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Postoperative anaemia increases unplanned readmission: an international prospective cohort study of patients undergoing major abdominal surgery

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Attributable to the POSTVenTT collaborative involving 101 hospitals over 13 countries

Introduction

Preoperative anaemia is observed in one-third of patients who present for surgery, and is associated with increased postoperative complications, length of stay, poorer quality of life and delayed recovery[1,2]. In the last decade, there has been a focus on the detection and management of anaemia, prevention of bleeding and appropriate blood transfusion practices, collectively termed patient blood management (PBM)[3]. Implementation of PBM programmes is associated with reduced blood transfusion use and shorter hospital stay[4,5].

In surgical patients, preoperative anaemia can be exacerbated by blood loss at the operation and repeated blood testing during and after the procedure. As iron deficiency is the commonest underlying cause of anaemia, the use of intravenous (IV) iron is a plausible and attractive therapeutic option to improve haemoglobin levels[6]. However, two recent large RCTs on the use of preoperative IV iron in major abdominal surgery, PREVENTT and FIT, did not show benefit in the immediate perioperative period on blood transfusion rates, complications or length of stay. However, an interesting finding in both trials was that the greatest treatment effect was increased haemoglobin levels at 6–8 weeks after surgery, which was associated with a reduction in unplanned hospital readmissions[7,8]. The association of postoperative anaemia and worse patient recovery was also observed in a large database analysis of patients undergoing surgery[9]. In a reanalysis of a large perioperative clinical trial, postoperative anaemia was associated with an increased risk of death and disability at 90 days[10].

The mechanism of postoperative anaemia leading to delayed postoperative recovery is possibly due to the symptoms associated with the condition, including impaired mental function and reduced physical exercise capacity[11]. In the elderly, anaemia is associated with functional loss and increased risk for developing frailty[12–15].

The prospective international POST-operative Variability in anaemia treatmenT and Transfusion (POSTVenTT) cohort study aimed to determine whether postoperative anaemia was associated with poorer recovery after surgery, with an increased rate of readmissions.

Methods

The POSTVenTT study was a prospective, multicentre, international observational cohort study involving sites across Australia, Aotearoa New Zealand, Europe, North Africa and the Middle East. The POSTVenTT study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621001517864; 8 November 2021). The trial protocol was approved by the South Metropolitan Health Service (Western Australia) Health Research Ethics Committee (EC00265), the Western Australia Research Governance System (RCG 4477), with local ethics and governance confirmed at each site before patient recruitment[16]. Sites were recruited utilizing collaborative research networks such as TASMAN and EuroSurg. This study is reported in concordance with the STROBE statement[17].

Study design

POSTVenTT was conducted by utilizing existing student- and trainee-led collaborative research models[18]. An advisory board of surgical trialists supported by the Western Australia Clinical Trials Unit oversaw a student- and trainee-led project management group. Data was collected over two 2-week periods during July 2021 at sites across Australia and Aotearoa New Zealand, and additionally in October 2021 at sites in Europe,

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Table 1 Demographic and preoperative clinical data, by readmission within 30 days of discharge

	Readmission (%)	No readmission (%)	P
Total *N*	343 (6.8)	4707 (93.2)	
Mean age (years)	58.7 (16.7)	55.3 (16.8)	<0.001
Sex			
Male	187 (6.4)	2757 (93.6)	0.174
Female	155 (7.4)	1949 (92.6)	
Mean BMI (kg/m^2)	29.2	29.5	0.549
ASA physical status			
1–2	181 (5.4)	3169 (94.6)	<0.001
3	137 (8.9)	1397 (91.1)	
4–5	23 (14.8)	132 (85.2)	
Cardiac disease	98 (8.5)	1055 (91.5)	0.012
Respiratory Disease	64 (8.0)	741 (92.0)	0.19
Diabetes mellitus			
Diet	8 (8.5)	86 (91.5)	0.07
Medication	45 (9.3)	438 (90.7)	
Insulin	15 (8.6)	159 (91.4)	
Neurological disease	25 (8.7)	262 (91.3)	0.235
Liver disease			
Mild	15 (11.7)	113 (88.3)	0.066
Moderate to severe	4 (9.3)	39 (90.7)	
Smoking			
Current	68 (7.9)	794 (92.1)	0.369
Previous	71 (6.5)	1027 (93.5)	

North Africa and the Middle East. Each site was responsible for a 30-day prospective follow-up after discharge.

