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Changes in perioperative red cell transfusion practice over time in patients undergoing surgery for upper gastrointestinal and liver cancer: a retrospective cohort study at a single tertiary centre

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ABSTRACT

Objectives Optimum transfusion trigger for adults undergoing cancer surgery is uncertain. Published guidelines recommend restrictive transfusion strategies in hospitalised adults. We aimed to measure the red cell transfusion rate and haemoglobin trigger in patients undergoing cancer surgery and how closely practice reflected published guidelines.

Design Retrospective cohort study.

Setting Single tertiary centre.

Participants Adult patients undergoing surgery for upper gastrointestinal or liver malignancy.

Exposure Postguideline change (2015–2017) versus preguideline change (2011–2012).

Outcome measures Primary: transfusion rate, secondary: transfusion trigger. Multivariable logistic regression was used to assess factors and adjust for confounders affecting our outcome measures.

Results 1578 surgical records were identified for 1520 patients. 946/1530 (62%) patients had preoperative anaemia. The transfusion rate decreased from 23% in 2011–2012 to 14% in 2015–2017. This change remained significant after adjusting for other variables associated with transfusion rates. Mean pretransfusion haemoglobin in those who were transfused was 78±13 g/L in 2011–2012 and 80±15 g/L in 2015–2017. This change in haemoglobin transfusion triggers was not significant.

Conclusion Transfusion rate has decreased over the study period in patients undergoing surgery for malignancy and is consistent with a restrictive transfusion strategy.

Strengths and limitations of this study

⇒ The study includes a large study cohort over 5 years with low rates of missing data.
⇒ The study used a multivariable logistic regression model and incorporated several confounding factors in predicting rate of transfusion.
⇒ Retrospective analysis of non-randomised data from a single tertiary centre.
⇒ During the study period, there has been an increase in the use of intravenous iron, which may be a confounding factor.
⇒ Information regarding long-term complications such as cancer recurrence and post-transfusion infection was not available.

INTRODUCTION

Healthy adult men and women should have haemoglobin levels above 130 g/L and 120 g/L, respectively.[1] However, up to 90% of patients with cancer have anaemia for reasons, which include nutritional deficiencies, blood loss, chronic illness, abnormal response to erythropoietin or bone marrow suppression from cancer treatment.[2 3] There is evidence associating preoperative anaemia with poorer patient outcomes such as increased mortality, prolonged stay in intensive care unit, risk of acute kidney injury (AKI) and cardiac ischaemia.[4–6] A retrospective review found that even patients with mild anaemia had a 10% increased risk of death from cardiac events and the risk rises to 52% with more severe anaemia.[7] In patients with gastrointestinal cancer where surgical resection remains an important treatment of malignant tumours,[8] perioperative blood loss may exacerbate pre-existing anaemia.

In the absence of major bleeding, the decision for red blood cell transfusion is driven by the belief that it will improve oxygenation to organs, reducing the risk of myocardial ischaemia, particularly among patients with cardiovascular heart disease (CVD) and AKI.[9] However, clinicians must also consider transfusion-related adverse effects such as fluid overload, increased postoperative infection[9] and tumour recurrence.[10 11] Studies of perioperative transfusion typically compare a

restrictive strategy (transfusion trigger of 70–80 g/L) with a more liberal one (transfusion trigger of 90–110 g/L),[12] although there is no consistent definition of either strategy with many studies using transfusion triggers of either 70 g/L or 80 g/L in restrictive strategies.[13] Moreover, many of the published trials excluded patients with coexisting CVD. In the UK, blood transfusion guidelines published in November 2015 by the National Institute of Health and Care Excellence (NICE),[14] and in July 2016, by the Association of Anaesthetists[15] recommend a restrictive transfusion threshold of 70 g/L, but these guidelines have also highlighted the lack of evidence and uncertainty about best practice, particularly if there is coexisting CVD.

