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The Impact of Pre-Operative Anaemia on One Year Amputation Free Survival and Re-Admissions in Patients Undergoing Vascular Surgery for Peripheral Arterial Disease: a National Vascular Registry Study

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WHAT THIS PAPER ADDS

This population based cohort study found that mild pre-operative anaemia was associated with 30% and moderate or severe anaemia with 50% increased risk of amputation or death at one year after lower limb revascularisation. Patients with pre-operative anaemia also experienced more re-admissions in the one year following surgical revascularisation compared with patients without anaemia. Pre-operative anaemia is a potential peri-operative therapeutic target to improve the outcomes of patients with peripheral arterial disease undergoing vascular surgery, as it is one of the few modifiable risk factors, and randomised studies should explore whether interventions to improve haemoglobin have a positive effect on patient outcomes.

Objective: Anaemia is common among patients undergoing surgery, but its association with post-operative outcomes in patients with peripheral arterial disease (PAD) is unclear. The aim of this observational population based study was to examine the association between pre-operative anaemia and one year outcomes after surgical revascularisation for PAD.

Methods: This study used data from the National Vascular Registry, linked with an administrative database (Hospital Episode Statistics), to identify patients who underwent open surgical lower limb revascularisation for PAD in English NHS hospitals between January 2016 and December 2019. The primary outcome was one year amputation free survival. Secondary outcomes were one year re-admission rate, 30 day re-intervention rate, 30 day ipsilateral major amputation rate and 30 day death. Flexible parametric survival analysis and generalised linear regression were performed to assess the effect of anaemia on one year outcomes.

Results: The analysis included 13 641 patients, 57.9% of whom had no anaemia, 23.8% mild, and 18.3% moderate or severe anaemia. At one year follow up, 80.6% of patients were alive and amputation free. The risk of one year amputation or death was elevated in patients with mild anaemia (adjusted HR 1.3; 95% CI 1.15 — 1.41) and moderate or severe anaemia (aHR 1.5; 1.33 — 1.67). Patients with moderate or severe anaemia experienced more re-admissions over one year (adjusted IRR 1.31; 1.26 — 1.37) and had higher odds of 30 day re-interventions (aOR 1.22; 1.04 — 1.45), 30 day ipsilateral major amputation (aOR 1.53; 1.17 — 2.01), and 30 day death (aOR 1.39; 1.03 — 1.88) compared with patients with no anaemia.

Conclusion: Pre-operative anaemia is associated with lower one year amputation free survival and higher one year re-admission rates following surgical revascularisation in patients with PAD. Research is required to evaluate whether interventions to correct anaemia improve outcomes after lower limb revascularisation.

Keywords: Amputation, Anaemia, Peripheral arterial disease, Revascularisation, Vascular surgery, United Kingdom
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INTRODUCTION

Anaemia is a common problem in patients undergoing surgery and, in conjunction with existing comorbidities, is associated with a cumulative increase in patient risk of perioperative morbidity and death.[1,2] To address this issue, national guidelines in various countries recommend the development of patient blood management pathways (PBM), which include the identification and management of pre-operative anaemia, prevention of bleeding and restrictive transfusion practice where appropriate.[3–6] Challenges preventing the application of PBM initiatives in vascular surgery remain, in part because of the urgent presentation of patients with vascular conditions.[7] This is concerning as patients in need of vascular surgery frequently have multiple comorbidities and undergo large operations, with relatively long in hospital stays and high rates of postoperative complications and re-admissions.

Lower limb peripheral arterial disease (PAD) is a common indication for surgery, with more than 6 000 open lower limb procedures performed per annum.[8] Optimisation of outcomes for PAD is a priority for patients and healthcare professionals,[9] as well as the National Health Service (NHS), which recently introduced financial incentives for healthcare providers to improve outcomes.[10] One plausible therapeutic target could be the management of anaemia to improve outcomes for patients undergoing vascular surgery, but the proportion of patients who have pre-operative anaemia and its effect on outcomes is unclear.

Previous studies evaluating the relationship between anaemia and post-operative outcomes in this patient group reported that pre-operative anaemia is associated with a higher mortality rate and higher rate of major amputation.[11–15] However, these studies had a small sample size[11,12,14] or measured only short term outcomes.[13] This study aimed to examine the association between preoperative anaemia and one year outcomes after surgical revascularisation for PAD using a large population based patient cohort.

METHODS

Patients and data

The study used an extract of data from the National Vascular Registry (NVR), linked to the national administrative hospital dataset for England, Hospital Episode Statistics (HES). The study cohort included all patients who underwent open surgical lower limb revascularisation procedures in English NHS vascular units between 1 January 2016 and 31 December 2019, whose NVR record could be linked to their corresponding HES record. The NVR collects information from hospital staff on patient level demographic, procedural, and in hospital and 30 day post-operative outcomes for vascular procedures performed in the UK,[16] and captures 88% of surgical lower limb revascularisation procedures undertaken in England.[8] The HES Admitted Patient Care database is an administrative database that contains information about all hospital admissions to NHS hospitals in England.[17]

The first surgical revascularisation (index) procedure that each patient had in the study period was included in the analysis. Patients who had surgery due to trauma were excluded, as were patients who underwent amputation or endovascular revascularisation procedures in the 30 days prior to the index procedure, as these procedures may have affected the pre-operative haemoglobin levels of the index procedure. Patient records with missing data on the indication for surgery, smoking status, and American Society of Anaesthesiologists (ASA) grade were also excluded. Patients were followed up from the date of surgery to 31 December 2020. The study was exempt from UK National Research Ethics Committee approval, as it involved the secondary use of existing registry and administrative data.