Eligibility criteria

All consecutive adult patients aged 18 years or above undergoing major emergency or elective abdominal surgery were eligible. Major abdominal surgery was defined as any operation with an incision into the abdominal cavity (open, laparoscopic, or robotic surgery) and an anticipated duration of more than 1 h. Patients were recruited upon booking for an eligible procedure and upon procedure completion the operation report was reviewed for eligibility. Patients with planned readmissions were included due to the existing potential for unplanned readmission. Full details of eligible procedures and eligibility criteria are listed in the study protocol[16].

Definitions and outcomes

Anaemia was defined using the WHO sex-specific cut-off haemoglobin values (<130 g/l for men, <120 g/l for non-pregnant women)[19]. Mild anaemia was defined as a haemoglobin >100 g/l, and moderate to severe anaemia <100 g/l. The primary outcome was the rate of unplanned readmission to the hospital within 30 days after initial discharge. Secondary outcomes included clinical frailty score, length of postoperative hospital stay, postoperative complications (defined by the Clavien–Dindo classification), packed red blood cell (pRBC) transfusion and the prevalence of anaemia at discharge and 30 days post-discharge. Frailty was defined according to the CSHA Clinical Frailty score, and further classified as 'Not Frail' (1–3), 'Mild Frailty' (4–5), and 'Moderate to Severe Frailty' (≥6)[20,21]. Prolonged length of hospital stay was defined as a postoperative hospital admission greater than that of the 75th centile of patients in the study.

Statistical analysis

R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. It was prespecified that data would only be included from hospitals with >95% data completeness as per the study protocol.[16] Categorical data were presented as numbers and percentages, analysed using the chi-square test. Continuous data were presented as means with standard deviations or medians with interquartile ranges as appropriate and analysed using the independent samples *t*-test or Kruskal–Wallis test.

Time to readmission within 30 days from discharge was analysed as a time-to-event variable, using multivariable Cox regression models, reported as adjusted hazard ratios (aHR) with associated 95% confidence intervals). To analyse postoperative changes in frailty, this outcome was dichotomized as 'more frail' *versus* 'unchanged/less frail' at 30 days follow-up compared with preoperative frailty, and this was analysed using multivariate logistic regression models, reported with adjusted odds ratios (aOR) and 95% c.i. These models were adjusted for age, sex, ASA, cardiac history, diabetes mellitus, preoperative frailty, operative urgency, operative procedure, wound contamination, postoperative complications, postoperative pRBC transfusion and country of treatment.

Adjusted restricted cubic spline models were used to investigate the effect of haemoglobin at discharge as a continuous variable, for both readmission and frailty outcomes. For these models, splines were placed at the 5th, 25th, 75th and 95th percentiles. Multiple imputations with the mice (Multivariate Imputations by Chained Equations) package were used to generate 10 imputed data sets, and these were pooled to conduct the analyses described above. A sensitivity analysis was also performed with non-imputed data and pairwise exclusion of patients with missing data.

A post-hoc sensitivity analysis was performed excluding patients undergoing cholecystectomy, as although defined as major surgery, cholecystectomy is often performed as a day-case procedure and is associated with lower risks of bleeding and anaemia.