Recent meta-analyses of clinical trials have highlighted these uncertainties.[16] Meta-analysis of trial data involving patients with CVD undergoing non-cardiac surgery found higher rates of acute coronary syndrome with restrictive transfusion practice (RR 1.78, 95% CI 1.18 to 2.70, p=0.01),[13] but there was substantial uncertainty regarding mortality. The uncertainty of outcomes for patients with coexisting CVD is supported by meta-analysis of trial data in cardiac surgery populations.[17] Hence, there is doubt if a restrictive transfusion strategy is ideal in patients with CVD. The aim of this study was to report mean transfusion trigger, transfusion rates, factors associated with transfusion in patients undergoing surgery for upper gastrointestinal or liver malignancy and ascertain whether transfusion practice had changed over time in surgical patients, particularly after the NICE guidance was published in 2015.

METHODS
Study design and setting
This was a retrospective cohort study at a single tertiary centre (Royal Infirmary of Edinburgh, Scotland). Patient identifier numbers (ie, Community Health Index numbers) were used for linkage between demographic, surgical and transfusion data but excluded in the final data set for analysis. As this was a retrospective study of National Health Service (NHS) data, this project met the criteria for service evaluation rather than research. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used when reporting.[18]

Participants
Patients having surgery between 1 January 2011 and 31 December 2018 were originally eligible for inclusion in this study. Inclusion criteria were adults who underwent oesophagectomy, gastrectomy, liver resection or pancreatectomy for cancer of the gastrointestinal system at the Royal Infirmary of Edinburgh. Exclusion criteria were patients aged below 18 years. Repeat surgical procedures occurring within 30 days of the index procedure were also excluded. Surgical procedures in the same patient occurring after 30 days were considered as a new surgical procedure.

Data sources
Eligible patients were identified using the Operating Room Scheduling and Office System, a local operating room database. Data on patient demographics, surgery and transfusion were then extracted from healthcare records by NHS Lothian Researcher Safe Haven. Patient demographic data included: age, gender, American Society of Anaesthesiologists physical status (ASA-PS). Other data extracted were haemoglobin, creatinine, troponin levels and mortality. Surgical data included type of surgery (surgical procedure), surgery date, urgency (National Confidential Enquiry into Patient Outcome and Death category), surgical start and end times, postoperative destination. Transfusion data including transfusion date and transfused products were obtained from the Scottish National Blood Transfusion Service. Only transfusion data within 1 month before surgery and 7 days postsurgery were collected.

Variables
Year of surgery was the explanatory variable of interest. Transfusions were described as 'preoperative' if administered in the month before the date of surgery, 'intraoperative' if administered on the day of surgery and 'postoperative' if administered in the 7 days following surgery. Preoperative haemoglobin was defined as the last haemoglobin measurement prior to surgery and postoperative haemoglobin as the lowest concentration within 7 days postoperation. Pretransfusion haemoglobin was defined as the lowest concentration on either the day of transfusion or the day before transfusion, and post-transfusion haemoglobin as the highest concentration within 7 days post-transfusion. Anaemia was defined according to the WHO criteria.[1] Baseline creatinine was defined as the last measurement prior to surgery and maximum creatinine as the highest concentration within 7 days postoperation. The presence of AKI during hospital stay was defined according to the Kidney Disease Improving Global Outcomes 2012 guidelines[19] using the difference between baseline and maximum creatinine. The presence of myocardial injury was defined according to Fourth Universal Definition of Myocardial Infarction[20] using the maximum troponin concentration above the upper reference limit (URL) within 7 days post-transfusion or 14 days postoperation (in non-transfused patients). The URL for the troponin assay used in our institution is 16.0 ng/L and 34.0 ng/L for women and men, respectively.