Anaemia definition and patient characteristics

Anaemia was measured using data in the NVR record on preoperative haemoglobin (Hb). A Hb level lower than 13 g/dL for men and 12 g/dL for women was used to define anaemia, and this was further categorised into mild (men: 11 – 12.9 g/dL, women: 11 – 11.9 g/dL), moderate (8 – 10.9 g/dL), and severe (< 8 g/dL) as per the WHO criteria.[18] As there were only 85 patients with severe anaemia, the categories of moderate and severe anaemia were combined for the analysis.

The NVR record was also the source of other baseline characteristics. These included age at the time of procedure, sex, comorbidities (diabetes, ischaemic heart disease, chronic heart failure, chronic kidney disease, and chronic lung disease), smoking status, medications (antiplatelet, statin), ASA grade, indication for surgery (chronic limb ischaemia Fontaine stage I–II or III–IV, acute limb ischaemia, lower limb aneurysm), admission method (elective or non-elective), most distal level of intervention (iliofemoral, popliteal, or crural), and pre-operative blood results (haemoglobin, white cell count [WCC], creatinine, and sodium). Some blood result values were outside plausible ranges for the variables: Hb levels < 3 g/dL or > 25 g/dL ($n = 56$), creatinine levels < 25 μmol/L ($n = 29$), WCC $< 2*10^9$/L or $> 40*10^9$/L ($n = 74$), and sodium levels > 160 mmol/L ($n = 4$). These were considered erroneous and were treated as missing values.

Outcomes

The primary outcome was one year amputation free survival (AFS). Secondary outcomes were the one year readmission rate, the 30 day re-intervention rate (revascularisation by any means), 30 day ipsilateral major lower limb amputation rate, and 30 day mortality rate. The follow up period was at least one year for all patients.

Information about major amputations and reinterventions were extracted from HES using pre-defined Office of Population, Censuses and Surveys (OPCS)-4 Classification codes[19] (Supplementary Table S1). Major amputations were defined as amputations above the ankle. Only ipsilateral major amputations were included in the analysis of 30 day and one year outcomes. Re-admissions over one year, defined as any admission to hospital after the index admission, were also identified in HES. Re-admissions for haemodialysis were excluded. If more than 10 admissions occurred over one year, the first 10 were captured.

Statistical analysis

All statistical analyses were performed in STATA 17 (StataCorp, College Station, TX, USA). Multiple imputation by chained equations (MICE)[20] was performed to handle missing values and produced 20 imputed datasets. Predictive mean matching (PMM) of 10 nearest neighbours was used to impute missing Hb and WCC values due to their skewed distributions. Data were assumed to follow the Missing at Random mechanism. There were 2 144 records missing Hb values (15.7%). WCC, creatinine, and sodium variables had less than 0.5% of the values missing.

Categorical variables are presented as frequencies and proportions, continuous normally distributed variables as mean and standard deviation (SD) and continuous non-normally distributed as median and interquartile range (IQR). Baseline characteristics by anaemia status were compared using chi square test for categorical variables and Mann—Whitney *U* test for continuous variables. Age by anaemia severity was compared using the Kruskal—Wallis test. A p value $< .050$ was considered statistically significant.

The Royston-Parmar (RP) flexible parametric survival model[21] was used to assess the effect of anaemia on one year amputation free survival, adjusting for age, sex, comorbidities (diabetes, ischaemic heart disease, chronic heart failure, chronic lung disease), ASA grade, antiplatelet medications, WCC, sodium, and creatinine levels as well as method of admission, indication for surgery, and most distal level of intervention. The admission mode and indication for surgery variables did not satisfy the proportional hazards assumption and the flexible parametric model included these variables as time varying components. The appropriate functional form of continuous variables and the number of degrees of freedom for the baseline spline function were chosen using the Bayesian Information Criterion. Model performance was assessed using Harrell's C discrimination index (C statistic) and Royston and Sauerbrei's D statistic.

A Poisson regression model was used to assess readmission rates at one year. Separate multivariable logistic regression models were used to estimate the effect of anaemia on 30 day re-interventions, 30 day ipsilateral major amputations, and 30 day mortality. Each model included patient and admission factors to adjust for confounding.

Finally, the overall impact on one year amputation free survival from anaemia was estimated within this cohort by calculating the population attributable risk (PAR) in the complete case dataset using the STATA "regpar" command.[22] This estimated the potential improvement in one year amputation free survival that might be achieved if no patients had pre-operative anaemia.

RESULTS

Linked records were available for 14 559 patients who underwent an index surgical lower limb revascularisation between January 2016 and December 2019. Patients were excluded who underwent amputation or endovascular revascularisation procedures 30 days before the index surgical revascularisation procedure ($n = 716$), those with records with missing data on indication for surgery, smoking status, and ASA grade ($n = 44$), and those undergoing procedures due to trauma ($n = 158$). A total of 13 641 patients was included in the final analysis.

Baseline demographics

The median age was 70 years (IQR 62, 77) and most patients were men ($n = 10\ 116$, 74.2%). Nearly two thirds of patients (63.1%, $n = 8\ 603$) had an elective admission and the most common indication for surgery was chronic limb threatening ischaemia (CLTI) (Fontaine stage III and IV) ($n = 7\ 532$, 55.2%). Overall, 11 497 patients (84.3%) had recorded haemoglobin levels, 57.8% ($n = 6\ 650$) had no anaemia, 23.9% ($n = 2\ 745$) had mild anaemia, 17.5% ($n = 2\ 017$) moderate, and 0.7% ($n = 85$) severe anaemia. Demographic and clinical characteristics of the patients by anaemia severity are presented in Table 1. Higher proportions of non-elective admissions, ASA grades 4 and 5, and CLTI (Fontaine III and IV) were found in the moderate and severe anaemia groups (Fig. 1). The proportions of patients within each anaemia group were similar in the imputed data (respectively, 57.9%, 23.8%, 17.5%, and 0.8%), and the distribution of patient characteristics within these groups was also comparable (see Supplementary Table S2).

