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Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients

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Editor's key points

- Anaemia is now recognized as an important and modifiable risk factor for surgery.
- This study confirms the strong relationship between anaemia and both mortality and greater resource use after surgery.
- The independent risks of anaemia and the consequential greater use of red cell transfusion require further study.
- Whether or not correction of anaemia can improve patient outcome requires a definitive large trial.

Background. Retrospective studies suggest that preoperative anaemia is associated with poor outcomes after surgery. The objective of this study was to describe mortality rates and patterns of intensive care resource use for patients with anaemia undergoing non-cardiac and non-neurological in-patient surgery.

Methods. We performed a secondary analysis of a large prospective study describing perioperative care and survival in 28 European nations. Patients at least 16 yr old undergoing in-patient surgery during a 7 day period were included in the study. Data were collected for in-hospital mortality, duration of hospital stay, admission to intensive care, and intensive care resource use. Multivariable logistic regression analysis was performed to understand the effects of preoperative haemoglobin (Hb) levels on in-hospital mortality.

Results. We included 39 309 patients in the analysis. Preoperative anaemia had a high prevalence in both men and women (31.1% and 26.5%, respectively). Multivariate analysis showed that patients with severe [odds ratio 2.82 (95% confidence interval 2.06–3.85)] or moderate [1.99 (1.67–2.37)] anaemia had higher in-hospital mortality than those with normal preoperative Hb concentrations. Furthermore, hospital length of stay ($P<0.001$) and postoperative admission to intensive care ($P<0.001$) were greater in patients with anaemia than in those with normal Hb concentrations.

Conclusions. Anaemia is common among non-cardiac and non-neurological surgical patients, and is associated with poor clinical outcome and increased healthcare resource use.

Clinical trial registration. NCT01203605 (ClinicalTrials.gov).

Keywords: anaemia; assessment, outcome; care, intensive; epidemiologic studies, cohort studies; mortality determinants

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Abnormal preoperative haemoglobin (Hb) concentrations are associated with increased perioperative morbidity and mortality in patients undergoing cardiac[1–4] and non-cardiac surgery.[5–10] Anaemia has a particularly high prevalence, and growing evidence suggests that red blood cell transfusions used to treat anaemia contribute to increased perioperative morbidity and mortality.[1 11–15] Additionally, acute treatment of anaemia with red blood cell transfusion results in increased cost when compared with preoperative elevation of Hb concentration with iron or erythropoietin substitution.[16–18] Several large-scale retrospective studies have reported that preoperative anaemia is associated with an increased risk of 30 day postoperative mortality.[6 8 10] These results indicate that preoperative anaemia is a risk factor for poor perioperative outcome.

Until now, little or no data are available describing duration of in-hospital stay and postoperative resource use in a large cohort of unselected surgical patients. The objective of the European Surgical Outcomes Study (EuSOS) was to describe mortality rates and patterns of intensive care resource use for patients undergoing non-cardiac and non-neurological surgery across several European nations.[19] In this secondary analysis of the EuSOS data set, we assessed whether patients with abnormal preoperative Hb concentrations had greater in-hospital mortality, a longer duration of in-hospital stay, or were more frequently admitted to intensive care units (ICUs) than those with normal preoperative Hb concentrations. Furthermore, we analysed whether these patients required more frequent use of non-invasive ventilation (NIV) or mechanical ventilation (MV), and more frequent use of inotropes or vasopressors within the first 24 h after surgery.

Methods

Settings

Data acquisition for this European cohort study was conducted between 09:00 a.m. (local time) on April 4, 2011, and 08:59 a.m. on April 11, 2011. All adult patients older than 16 yr admitted to participating centres for elective or non-elective in-patient surgery starting during the 7 day cohort period were eligible for inclusion. Patients undergoing planned day-case surgery, cardiac surgery, neurosurgery, radiological, or obstetric procedures were excluded. Study design and procedures have been described previously,[19] and can be accessed via eusos.esicm.org. Patient characteristics and comorbidities, the surgical category and site, and the anaesthetic technique and selected preoperative lab results were recorded with paper case report forms, and entered onto a secure Internet-based case report form (OpenClinica, Boston, MA, USA) in anonymous fashion. Furthermore, the urgency and severity of surgery (elective: not immediately life saving, planned within months or weeks; urgent: planned surgery within hours or days of the decision to operate; emergency: as soon as possible, no delay to plan care, ideally within 24 h) were recorded in the case report form. Patients were followed up until hospital discharge or death for a maximum of 60 days after surgery.

Approval was obtained from each local and national ethics committees. Centres in Denmark were exempt from ethics approval because this study was deemed to be a clinical audit. In Finland, written informed consent had to be obtained from individual patients. The study is registered with ClinicalTrials.gov, number NCT01203605.