Outcomes
The primary outcome was the requirement for red cell transfusion (yes/no) from 1 month before surgery until 7 days postsurgery. Secondary outcome was the transfusion haemoglobin trigger, defined as the last recorded haemoglobin in the 24 hours preceding blood transfusion. The primary exposure of interest for both outcomes was the year of surgery.
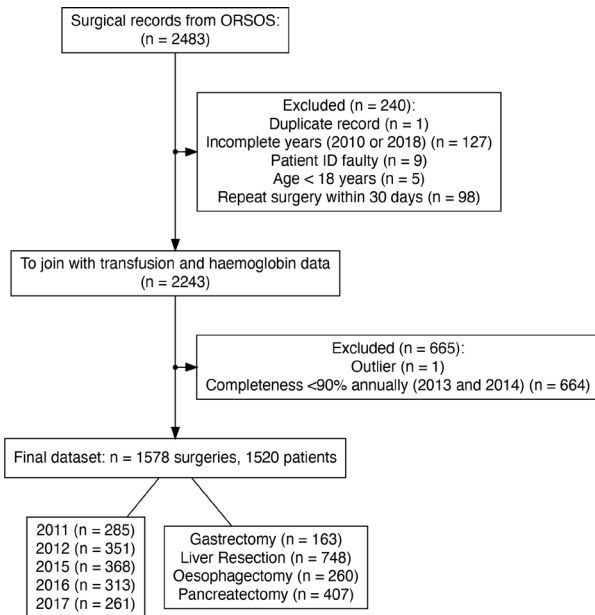
Figure 1 Flowchart illustrating surgical records identification and eligibility. ORSOS, Operating Room Schedule and Office System.

Statistical analyses

Means and SD were used to present continuous data and frequency tabulation with percentage for categorical variables. Between-group comparisons were made using Pearson's χ^2 test for categorical variables and analysis of variance for continuous variables. Multivariable logistic regression was used to test the association between year of surgery and transfusion occurrence (dichotomous variable) and multivariable linear regression for the association between year of surgery and transfusion trigger (continuous variable). Variable selection in model building incorporated characteristics known from previous studies to be associated with outcomes, together with variables strongly associated with the outcome and explanatory variable of interest in univariable analyses. First-order interactions were tested for and included in models if found to contribute significantly to model fit. Results were reported as ORs and beta coefficients, with 95% CIs. Statistical significance was set at p<0.05.

All analyses were carried out using R (R Core Team V.3.6.3, Vienna, Austria), with packages including *dplyr, lubridate, ggplot2, forcats, tidyr, finalfit* and *knitr* and Microsoft Excel (V.2016) in an NHS secure password-protected environment.

Patient and public involvement

Since the study was based on NHS held data, the patients and public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS
Eligible data

The original years of inclusion were 2010 to 2018, however, on review of the extracted data, there were incomplete data for the years 2010, 2013, 2014 and 2018. Therefore, these years were not included in the final analysis. Patients were divided in to two groups based on whether they underwent their procedure prior to the publication of NICE guidance (2011–2012) or after (2015–2017). A total of 2483 surgical records were originally extracted, of which 1578 were eligible after excluding 791 (31.9%) records from incomplete years, 98 (4.0%) surgical procedures within 30 days of the index procedure, 9 (0.4%) records with missing record identification numbers, 5 (0.2%) records where patients were aged below 18 years, 1 (<0.1%) outlier and 1 (<0.1%) duplicated record (figure 1).

Errors in the recording of anaesthetic time and duration of surgery were identified and corrected or excluded from analysis where not possible. Outliers that were at least 1.5 IQRs above the third quartile were also identified as likely erroneous and excluded from analysis. Duplicated data were excluded from analysis and missing data were reported. Missing data were handled using the 'not available' (na.rm) function in R.

Patient demographics, surgical and outcome details

Patient demographics and surgical details are summarised in table 1. Overall, 1520 patients had 1578 eligible surgical procedures. Of 51 (3.4%) patients underwent more than one procedure during the study period due to an unsuccessful previous operation, cancer recurrence or complications. 18 (1.2%) patients died within 30 days of surgery.