Amputation free survival

At one year follow up, 80.6% of patients ($n = 10\ 999$) were alive and amputation free, 8.2% ($n = 1\ 115$) had undergone ipsilateral major amputation, and 11.2% had died ($n = 1\ 527$). Pre-operative anaemia was associated with worse one year amputation free survival ($p < .001$) (Fig. 2). The risk of one year amputation or death was elevated in patients with mild anaemia (adjusted hazard ratio (aHR) 1.27; 95% CI 1.15 — 1.41) and moderate or severe anaemia (aHR 1.49; 95% CI 1.33 — 1.67) (Supplementary Table S3). A decrease in haemoglobin levels by one unit (g/dL) was associated with a 9% reduction in the rate of one year amputation free survival (aHR 0.91; 95% CI 0.89 — 0.94). The hazard ratios were similar in the imputed and complete case datasets (Supplementary Table S4).

Figure 3 shows the predicted one year amputation free survival by anaemia severity, age, admission method, and indication, with the other model covariables fixed at their means. Patients with moderate or severe anaemia undergoing non-elective procedures for CLTI at 80 years of age have an estimated probability of 62.5% of being alive and amputation free at one year compared with 72.7% for those without anaemia.

If it was possible to correct the pre-operative anaemia before revascularisation, there would be a 2.5% (95% CI 5.8 — 7.1%) absolute reduction in one year amputation or death (Population Attributable Risk [PAR]). This corresponds to the difference in the estimated rate of death or major

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Table 1. Baseline patient and clinical characteristics by anaemia status for 13 641 patients who underwent an index surgical lower limb revascularisation between January 2016 and December 2019

Characteristics	No anaemia (n = 6 650; 48.8%)	Mild anaemia (n = 2 745; 20.1%)	Moderate/severe anaemia (n = 2 102; 15.4%)	Missing haemoglobin (n = 2 144; 15.7%)	p
Age	67 (60, 74)	72 (64, 78)	73 (65, 80)	70 (61, 77)	<.001
White cell count	8.5 (7, 10.3)	8.8 (7, 11)	9.6 (7.4, 12.3)	8.8 (7.1, 10.8)	<.001
Creatinine	78 (66, 92)	81 (66, 102)	84 (65, 112)	79 (65, 96)	<.001
Sodium	139 (136, 141)	138 (135, 140)	137 (134, 139)	138 (135, 140)	<.001
Gender					<.001
Men	4 996 (75.1)	2 198 (80.1)	1 340 (63.7)	1 582 (73.8)	
Women	1 654 (24.9)	547 (19.9)	762 (36.3)	562 (26.2)	
Diabetes	1 859 (28.0)	1 092 (39.8)	958 (45.6)	720 (33.6)	<.001
Chronic lung disease	1 669 (25.1)	710 (25.9)	479 (22.8)	502 (23.4)	.035
Ischaemic heart disease	2 128 (32.0)	1 082 (39.4)	863 (41.1)	743 (34.7)	<.001
Chronic heart failure	312 (4.7)	252 (9.2)	224 (10.7)	126 (5.9)	<.001
Chronic kidney disease	423 (6.4)	364 (13.3)	470 (22.4)	231 (10.8)	<.001
Antiplatelet	5 576 (83.8)	2 270 (82.7)	1 732 (82.4)	1 796 (83.8)	.30
Statin	5 472 (82.3)	2 292 (83.5)	1 684 (80.1)	1 778 (82.9)	.017
Smoking status					<.001
Current smoker	2 551 (38.4)	843 (30.7)	592 (28.2)	730 (34.0)	
Ex smoker	3 521 (52.9)	1 582 (57.6)	1 233 (58.7)	1 178 (54.9)	
Never smoked	578 (8.7)	320 (11.7)	277 (13.2)	236 (11.0)	
ASA grade					<.001
1–2	1 493 (22.5)	369 (13.4)	182 (8.7)	512 (23.9)	
3	4 858 (73.1)	2 120 (77.2)	1 584 (75.4)	1 449 (67.6)	
4–5	299 (4.5)	256 (9.3)	336 (16.0)	183 (8.5)	
Indication for surgery					<.001
Fontaine I/II	2 163 (32.5)	492 (17.9)	243 (11.6)	540 (25.2)	
Fontaine III/IV	3 154 (47.4)	1 719 (62.6)	1 503 (71.5)	1 156 (53.9)	
Acute limb ischaemia	750 (11.3)	363 (13.2)	265 (12.6)	297 (13.9)	
Aneurysm	583 (8.8)	171 (6.2)	91 (4.3)	151 (7.0)	
Mode of admission					<.001
Elective	4 820 (72.5)	1 562 (56.9)	878 (41.8)	1 343 (62.6)	
Non-elective	1 830 (27.5)	1 183 (43.1)	1 224 (58.2)	801 (37.4)	
Level of intervention					<.001
Iliofemoral	3 312 (49.8)	1 285 (46.8)	943 (44.9)	930 (43.4)	
Popliteal	2 303 (34.6)	872 (31.8)	671 (31.9)	843 (39.3)	
Crural	1 035 (15.6)	588 (21.4)	488 (23.2)	371 (17.3)	

Data are presented as median (interquartile range) and as n (%). ASA = American Society of Anaesthesiologists.