Results

In total, 5266 patients undergoing major abdominal surgery at 101 hospitals across 13 countries, with a median of 47 patients (i.q.r. 21–77) per hospital were included, of whom 5143 (97.7%) were discharged before the end of the study. Data were complete for 99.3% of all data fields. Of those discharged prior to the end of the study, 30-day follow-up data were completed for 5050 patients (98.2%). Only patients with 30-day follow-up were

Table 2 Operative clinical data, by readmission within 30 days of discharge

	Readmission (%)	No readmission (%)	Total	P
Surgical specialty				
Colorectal	126 (9.8)	1157 (90.2)	1283	<0.001
Gynaecology	28 (5.7)	459 (94.3)	487	
HPB	98 (5.0)	1843 (95.0)	1941	
Transplant	12 (26.1)	34 (73.9)	46	
Upper GI	48 (5.6)	806 (94.4)	854	
Urology	30 (7.7)	361 (92.3)	391	
Vascular	1 (2.1)	47 (97.9)	48	
Operative urgency				
Immediate	7 (9.0)	71 (91.0)	78	0.001
Urgent	77 (9.9)	698 (90.1)	775	
Expedited	53 (7.4)	662 (92.6)	715	
Elective	206 (5.9)	3272 (94.1)	3478	
Operative contamination				
Clean	122 (5.4)	2145 (94.6)	2267	0.001
Clean–contaminated	179 (7.7)	2141 (92.3)	2320	
Contaminated	29 (8.5)	314 (91.5)	343	
Dirty	12 (11.8)	90 (88.2)	102	
Intraoperative allogenic PRBC Transfusion				
No	308 (6.4)	4482 (93.6)	4790	<0.001
Yes	34 (13.1)	225 (86.9)	259	
Postoperative ICU admission				
No	264 (6.4)	3873 (93.6)	4137	0.012
Yes—planned	66 (8.2)	743 (91.8)	809	
Yes—unplanned	13 (12.5)	91 (87.5)	104	

Table 3 Postoperative clinical data, by readmission within 30 days of discharge

	Readmission (%)	No readmission (%)	Total	P
Postoperative complications				
None	225 (5.5)	3883 (94.5)	4108	<0.001
Minor	82 (11.1)	656 (88.9)	738	
Major	36 (17.7)	167 (82.3)	203	
Postoperative PRBC transfusions	56 (13.9)	355 (7.3)	411	<0.001
Reoperation				
No	330 (6.7)	4610 (93.3)	4940	0.05
Yes	13 (11.9)	96 (88.1)	109	
Length of stay				
Mean(s.d.)	7.7(8.3)	5.2(6.8)	5.3 (7.0)	<0.001
Anaemia at Discharge				
No Anaemia	73 (5.5)	1259 (94.5)	1332	<0.001
Anaemia	223 (9.5)	2117 (90.5)	2340	
Haemoglobin at discharge				
Mean(s.d.)	110.9(17.5)	117.3(17.3)	116.8 (17.4)	<0.001
Postoperative iron therapy				
None	306 (6.5)	4410 (93.5)	4716	<0.001
Oral iron	12 (6.8)	164 (93.2)	176	
IV iron	25 (16.1)	130 (83.9)	155	

included in the analysis. The mean age was 55.6 (s.d. 16.8) years, and 2944 (58.3%) were women (*Table 1*).

The most common operations were hepatopancreatobiliary (38.4%), colorectal (25.4%) or upper gastrointestinal (16.9%). Urgent or immediate surgery occurred in 853 patients (16.9%). Postoperative (in-hospital) complications occurred in 941 patients (18.6%), of which 203 (4.0%) were classified as major (Clavien–Dindo ≥3). Blood transfusion was used intraoperatively in 259 patients (5.1%) and postoperatively in 354 patients (7.0%) (*Table 2*).

Overall, the median length of hospital stay was 3 days (i.q.r. 1–6 days). Haemoglobin values were measured for 3672 patients (72.7%) postoperatively, with a mean haemoglobin at discharge of 116.8 g/l (s.d. 17.4 g/l). Anaemia was common on discharge; 2340 patients (46.3%) of whom 1698 (33.6%) had mild anaemia (Hb > 100 g/l) and 642 patients (12.7%) moderate–severe anaemia (Hb < 100 g/l). Among patients with anaemia at discharge, 709 (30.3%) had a follow-up haemoglobin measurement. Of those who had follow-up haemoglobin measurements, 501 (70.7%) had anaemia at 30 days (*Table 3*).