Haemoglobin levels and transfusion rates

Of the 1530 procedures with a recorded preoperative haemoglobin measurement, 946 (62%) had preoperative anaemia comprising 359 female and 587 male patients based on WHO's definitions. Patients undergoing gastrectomy had the lowest mean preoperative haemoglobin (111±20 g/L, p<0.001), followed by those undergoing pancreatectomy (112±20 g/L), oesophagectomy (129±15 g/L) and liver resection (120±21 g/L). Mean pretransfusion haemoglobin (ie, transfusion trigger) of those who required blood transfusion was 78±14 g/L, with oesophaghectomy having the lowest (74±10 g/L, p=0.257), followed by pancreatectomy (78±15 g/L), gastrectomy (79±15 g/L) and liver resection having the highest (80±14 g/L) (table 2).

Procedural blood transfusion rate was found at 17% (n=274/1578). Gastrectomy (n=52/163, 32%) had the highest transfusion rate, followed by pancreatectomy (n=84/407, 21%), liver resection (n=112/748, 15%) and oesophagectomy (n=26/260, 10%).

Primary outcome
Requirement for red cell transfusion

In a multivariable model (figure 2), transfusion rate decreased in the preguideline and postguideline 2-year groups. Surgical procedures particularly were associated with reduced transfusion rate. Factors associated with increased transfusion rate included: ASA 3–4 (1.79, 1.35

Table 1 Demographics, surgical details and outcomes

	2011–2012	2015–2017	Total	P value
N	636	942	1578	
Transfused, n (%)	145 (22.8)	129 (13.7)	274 (17.4)	<0.001
Pretransfusion Hb (g/L), mean±SD	77.5±13.4	79.5±15.0	78.5±14.2	0.240
Procedure, n(%)				
Gastrectomy	60 (9.4)	103 (10.9)	163 (10.3)	0.660
Liver resection	309 (48.6)	439 (46.6)	748 (47.4)	
Oesophagectomy	100 (15.7)	160 (17.0)	260 (16.5)	
Pancreatectomy	167 (26.3)	240 (25.5)	407 (25.8)	
Gender, n (%)				
Female	222 (34.9)	382 (40.6)	604 (38.3)	0.027
Male	414 (65.1)	560 (59.4)	974 (61.7)	
Age (years), mean±SD	63.0±11.8	63.6±11.8	63.4±11.8	0.290
ASA, n (%)				
1	57 (9.0)	49 (5.2)	106 (6.7)	0.001
2	380 (59.7)	588 (62.4)	968 (61.3)	
3	184 (28.9)	284 (30.1)	468 (29.7)	
4	15 (2.4)	6 (0.6)	21 (1.3)	
(Missing)	0 (0.0)	15 (1.6)	15 (1.0)	
Urgency, n (%)				
Elective	604 (95.0)	924 (98.1)	1528 (96.8)	0.001
Emergency	32 (5.0)	17 (1.8)	49 (3.1)	
(Missing)	0 (0.0)	1 (0.1)	1 (0.1)	
Surgical duration (per 60 min), mean±SD	4.0±2.2	4.1±2.3	4.1±2.3	0.111
Timing of transfusion, n (%)				
Postoperative transfusion	87 (60.0)	93 (72.1)	180 (65.7)	0.050
Preoperative transfusion	58 (40.0)	35 (27.1)	93 (33.9)	
Intraoperative transfusion		1 (0.8)	1 (0.4)	
Postoperative destination, n(%)				
Day bed unit	1 (0.2)	21 (2.2)	22 (1.4)	0.003
High dependency unit	404 (63.5)	558 (59.2)	962 (61.0)	
Inpatient ward	97 (15.3)	103 (10.9)	200 (12.7)	
Intensive care unit	126 (19.8)	160 (17.0)	286 (18.1)	
Other destination	1 (0.2)	2 (0.2)	3 (0.2)	
(Missing)	7 (1.1)	98 (10.4)	105 (6.7)	
Presence of AKI, n(%)	41 (6.4)	55 (5.8)	96 (6.1)	0.698
Presence of MI, n(%)	12 (1.9)	19 (2.0)	31 (2.0)	1.000

N indicates number of procedures.
AKI, acute kidney injury; ASA, American Society of Anaesthesiologists Physical Status; Hb, haemoglobin; MI, myocardial injury.

to 2.38, p<0.001), emergency procedures (2.32, 1.21 to 4.37, p=0.003).