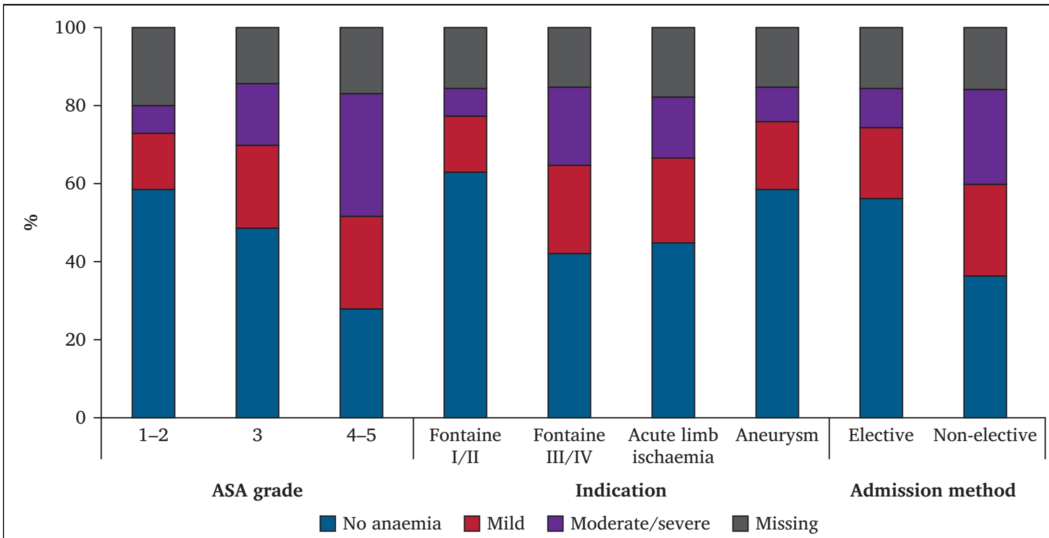

Figure 1. Association between anaemia severity and patient factors for 13 641 patients who underwent an index surgical lower limb revascularisation between January 2016 and December 2019. ASA = American Society of Anaesthesiologists.

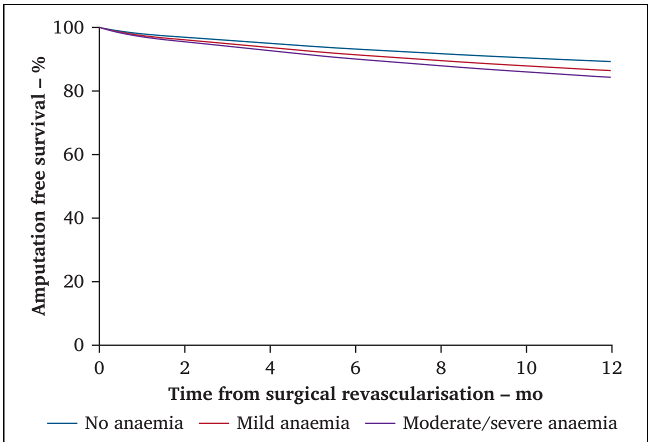

Figure 2. Adjusted amputation free survival by pre-operative anaemia severity for a typical patient (70 year old man, with American Society of Anaesthesiologists 3, white cell count 9×10^3/uL, sodium 138 mmol/L, creatinine 79 μmol/L, without diabetes, chronic lung disease, ischaemic heart disease, or chronic heart failure, on antiplatelet medication, admitted electively with Fontaine III/IV, and undergoing iliofemoral intervention).

amputation at one year (19.3%) resulting from the observed prevalence of anaemia in this population, and the rate in a fictional population in which no patient had pre-operative anaemia (16.8%).

Re-admissions

Two thirds of the patients had subsequent re-admissions to hospital after the index revascularisation during a one year follow up period (n = 8 986, 65.9%). Overall, 23.6% of patients (n = 3 215) had one re-admission, 16.0% (n = 2 178) had two, 10.2% (n = 1 393) had three, and the rest (n = 2 200, 16.1%) had four or more re-admissions. Patients with pre-operative anaemia experienced more re-admissions over the one year after the index surgical revascularisation, with the adjusted incidence rate ratio (IRR) for mild anaemia and moderate or severe anaemia being 1.20 (95% CI 1.16 – 1.25) and 1.31 (1.26 – 1.37), respectively (Fig. 4). Lower haemoglobin levels were also associated with a higher incidence of re-admissions (adjusted IRR per unit increase in Hb [g/dL] 0.94; 95% CI 0.93 – 0.95; $p <$ .001) (Supplementary Table S5).

Thirty day re-interventions

The overall 30 day re-intervention rate was 9.6%. Patients with moderate or severe anaemia had higher odds of 30 day surgical and endovascular re-interventions (with curative revascularisation intent), compared with patients with no anaemia (adjusted OR 1.22; 95% CI 1.04 – 1.45), after adjusting for age, gender, diabetes, chronic heart failure, method of admission, ASA grade, indication for surgery, and level of intervention (Fig. 5). This effect was not observed for patients with mild anaemia (adjusted OR 1.04; 95% CI 0.89 – 1.21) (Supplementary Table S6).

Thirty day major amputation and mortality rates

The overall 30 day mortality rate was 2.60% and the 30 day ipsilateral major amputation rate was 3.39%. Moderate or severe pre-operative anaemia was associated with higher odds of 30 day ipsilateral major amputation (adjusted OR 1.53; 95% CI 1.17 – 2.01) and higher odds of 30 day death (adjusted OR 1.39; 95% CI 1.03 – 1.88) (Fig. 6). Increased haemoglobin levels (in g/dL) were associated with statistically significantly lower odds of 30 day amputation (adjusted OR 0.92; 95% CI 0.87 – 0.97) (Supplementary Table S7), and lower odds of 30 day death (adjusted OR 0.94; 95% CI 0.88 – 1.001), which did not reach statistical significance (Supplementary Table S8).