Readmission within 30-days of discharge

Within 30 days of discharge 343 patients (6.8%) were readmitted to hospital, with a median time to readmission of 10 days (i.q.r. 5–18 days). Of the patients readmitted, 314 (91.5%) were unplanned readmissions. The most common reasons for readmission were postoperative surgical complications, general infections and wound infections, 45.5%, 16.6%, and 14.3% respectively (*Table S1*).

Patients with postoperative anaemia were more likely to be readmitted within 30 days, 223/2340, 9.5% *versus* 73/1332, 5.5% patients without anaemia, $P < 0.001$. Both unadjusted and adjusted Cox regression models confirmed postoperative anaemia was associated with an increased risk of readmission (unadjusted HR 1.80, 95% c.i. 1.38 to 2.36, $P < 0.001$, and aHR

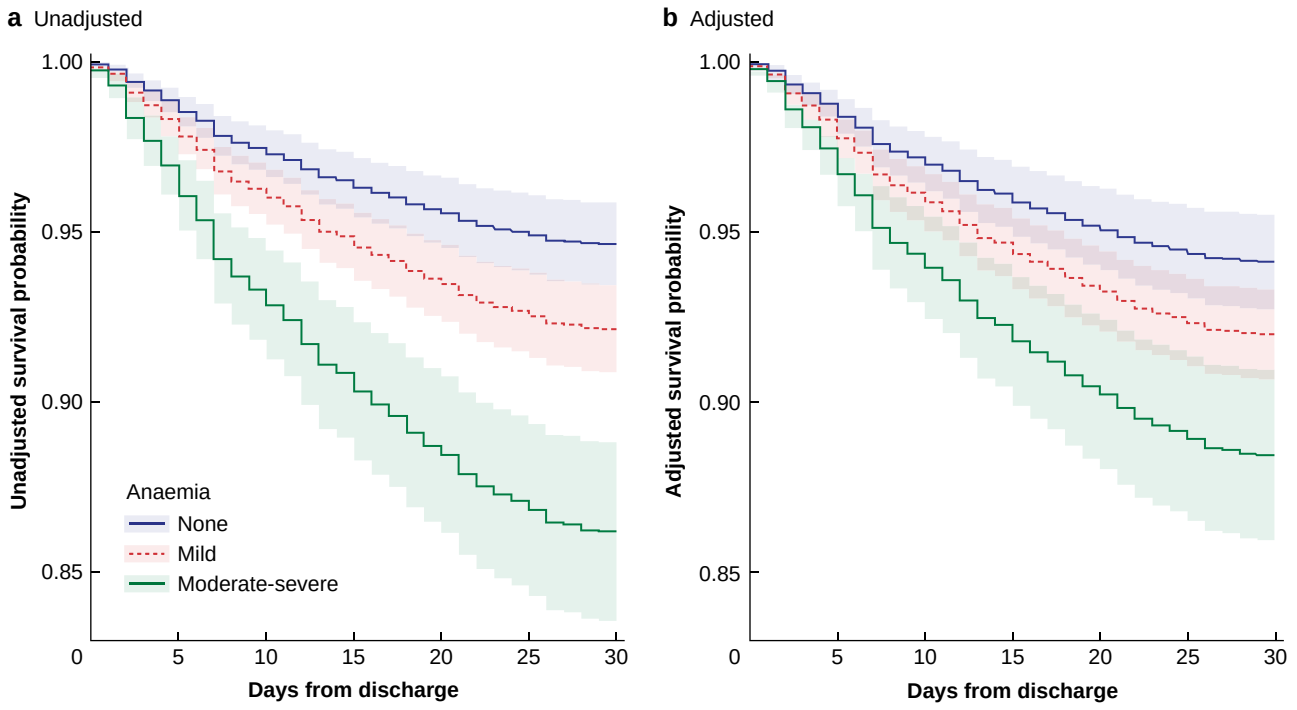

Fig. 1 a Unadjusted and b adjusted Cox regression curves for readmission-free survival for patients discharged without anaemia, and with mild or moderate–severe anaemia