Secondary outcome

Transfusion haemoglobin trigger

Transfusion triggers did not change over the study period (table 3). Multivariable analysis found a negative association between transfusion trigger and emergency procedures (−9.31,−16.20 to −2.41, p=0.015).

DISCUSSION

The principal finding of this study is that in patients from a single-centre undergoing surgery for upper gastrointestinal cancer resection, the transfusion rate decreased from 23% in 2011–2012 to 14% in 2015–2017. This change remained significant after adjusting for other variables associated with transfusion rates. The mean pretransfusion haemoglobin in those who were transfused was 78±13 g/L in 2011–2012 and 80±15 g/L in 2015–2017.

Table 2 Transfusion data by procedure

	Gastrectomy	Liver resection	Oesophagectomy	Pancreatectomy	Total	P value
N	163	748	260	407	1578	
Transfused, n (%)	52 (31.9)	112 (15.0)	26 (10.0)	84 (20.6)	274 (17.4)	<0.001
Pretransfusion Hb (g/L), mean±SD	110.9±19.6	119.8±20.8	128.8±14.9	112.8±20.1	78.5±14.2	<0.001
Surgical duration (per 60 min), mean±SD	3.9±1.7	3.1±1.8	6.7±1.3	4.3±2.4	4.1±2.3	<0.001
Timing of transfusion, n (%)						<0.001
Postoperative transfusion	33 (63.5)	81 (72.3)	26 (100.0)	40 (47.6)	180 (65.7)	
Preoperative transfusion	19 (36.5)	31 (27.7)		43 (51.2)	93 (33.9)	
Intraoperative transfusion				1 (1.2)	1 (.04)	

N indicates number of procedures.
Hb, haemoglobin.

After adjustment, the change in haemoglobin transfusion triggers between these periods was not significant.

In our cohort, 62% of adult patients with upper gastro-intestinal or liver malignancy had preoperative anaemia based on the WHO's definition of anaemia and 17.4% of all procedures required red cell transfusion in the perioperative period. Red cell transfusion was more likely in emergency procedures, ASA-PS 3 and 4. Our findings suggest that red cell transfusion decreased in the period after the NICE guidance was published in 2015; however, transfusion trigger appeared unchanged. These findings, therefore, are more consistent with pre-existing
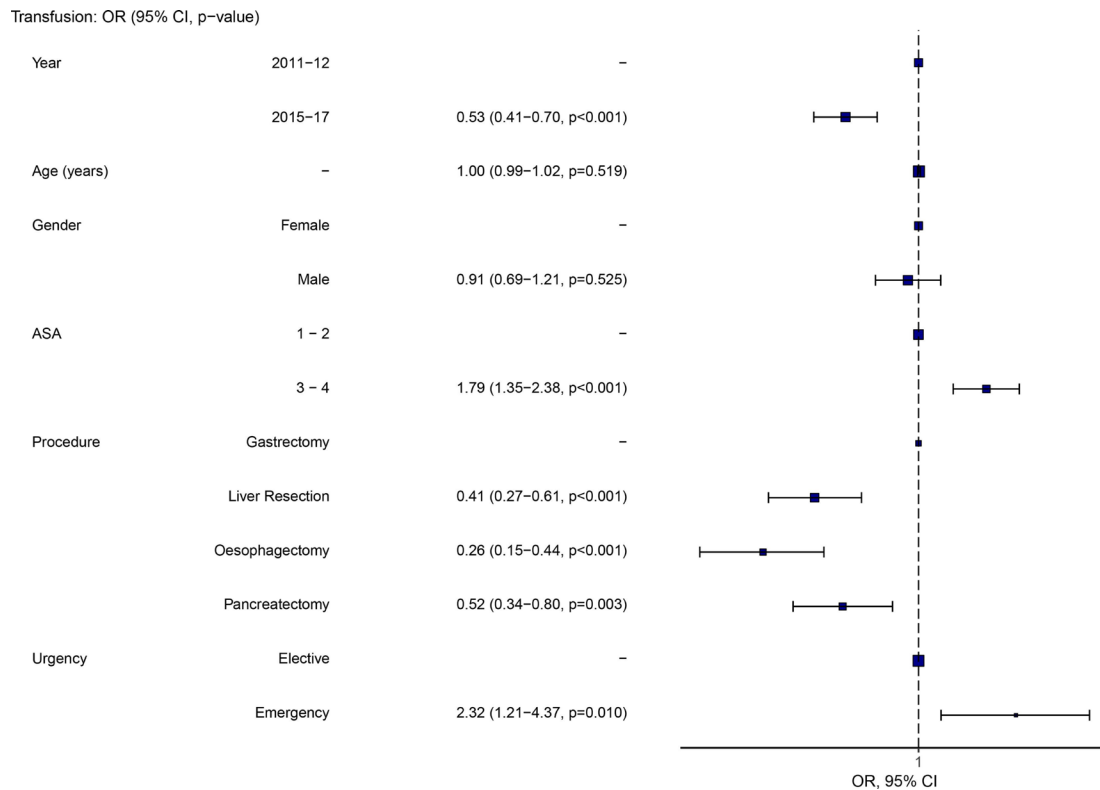