DISCUSSION

In this cohort study of 13 641 patients, it was found that the increasing severity of pre-operative anaemia was statistically significantly associated with a worse amputation free survival at one year. Mild anaemia was associated with a nearly 30%, and moderate or severe anaemia with a 50% greater risk of amputation or death. It is estimated that, within a patient population with this pattern of anaemia, being able to correct anaemia in all patients would produce an absolute reduction of 2.5% in the rate of one year amputation and death. Patients with mild and moderate or severe pre-operative anaemia also experienced more re-admissions in the year following surgical revascularisation compared with patients without anaemia. This finding is pertinent not least because the cost associated with an average non-elective admission in the UK is in the order of £1,600,[23] but also the associated detrimental impact of higher number of re-admissions on patient outcomes.[24]

Although anaemia as a potential predictor for adverse outcomes has been observed in other studies of surgical practice,[11,12] there has not yet been a study of this scale on patients with PAD with one year post-operative outcomes. The findings regarding amputation free survival, re-admissions, and re-interventions are unique and of relevance to healthcare systems and patients alike.

There are some hypotheses regarding the type of pre-operative anaemia that vascular patients with PAD experience. Typically, the cause of anaemia is predominantly iron deficiency. This can be absolute, due to reduced intake or excess loss, or functional, secondary to inflammation leading to impaired iron mobilisation, which if sustained leads to anaemia of chronic disease. Functional iron deficiency anaemia is common in patients with CLTI, due to inflammation of the disease process itself and is compounded by patient comorbidities.

The effects of iron deficiency are widespread. Although iron is needed for haemoglobin, it is also an essential component of the cytochromes in the mitochondrial respiratory chain needed to metabolise oxygen and glucose to generate energy (ATP) through aerobic metabolism.[25] Iron deficiency leads to reduced muscle function,[26] a key contributor to sarcopenia – the loss of skeletal muscle mass and strength with advancing age that is an aetiological

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Indication	Age	Elective procedure: No anaemia	Elective procedure: Mild anaemia	Elective procedure: Moderate/ severe anaemia	Non-elective procedure: No anaemia	Non-elective procedure: Mild anaemia	Non-elective procedure: Moderate/ severe anaemia
Fontaine I/II	50	96.1%	94.9%	93.8%	92.7%	90.7%	88.8%
	60	95.1%	93.7%	92.4%	91.1%	88.6%	86.4%
	70	94.0%	92.2%	90.7%	89.0%	86.1%	83.5%
	80	92.6%	90.5%	88.6%	86.6%	83.2%	80.2%
Fontaine III/IV	50	90.9%	88.4%	86.2%	84.0%	80.0%	76.6%
	60	88.9%	85.9%	83.3%	80.7%	76.1%	72.3%
	70	86.5%	83.0%	80.0%	76.9%	71.8%	67.6%
	80	83.6%	79.6%	76.1%	72.7%	67.0%	62.5%
Acute limb ischaemia	50	90.5%	87.9%	85.6%	83.2%	79.1%	75.6%
	60	88.4%	85.2%	82.6%	79.8%	75.1%	71.2%
	70	85.8%	82.2%	79.1%	76.0%	70.6%	66.4%
	80	82.9%	78.6%	75.1%	71.6%	65.8%	61.2%
Aneurysm	50	95.8%	94.6%	93.5%	92.3%	90.1%	88.2%
	60	94.8%	93.3%	91.9%	90.5%	87.9%	85.6%
	70	93.6%	91.7%	90.1%	88.4%	85.3%	82.6%
	80	92.1%	89.9%	87.9%	85.9%	82.2%	79.1%

Figure 3. Estimated one year amputation free survival for specific age, admission method, indication for surgery and anaemia severity, with other covariables fixed at their mean.

component of the physical frailty syndrome. The present authors have previously shown sarcopenia to be independently associated with adverse outcomes in patients with CLTI, with sarcopenic patients having worse survival (HR 4.8; 95% CI 1.5 − 15.8) and a higher rate of limb loss (50% *vs.* 23%, $p = .050$).[27] Therefore, correction of iron deficiency anaemia in the pre-operative period may be of benefit to patients through these physiological mechanisms.

The novel findings in this study are pertinent given the recent focus of the NHS on improving outcomes for patients with CLTI,[10] as well as its position high in the research agenda for patients and clinicians.[9] Even though additional factors associated with worse one year amputation free survival were identified in this study, such as the presence of diabetes and the severity of PAD, anaemia is a potentially modifiable factor for this patient group. The present results lead to hypotheses about how the optimisation of haemoglobin for patients with PAD may have a positive effect on patient outcomes. Interventions to correct anaemia include oral and intravenous iron supplementation, erythropoietin, oral hypoxia inducible factor prolyl hydroxylase (PHD) inhibitors, and blood transfusion. To date, trials of such interventions have not reported consistent clinical benefits,[28−33] but the evidence on the effectiveness of these treatments has various limitations and there is a need for further research in this area, particularly on physical performance metrics. Additionally, implementation of these interventions requires a holistic approach to the patient by vascular surgeons to recognise pre-operative anaemia, as well as knowledge on how to treat it.

The key strengths of this study include the large sample size and the availability of long term outcomes, through linkage of a clinical database with a national administrative dataset. Additionally, robust statistical methods were used to examine the effect of anaemia on both the short and long term patient outcomes, and which adjusted for relevant patient and admission factors.

This study also has limitations. Although the clinical registry provides a large scale representation of real world practice for PAD, it contained some implausible values (potentially due to data entry errors) and missing data. Additionally, the data on patient outcomes were derived from the HES administrative dataset. Outcomes like readmission rates and death are generally well recorded, but amputation rates may be affected by incomplete coding or coding errors. However, major procedures like amputation are typically well coded and so any underestimation is likely to be small. There is also no reason to believe that these errors would disproportionally affect patients with anaemia.