1.56, 95% c.i. 1.18 to 2.08, $P = 0.002$; *Table 3*). Moreover, a severity-dependent effect was seen; the more severe the anaemia, the greater the associated risk of readmission: moderate–severe postoperative anaemia (aHR 2.08, 95% c.i. 1.46 to 2.96, $P < 0.001$) and mild anaemia (aHR 1.41, 95% c.i. 1.04 to 1.90, $P = 0.03$) compared to patients without anaemia (*Fig. 1*). Adjusted restricted cubic spline regression demonstrated higher adjusted odds of readmission associated with lower haemoglobin values at discharge from the hospital (*Fig. 2a*).

Frailty

Clinical frailty scores were recorded for 99.3% of patients before surgery, and 95.9% of patients at 30-day follow-up. Preoperatively, 651 patients (12.9%) were classified as having mild frailty and 129 (2.6%) had moderate or severe frailty. Preoperative frailty was associated with an increased risk of postoperative complications (aOR 1.26, 95% c.i. 1.01 to 1.57, $P = 0.049$), prolonged length of stay (aOR 1.28, 95% c.i. 1.00 to 1.63, $P = 0.048$) and readmission within 30 days of discharge (aHR 1.41, 95% c.i. 1.05 to 1.88, $P = 0.02$). At 30-day follow-up, 867 patients (17.2%) reported increased frailty, with a mean increase in the clinical frailty score of 1.3 points (s.d. 0.7) in this group (*Table S2*).

Patients discharged with postoperative anaemia were more likely to report an increase in frailty at 30-day follow-up (24.9% anaemic *versus* 14.8% not anaemic; aOR 1.64, 95% c.i. 1.35 to 2.01, $P < 0.001$). The severity of anaemia was associated with a greater risk of worsening clinical frailty score; moderate–severe anaemia (aOR 2.05, 95% c.i. 1.44 to 2.91, $P < 0.001$), and mild anaemia (aOR 1.36, 95% c.i. 1.01 to 1.85, $P = 0.04$) at discharge were both associated with increasing frailty scores at 30-day follow-up. Restricted cubic spline analysis also showed lower haemoglobin values at discharge were associated with higher odds of increased frailty at 30-day follow-up (*Fig. 2b*).

Sensitivity analyses

Sensitivity analyses performed using pairwise exclusion of missing data rather than multiple imputations showed no meaningful differences compared to the main analysis. A subgroup analysis excluding patients undergoing laparoscopic cholecystectomy was also performed ($n = 3323$). Postoperative anaemia was associated with an increased risk of readmission (aHR 1.68, 95% c.i. 1.19 to 2.38, $P = 0.004$), and an increase in frailty at 30-day follow-up (aOR 1.57, 95% c.i. 1.24 to 1.99, $P < 0.001$). The severity of anaemia increased the risk of both readmission (mild aHR 1.52, 95% c.i. 1.06 to 2.19, $P = 0.02$; moderate–severe aHR 2.11, 95% c.i. 1.41 to 3.18, $P < 0.001$) and becoming more frail at 30-day follow-up (mild aOR 1.49, 95% c.i. 1.17 to 1.90, $P = 0.001$; moderate–severe aOR 1.82, 95% c.i. 1.35 to 2.45, $P < 0.001$).

Discussion

In this international prospective study (POSTVenTT), anaemia after major surgery was common and had a negative impact on patient recovery, with an increased risk of unplanned readmission and increased frailty at 30 days. These results confirm the findings of previous retrospective database analyses and build on the secondary findings seen in the PREVENTT and FIT RCTs, including the reanalysis of trials which suggested a greater risk of mortality or disability up to 90 days following surgery, postoperative delirium and a longer length of stay[9,10,22].