Figure 2 OR predicting factors associated with transfusion. Outcome was transfusion, primary exposure year of surgery. Multivariable model is adjusted for age, gender, type of procedure, ASA and urgency. ASA, American Society of Anaesthesiologists.

Table 3 Univariate and multivariate linear regression of factors associated with transfusion haemoglobin trigger

Dependent: transfusion trigger	Mean±SD	Univariable coefficient (95% CI, p value)	Multivariable coefficient (95% CI, p value)
Year			
2011–2012 (ref)	77.5±13.4	–	–
2015–2017	79.5±15.0	2.02 (–1.36 to 5.39, p=0.240)	1.40 (–2.01 to 4.81, p=0.420)
Age	78.5±14.2	0.06 (–0.09 to 0.21, p=0.421)	0.06 (–0.09 to 0.22, p=0.430)
Gender			
Female (ref)	77.6±14.8	–	–
Male	79.0±13.8	1.49 (–1.97 to 4.96, p=0.397)	2.51 (–0.98 to 6.00, p=0.157)
ASA			
1–2 (ref)	79.1±14.2	–	–
3–4	77.4±14.0	–1.70 (–5.09 to 1.68, p=0.322)	–0.61 (–4.27 to 3.04, p=0.741)
Type of procedure			
Gastrectomy (ref)	78.2±15.2	–	–
Liver resection	80.0±13.7	1.79 (–2.89 to 6.46, p=0.452)	1.58 (–3.41 to 6.56, p=0.534)
Oesophagectomy	74.0±9.8	–4.23 (–10.92 to 2.46, p=0.214)	–5.11 (–11.88 to 1.65, p=0.138)
Pancreatectomy	78.0±15.1	–0.28 (–5.19 to 4.63, p=0.911)	1.36 (–3.64 to 6.36, p=0.593)
NCEPOD category			
Elective (ref)	79.3±14.3	–	–
Emergency	69.8±8.4	–9.49 (–15.74 to –3.25, p=0.003)	–9.31 (–16.20 to –2.41, p=0.008)

Outcome was transfusion trigger, primary exposure year of surgery.
ASA, American Society of Anaesthesiologists; NCEPOD, National Confidential Enquiry into Patient Outcome and Death.

restrictive transfusion practice and changes in transfusion rate may be explained by better management of preoperative anaemia (including the increased use of intravenous iron), better surgical techniques or increased use of minimally invasive surgery.