Conclusion

This analysis of population based data found that pre-operative anaemia affected a statistically significant

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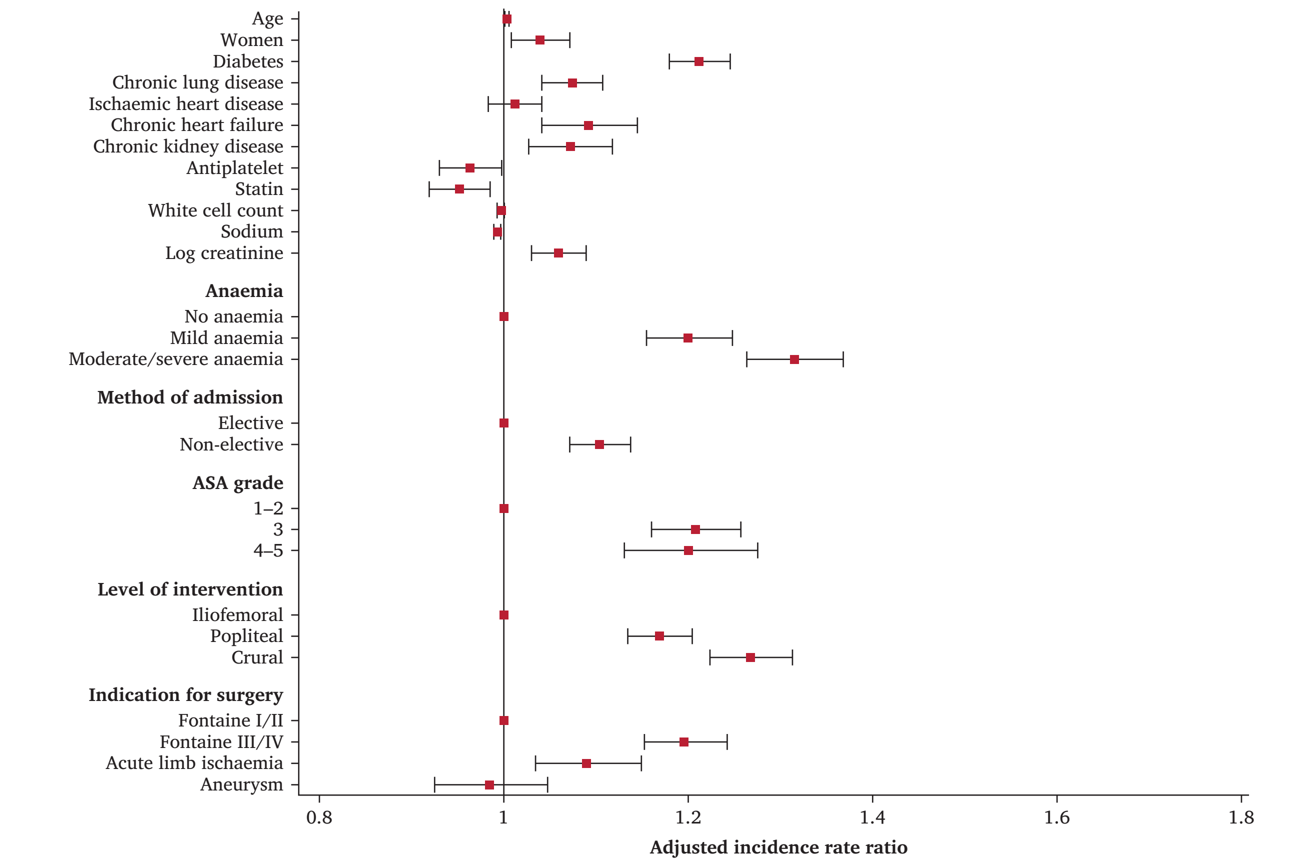

Figure 4. Coefficients plot depicting the effect of severity of anaemia (adjusted incidence rate ratio and 95% confidence intervals) on one year re-admissions, adjusting for patient and admission factors. ASA = American Society of Anaesthesiologists.

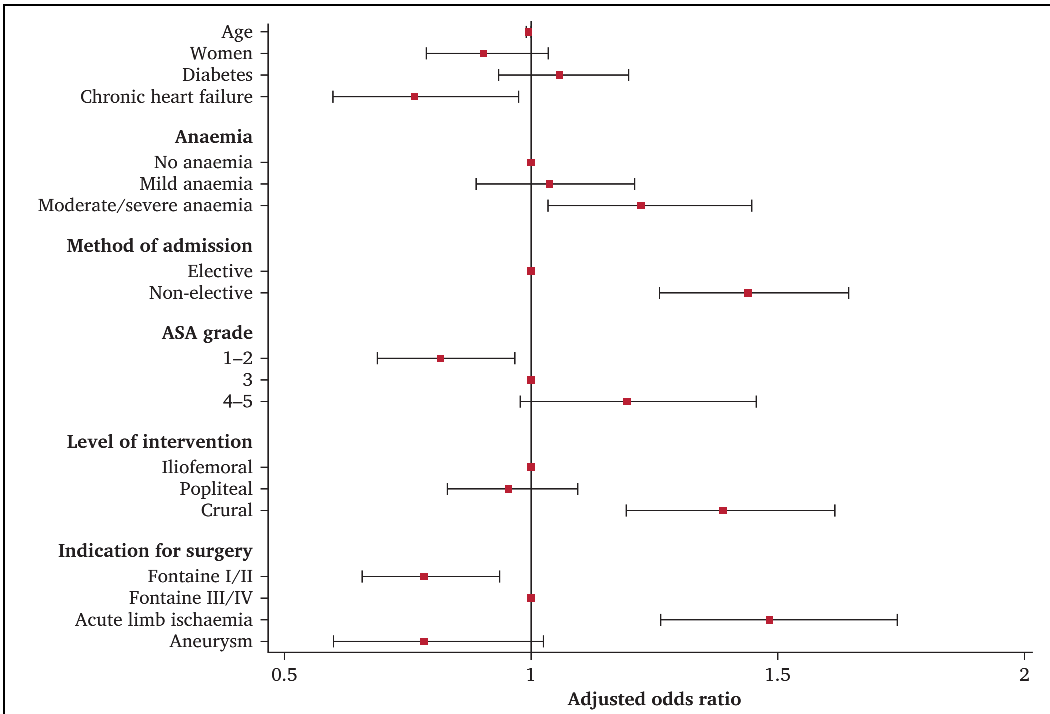

Figure 5. Coefficients plot depicting effect of anaemia severity (adjusted odds ratio and 95% confidence intervals) on 30 day re-interventions, adjusting for various patient and admission factors using multivariable logistic regression models. ASA = American Society of Anaesthesiologists.

