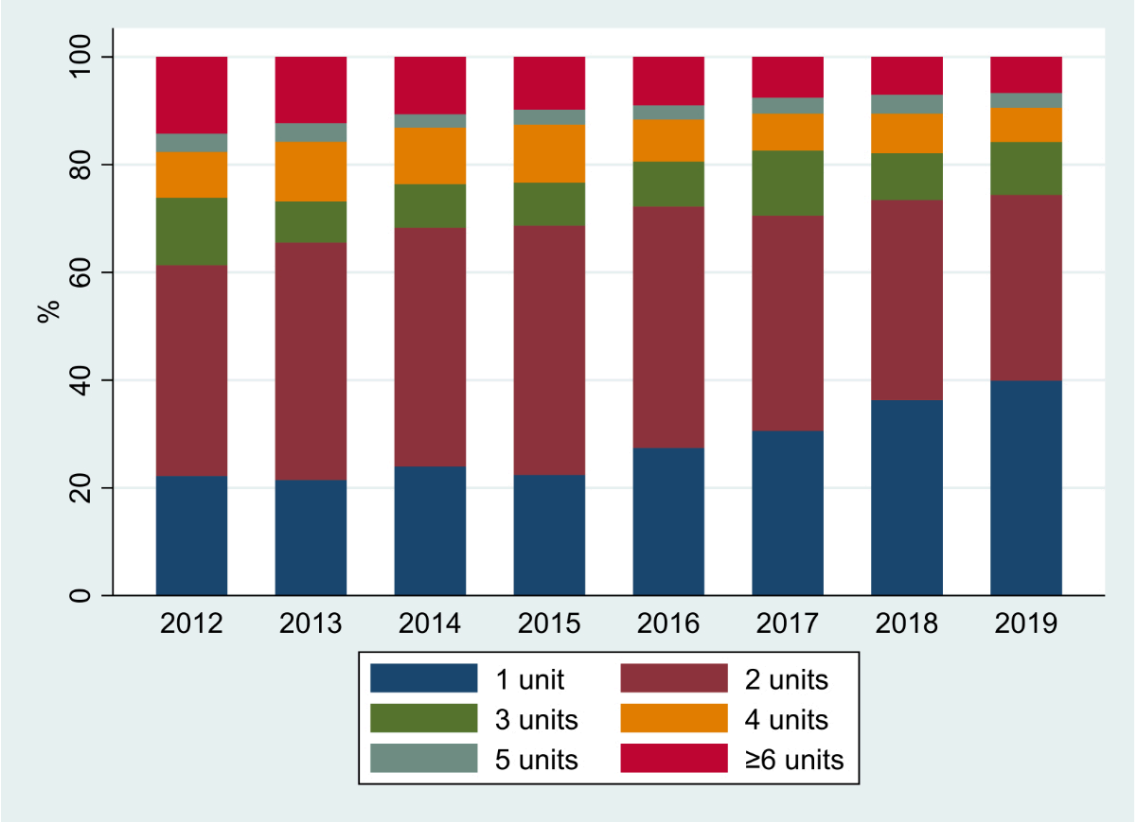

Figure S4: Minimal haemoglobin (Hb) during hospitalisation over time amongall patients receiving a red blood cell transfusion during the study period from 2012 to 2019. Data on minimal haemoglobin were missing for 93 of the 28,243 cases with a Swiss Operations Classification code for red blood cell transfusion (0.3%).