Anaemia is common in the surgical population. A review of 18 large observational studies comprising over 600 000 surgical patients found preoperative anaemia in 35% of patients.[4] Another study involving over 39 000 surgical patients found 31.1% and 26.5% of men and women, respectively, to be anaemic preoperatively.[21] Our study found a much higher prevalence of anaemia; however, this may represent a particular association with upper gastrointestinal tract malignancy. Observational studies have reported that preoperative anaemia is associated with poorer postoperative outcomes such as morbidity, mortality and prolonged length of hospital stay, although it is likely that these findings are confounded with other chronic disease.[4 22] The current standard care for anaemia during surgical admission is red blood cell transfusion, although there is interest in perioperative treatment with haematopoietic agents such as intravenous iron where time permits.[23] Preoperative anaemia remains an independent predictor of perioperative red blood cell transfusion.[22]

Restrictive transfusion practice has become a standard practice in stable hospitalised adult patients, and although exact definitions do not exist, this is generally considered to be a target haemoglobin range of 70–90 g/L. The optimum transfusion threshold for patients undergoing surgery, particularly cancer surgery, or those with coexisting CVD remains uncertain and these patients were typically excluded from clinical trials of transfusion.[12] Current practice guidelines demonstrate lack of consistency although most broadly recommend restrictive strategies but with differing transfusion thresholds.[14 15 24 25] The NICE, the Association of Anaesthetists and international groups recommend restrictive transfusion practice using 70 g/L as the default threshold, but some suggest caution and higher thresholds for patients with coexisting CVD, acute coronary syndromes or, in particular, surgical groups, including elderly patients undergoing orthopaedic surgery. Two relevant systematic reviews have been published in the last 5 years.[13 26] The overall quality of the evidence was considered to be low and these studies report inconsistent effects of restrictive transfusion strategies. Moreover, a range of transfusion triggers were used by each study and no standard definition of a restrictive or liberal strategy. Of note, in both these reviews, restrictive transfusion strategies were associated with increased rates of cardiac complications, but not mortality. Anaemia has also been associated with a higher rate of AKI in surgical patients.[27] In our study, 2% and 6% of patients suffered a postoperative cardiac injury and kidney injury, respectively, a small but appreciable number.

The association between transfusion and cancer recurrence is similarly unclear. In patients with cancer, a review of 36 observational studies found that perioperative blood transfusion was associated with colorectal

cancer recurrence (1.42, 1.20 to 1.67).[13] A meta-analysis reported that the risk of colorectal cancer recurrence increased by 40% after 1–2 units of transfused blood (1.40, 1.18 to 1.67) and 69% after 3–4 units (1.69, 1.40 to 2.04).[28] Systematic review of 20 795 surgical patients with colorectal cancer revealed transfusion increased the risk of cancer-related mortality (1.71, 1.43 to 2.05).[10] These findings would indicate caution for transfusion in patients with cancer, however, good quality randomised data are lacking—more difficult oncological procedures are associated with both bleeding and increased recurrence, and residual confounding is likely to exist in observational studies.

The strength of this study is that it included a large cohort of patients and used robust data linkage between NHS institutional data and the blood transfusion service. Rates of missing data were low. However, this was a retrospective analysis of non-randomised data from a single centre. Therefore, our findings may not reflect the whole of the United Kingdom accurately. There are other limitations to this study. Our institution did not have a dedicated preoperative anaemia or intravenous iron service during the period of study. However, we do not have robust data on the use of intravenous iron or other anaemia treatments over the study period. Some haemoglobin measurements using point of care technology may not have been captured by the laboratory system (eg, Haemocue), although arterial blood gas haemoglobin measurements are captured. It is also possible that red cell transfusion decisions may be made in response to rapid blood loss without measurement of haemoglobin. Finally, information regarding longer term complications such as cancer recurrence and post-transfusion infection was not available.

CONCLUSION

Our findings suggest that transfusion rates have fallen over time, however, it is uncertain if this reflects changes in guidance or better surgical techniques and better preoperative management of anaemia. There is a need for a large, well-designed, randomised trial with low risk of bias to confirm the optimal perioperative transfusion strategies in surgical oncology, to explore its effect on cardiovascular and other morbidity and its effect on cancer recurrence in these patients.

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