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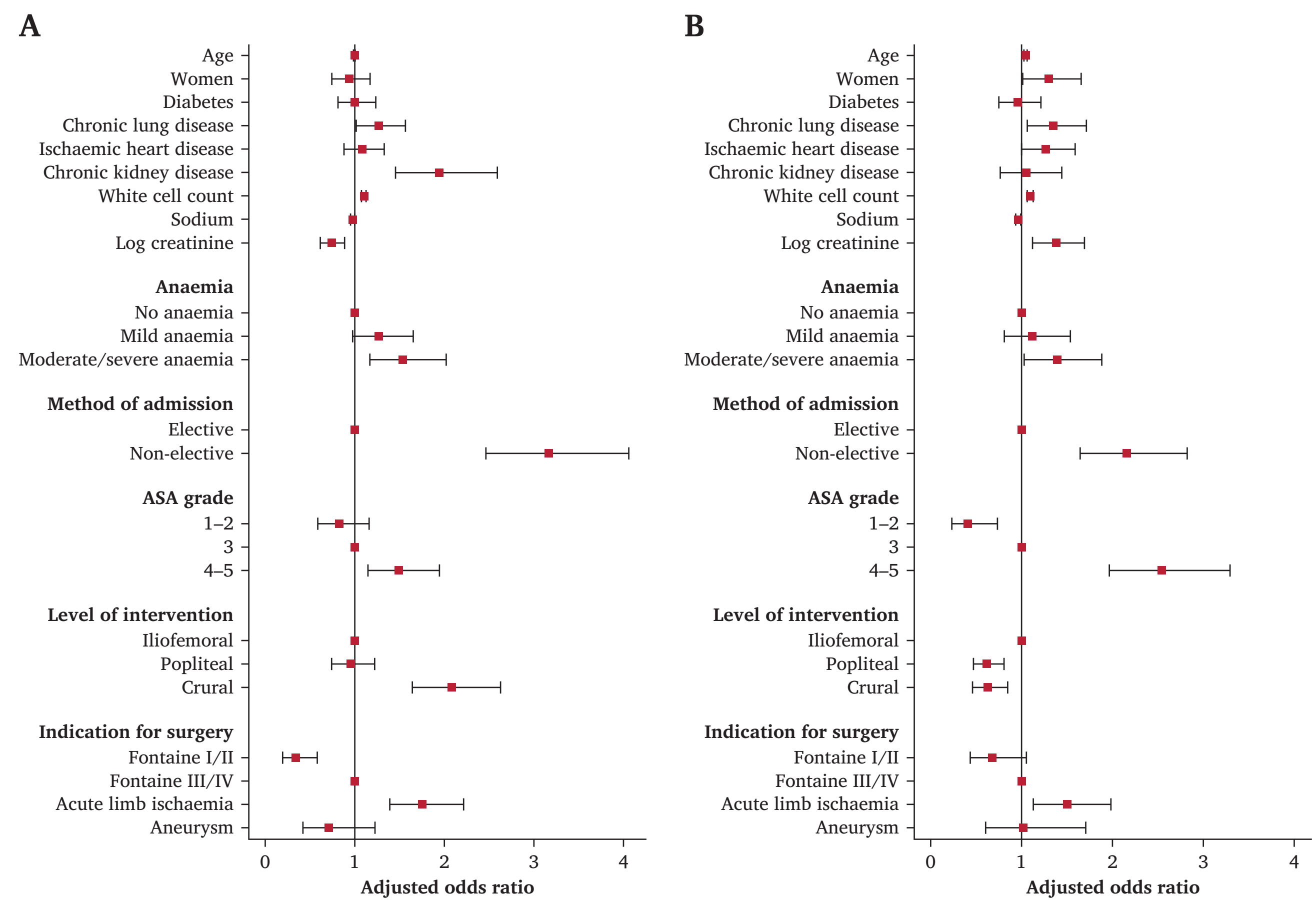

Figure 6. Coefficients plot depicting effect of anaemia severity (adjusted odds ratio and 95% confidence intervals) on (A) 30 day ipsilateral major amputation and (B) 30 day mortality. ASA = American Society of Anaesthesiologists.

proportion of patients with PAD who had surgical revascularisation. The study identified that increasing severity of anaemia was associated with lower one year amputation free survival and higher re-admission rates at one year. Further research is required to examine whether interventions aiming to correct anaemia can improve postoperative patient outcomes.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2023.05.003

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REFERENCES

1 Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. *Br J Surg* 2015;**102**:1314–24.

2 Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* 2011;**378**:1396–407.

3 National Clinical Guideline Centre. NICE guideline NG24: Blood transfusion. NICE; 2015. Report No.: NG24. Available at: https://www.nice.org.uk/guidance/ng24 [Accessed 21 June 2022].

4 Kotzé A, Harris A, Baker C, Iqbal T, Lavies N, Richards T, et al. British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia. *Br J Haematol* 2015;**171**:322–31.

5 Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* 2017;**72**:233–47.

6 American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology* 2015;**122**:241–75.

7 Nandhra S, Chau M, Klein AA, Yeates JA, Collier T, Evans C, et al. Preoperative anaemia management in patients undergoing vascular surgery. *Br J Surg* 2020;**107**:1558–61.