Postoperative anaemia is more common when there is pre-existing anaemia, significant blood loss, frequent blood sampling, excessive intravenous fluid administration, inflammation and nutritional deficiencies before or after surgery[23]. PBM strategies, such as a short-term administration of intravenous iron especially in the postoperative setting, should be considered

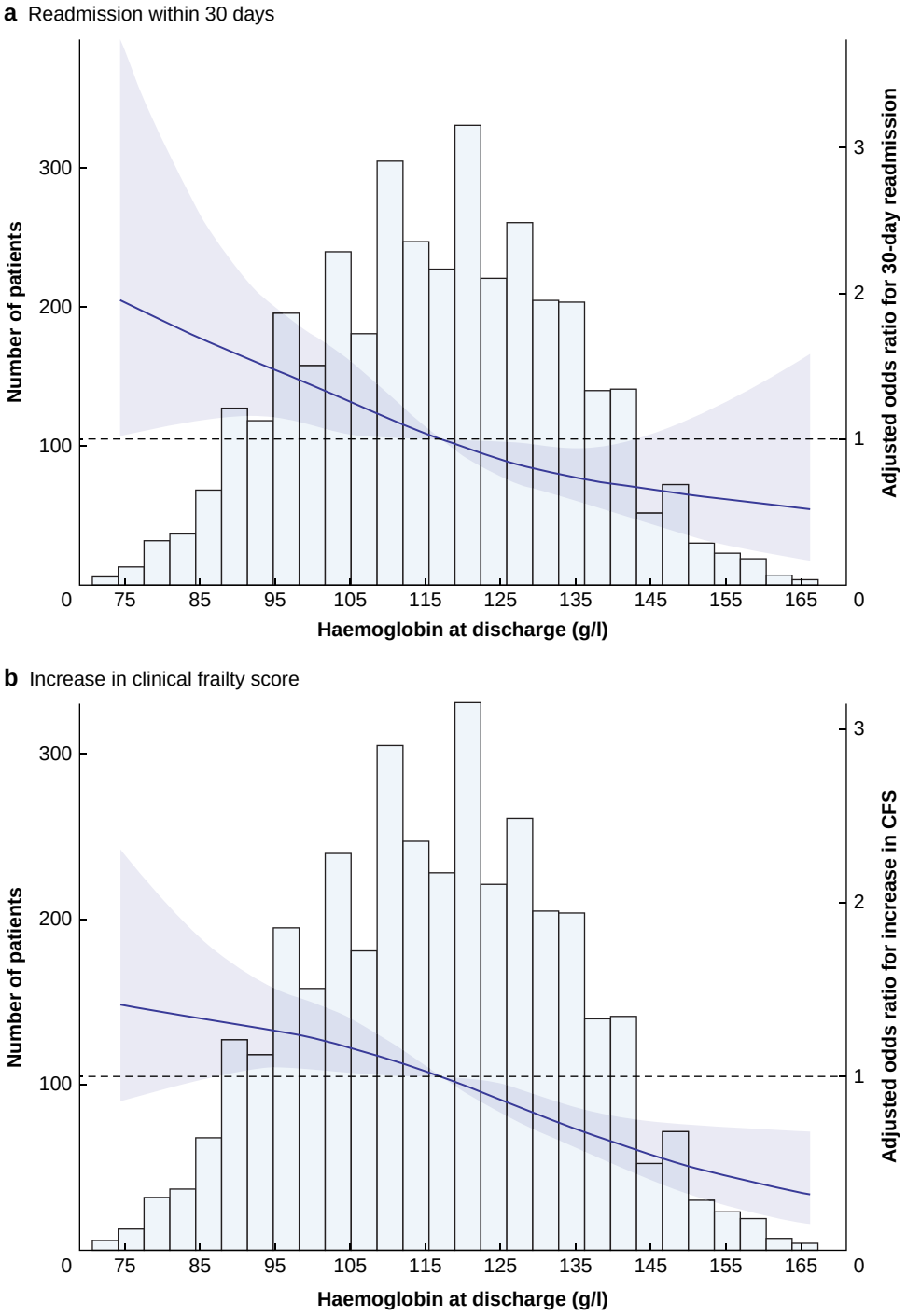

Fig. 2 Restricted cubic spline regression for the association between haemoglobin at discharge and a adjusted odds for readmission within 30 days of discharge, and b adjusted odds for increase in frailty at 30-day follow-up

Knots are placed at percentiles 5, 25, 75, 95; Hb = 88, 104, 129, 145 g/l. CFS, clinical frailty score.

for patients with moderate-to-severe iron deficiency to address postoperative anaemia[24]. Also, tranexamic acid use has been consistently reported to be effective in the perioperative period, but it is still under-utilized[25,26].