Definitions

The preoperative Hb concentration was defined as the last Hb value measured before surgery, with all Hb measurements obtained within 28 days before surgery. Anaemia and its subclassifications were defined according to WHO criteria.[20] Detailed reference values for anaemia are listed in Supplementary Table S1. The primary outcome measure of the study was in-hospital mortality. In this analysis, we also evaluated the duration of in-hospital stay and admission to ICUs. Furthermore, predefined parameters of intensive care resource use, such as initiation of NIV or MV and use of inotropes or vasopressors within 24 h of surgery, and insertion of central venous catheters and use of cardiac output monitoring were assessed.

Statistical analysis

Statistical analysis was performed with SAS (version 9.2) and R (version 2.13.0). Binary logistic regression models were constructed to assess the association of preoperative Hb concentrations (as defined in Supplementary Table S1) with in-hospital mortality. Factors with a significant relation to outcome in the univariate analysis ($P<0.05$) were entered as co-variables into a generalized estimating equation regression model, accounting for clustering within sites. Patients with missing values in one of the co-variables were excluded from analysis. Results are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs) compared with patients with normal Hb concentrations. To account for multiple testing, an adjusted two-sided significance level of $0.05/4=0.0125$ was applied. Furthermore, a multiple imputation analysis was performed to assess the impact of patients with missing Hb concentrations. Missing Hb concentrations were imputed based on the variables used in the regression model. Only patients with missing values in any other co-variable were excluded from analysis.

In order to illustrate the influence of preoperative Hb concentrations on mortality, a logistic regression function was estimated between predefined Hb concentrations. The functions between the predefined Hb concentrations, also known as splines, were used to model mortality over the range of Hb concentrations. The prediction of mortality from very low or high Hb concentrations is not reliable due to the very low number of patients at these concentrations. Thus, patients with Hb values from the lowest and highest 0.25% were not included in the analysis.

Comparisons for binary secondary outcome variables were performed by the χ^2 tests at a multiplicity-adjusted two-sided significance level of $0.05/2=0.025$. The length of stay for different Hb categories was compared by a Fine and Gray competing risk model[21] for the events discharge and death.

Results

After quality control of the data, we enrolled 46 539 patients in the study. To account for possible problems with data collection, patients from centres which enrolled 10 patients or fewer (206 patients) and those with a reported mortality $<$5th percentile or $>$95th percentile (738 patients) were excluded from the analysis. Furthermore, 6286 patients were excluded from the analysis due to missing values (6251 patients missing Hb values, 20 patients missing in-hospital mortality, 10 patients missing urgency of surgery, and five patients missing sex). Primary and secondary endpoints were separately evaluated for these patients. In-hospital mortality and intensive care resource use were lower in patients with missing Hb values compared with the 39 309 patients included in the analysis ($P<0.001$). A detailed characterization of the cohort is listed in Supplementary Table S2.

Prevalence of preoperative anaemia

Patients with preoperative anaemia accounted for 11 295 (28.7%) of the study population, of whom 7231 (18.4%)

presented with mild anaemia, 3427 (8.7%) with moderate anaemia, and 637 (1.6%) with severe anaemia. Preoperative anaemia was present in 5922 (31.1%) male and in 5373 (26.5%) female patients.

In-hospital mortality

In order to assess in-hospital mortality, univariate and multivariate analyses were performed. Results of the univariate analysis are listed in Table 1. Based on these data, a regression model with Hb concentration as the independent variable was computed. The model included all co-variables significant in the univariate analysis to adjust for age, sex, grade and urgency of surgery, ASA classification, surgical speciality, co-morbidities, and country.

In the univariate analyses, all three forms of anaemia were associated with an increased risk of in-hospital mortality when compared with normal preoperative Hb concentrations (Table 1). After adjusting for multiple testing, the severe [OR 2.82 (95% CI 2.06–3.85)] and moderate [1.99 (1.67–2.37)] form of anaemia remained significant. The results of the multivariate analysis were confirmed by a multiple imputation analysis, which incorporated patients with missing values (Table 1). Despite having lower in-hospital mortality, inclusion of data from patients with missing values did not change the results of the multiple imputation analysis significantly.

To illustrate the association of mortality with preoperative Hb concentrations, a logistic regression model including Hb concentration as quantitative variable was estimated (Fig. 1). In-hospital mortality was lowest at normal preoperative Hb concentrations, and increased continuously with lower Hb concentrations.

Preoperative anaemia increases length of stay in surgical patients

Patients with low preoperative Hb concentrations were discharged from the hospital later than those with normal preoperative Hb concentrations ($P<0.001$, Fig. 2). Hospital length of stay was greatest in patients suffering from severe and moderate preoperative anaemia, and was even prolonged in patients with mild preoperative anaemia when compared with those with normal preoperative Hb concentrations ($P<0.001$).