8 Waton S, Johal A, Birmpili P, Li Q, Cromwell D, O'Neill R, et al. National Vascular Registry: 2021 Annual Report. London: The Royal College of Surgeons of England; 2021 Nov. Available at: https://www.vsqip.org.uk/reports/2021-annual-report/ [Accessed 21 June 2022].

9 Pymer S, Harwood A, Long J, Chetter I, Saratzis A, Coughlin P, et al. Research priorities for patients with peripheral arterial disease: a James Lind Alliance Priority Setting Partnership. *J Vasc Soc G B Irel* 2022;**1**:23–9.

10 NHS England and NHS Improvement. Commissioning for Quality and Innovation (CQUIN) 2022/23 Annex: Indicator specifications [Internet]. 2022 Jan. Available at: https://www.england.nhs.uk/publication/combined-ccg-icb-and-pss-commissioning-for-quality-and-innovation-cquin-indicator-specification/ [Accessed 21 June 2022].

11 Theuma F, Nickinson ATO, Cullen S, Patel B, Dubkova S, Davies RSM, et al. The impact of anemia on one-year amputation-free survival in patients undergoing revascularization for chronic limb-threatening ischemia: a retrospective cohort study. *Ann Vasc Surg* 2022;**79**:201–7.

12 Nandhra S, Boylan L, Prentis J, Nesbitt C, Northern Vascular Centre. The influence of preoperative anemia on clinical outcomes after infrainguinal bypass surgery. *Ann Vasc Surg* 2020;**66**:586–94.

13 Bodewes TCF, Pothof AB, Darling JD, Deery SE, Jones DW, Soden PA, et al. Preoperative anemia associated with adverse outcomes after infrainguinal bypass surgery in patients with chronic limb-threatening ischemia. *J Vasc Surg* 2017;**66**:1775–85.e2.

14 Velescu A, Clará A, Cladellas M, Peñafiel J, Mateos E, Ibañez S, et al. Anemia increases mortality after open or endovascular treatment in patients with critical limb ischemia: a retrospective analysis. *Eur J Vasc Endovasc Surg* 2016;**51**:543–9.

15 Dunkelgrun M, Hoeks SE, Welten GMJM, Vidakovic R, Winkel TA, Schouten O, et al. Anemia as an independent predictor of perioperative and long-term cardiovascular outcome in patients scheduled for elective vascular surgery. *Am J Cardiol* 2008;**101**:1196–200.

16 Healthcare Quality Improvement Partnership (HQIP). National Vascular Registry (NVR). Available at: https://www.hqip.org.uk/a-z-of-nca/national-vascular-registry [Accessed 21 June 2022].

17 Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017;**46**:1093–1093i.

18 World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2011. Report No.: WHO/NMH/NHD/MNM/11.1. Available at: https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf [Accessed 21 June 2022].

19 NHS Digital. National Clinical Coding Standards OPCS-4.8 Reference Book. Leeds: NHS Digital; 2017.

20 Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;**338**:b2393–b2393.

21 Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *Stata J* 2009;**9**:265–90.

22 Newson RB. Attributable and unattributable risks and fractions and other scenario comparisons. *Stata J* 2013;**13**:672–98.

23 Brookes MJ, Farr A, Phillips CJ, Trudgill NJ. Management of iron deficiency anaemia in secondary care across England between 2012 and 2018: a real-world analysis of hospital episode statistics. *Frontline Gastroenterol* 2021;**12**:363–9.

24 Fluck D, Murray P, Robin J, Fry CH, Han TS. Early emergency readmission frequency as an indicator of short-, medium- and long-term mortality post-discharge from hospital. *Intern Emerg Med* 2021;**16**:1497–505.

25 van der Meer P, van der Wal HH, Melenovsky V. Mitochondrial function, skeletal muscle metabolism, and iron deficiency in heart failure. *Circulation* 2019;**139**:2399–402.

26 Frise MC, Holdsworth DA, Johnson AW, Chung YJ, Curtis MK, Cox PJ, et al. Abnormal whole-body energy metabolism in iron-deficient humans despite preserved skeletal muscle oxidative phosphorylation. *Sci Rep* 2022;**12**:998.

27 Sivaharan A, Boylan L, Witham MD, Nandhra S, Northern Vascular Centre. Sarcopenia in patients undergoing lower limb bypass surgery is associated with higher mortality and major amputation rates. *Ann Vasc Surg* 2021;**75**:227–36.

28 Ng O, Keeler BD, Mishra A, Simpson JA, Neal K, Al-Hassi HO, et al. Iron therapy for preoperative anaemia. *Cochrane Database Syst Rev* 2019;**12**:CD011588.

29 Scrimshire AB, Booth A, Fairhurst C, Kotze A, Reed M, McDaid C. Preoperative iron treatment in anaemic patients undergoing elective total hip or knee arthroplasty: a systematic review and meta-analysis. *BMJ Open* 2020;**10**:e036592.

30 Richards T, Baikady RR, Clevenger B, Butcher A, Abeysiri S, Chau M, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. *Lancet* 2020;**396**:1353–61.

31 Kaufner L, von Heymann C, Henkelmann A, Pace NL, Weibel S, Kranke P, et al. Erythropoietin plus iron versus control treatment including placebo or iron for preoperative anaemic adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev* 2020;**8**:CD012451.

32 Chertow GM, Pergola PE, Farag YMK, Agarwal R, Arnold S, Bako G, et al, PRO2TECT Study Group. Vadadustat in patients with anemia and non-dialysis-dependent CKD. *N Engl J Med* 2021;**384**:1589–600.

33 Singh AK, Carroll K, McMurray JJV, Solomon S, Jha V, Johansen KL, et al, ASCEND-ND Study Group. Daprodustat for the treatment of anemia in patients not undergoing dialysis. *N Engl J Med* 2021;**385**:2313–24.

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