Current recommendations propose the use of IV iron to treat patients with anaemia, ideally 4 weeks before their planned surgery[27]. However, this may not be feasible in the timelines before abdominal surgery with most clinical trials recruiting about 2 weeks before operation[28]. There is debate about the efficacy of IV iron to increase haemoglobin levels before surgery, particularly as it is not clear about the impact of inflammation and chronic disease on iron transport and sequestration. Although absolute iron deficiency would mandate treatment in any hospitalized patients with ferritin < 30 μg/l, the proposal for treatment in patients with ferritin < 100 μg/l or transferrin saturations < 20% may be less effective[29]. This in part may explain why IV iron may be more beneficial in patients undergoing bowel surgery, where the cause of anaemia is likely gastrointestinal blood loss[30]. As such, administration of IV iron after surgery where anaemia may

be caused by blood loss at operation and in the postoperative period may have a more direct impact on iron stores that may override the inflammatory mediated iron sequestration. Similarly, administration of IV iron after surgery, when the patient is on the ward, with IV access and monitoring, would be easier and less expensive than intravenous iron administered at preoperative visits[26,31].

The present study has demonstrated an association between anaemia at discharge and increasing frailty at 30 days post-surgery (aOR 1.65, $P < 0.001$). This highlights the importance of evaluating frailty in anaemic individuals and investigating any potential negative consequences of the co-existence of these two conditions. Previous research supports the relationship between anaemia and frailty[31,32]. The connection between anaemia and frailty may be due to the requirement for iron by cellular and mitochondrial metabolism and its impact on skeletal muscle function, leading to sarcopenia and myopathy[33]. These findings have clinical implications as they highlight the need to evaluate frailty in anaemic individuals.

A significant strength of the study was the diversity of the study population from various countries in different geographical regionals (Australia and Aotearoa New Zealand, Europe, North Africa and the Middle East) and economic status, with a high (98%) degree of data ascertainment. The results should therefore be reliable and readily translated globally.

The POSTVenTT study has several limitations. The study design was observational, which only allows for the identification of correlations between anaemia and postoperative outcomes, limiting the causal inferences that can be made. Additionally, the measurement of haemoglobin values was incomplete, covering only 72.7% of patients postoperatively, which may affect the generalizability of the results. This observational study was susceptible to variable sampling bias in the different specialties and hospitals, which may have influenced the apparent variation in adherence to guidelines. Furthermore, as the clinical frailty score was collected preoperatively and at 30 days after surgery, further research is required to determine if the impact on frailty is longer lasting. Patients who underwent staged procedures with the index surgery prior to the recruitment period but subsequent surgery fell within the recruitment period were included in the study. Unfortunately, data was not collected to quantify the number of patients who met this criteria. These patients would understandably be at higher risk for readmission and complications, and thus a potential unquantified confounder of the data set.

A further limitation is the range of procedures included and by association the range of primary pathology treated. The primary pathology often dictates the morbidity of patients and residual confounding could have played a role in the outcomes seen in this study. However, to address this potential limitation, a sensitivity analysis was performed together with reanalysis of the data without including patients undergoing laparoscopic cholecystectomy (the most common procedure performed). This analysis had the same findings as the whole study population.

Future research should build on the POSTVenTT study through RCTs that aggressively correct perioperative anaemia prior to discharge to determine if anaemia alone causes an increased rate of readmission, rather than act as a marker of co-morbidity.

Collaborators

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Research data and other material (for example, study protocol, data analysis plan) will be available to the scientific community, immediately upon publication, with as few restrictions as possible. All requests should be submitted to the corresponding author for consideration.

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