Admission to ICUs

Patients suffering from preoperative anaemia were more frequently admitted to ICUs compared with those with normal preoperative Hb concentrations (Table 2). Postoperative admission to ICUs was greatest in patients with severe anaemia. Men were more frequently admitted to ICUs than women, irrespective of the preoperative Hb concentration (data not shown).

Intensive care resource use

NIV and MV were more often initiated within 24 h after surgery in patients with anaemia ($P<0.001$) than in those with normal preoperative Hb concentrations ($P<0.001$, Table 2). Similarly, therapy with inotropes or vasopressors was initiated more often in patients with anaemia within 24 h after surgery when compared with those with normal preoperative Hb concentrations ($P<0.001$). Placement of central venous catheters and monitoring of cardiac output was performed more often in patients with anaemia ($P<0.001$) when compared with those with normal preoperative Hb concentrations.

Discussion

In the current study, we report a high prevalence of anaemia in non-cardiac and non-neurological surgical patients. Patients with severe and moderate preoperative anaemia had greater in-hospital mortality when compared with those with normal preoperative Hb concentrations. Furthermore, anaemic patients were more often admitted to ICUs after surgery and required greater use of intensive care resources.

Several retrospective studies have reported increased preoperative mortality in non-cardiac patients with abnormal preoperative Hb concentrations. In a retrospective cohort analysis, Wu and colleagues[6] evaluated data from more than 300 000 mostly male patients older than 65 yr undergoing major non-cardiac surgery. The authors reported that both preoperative anaemia and polycythaemia were associated with an increased risk of 30 day postoperative mortality and cardiac events in these patients. In another large-scale retrospective cohort study, Musallam and colleagues[8] analysed data from more than 200 000 patients undergoing major non-cardiac surgery. Their results indicate that preoperative anaemia is independently associated with an increased risk of 30 day morbidity and mortality in these patients. Neither age nor gender altered the negative outcomes associated with preoperative anaemia. In agreement with the data published by Musallam and colleagues, we report that in-hospital mortality was greater in anaemic patients when compared with patients with normal preoperative Hb concentrations, and increased with the severity of anaemia.

In a retrospective analysis of more than 500 000 patients, Saager and colleagues[10] found anaemia to be associated with increased 30 day mortality. After adjusting for baseline diseases, however, anaemia remained a rather weak independent predictor of postoperative mortality. Preoperative anaemia is commonly associated with comorbidities such as coronary heart disease, diabetes mellitus, or cirrhosis. These diseases are *per se* associated with increased mortality, and could potentially confound the results. Furthermore, the grade and urgency of surgery are possible confounding factors, with emergency surgeries having the highest mortality (Table 1). To limit the influence of possible confounders, factors with a significant relation to outcome in the univariate analysis were entered into a multivariate regression model. After adjusting for co-morbidities and severity of the surgery, the OR for moderate anaemia was 1.99 (95% CI 1.67–2.37), indicating that these patients had a higher likelihood of in-hospital mortality than patients with normal preoperative Hb concentrations. Severe anaemia was associated with an even greater likelihood of in-hospital mortality [OR 2.82 (95% CI 2.06–3.85)]. Thus, in our study, both moderate and severe anaemia are strong

Table 1 Influence of preoperative Hb concentration and confounding factors on in-hospital mortality. COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; Hb, haemoglobin; (N)IDDM, (non)insulin-dependent diabetes mellitus

	Univariate analysis			Multivariate analysis			Multiple imputation of missing values		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.02	1.02–1.03	<0.001	1.01	1–1.02	0.19	1.01	1–1.02	0.04
Male gender	1.13	1.01–1.26	0.03	0.93	0.81–1.06	0.29	0.95	0.83–1.08	0.42
Preoperative Hb concentration									
Normal	Reference								
Severe anaemia	5.64	4.35–7.30	<0.001	2.82	2.06–3.85	<0.001	2.74	2.01–3.74	<0.001
Moderate anaemia	4.15	3.59–4.79	<0.001	1.99	1.67–2.37	<0.001	1.97	1.66–2.35	<0.001
Mild anaemia	1.82	1.58–2.10	<0.001	1.20	1.01–1.42	0.04	1.20	1.02–1.41	0.03
Polycythaemia	0.78	0.42–1.47	0.45	0.66	0.33–1.33	0.25	0.68	0.37–1.24	0.21
Grade of surgery									
Minor	Reference								
Intermediate	0.91	0.78–1.06	0.22	0.84	0.71–1	0.05	0.84	0.71–0.98	0.03
Major	1.87	1.61–2.18	<0.001	1.31	1.08–1.58	0.006	1.26	1.06–1.5	0.008
Urgency of surgery									
Elective	Reference								
Urgent	2.17	1.91–2.47	<0.001	1.65	1.4–1.92	<0.001	1.65	1.42–1.92	<0.001
Emergency	4.46	3.81–5.24	<0.001	2.73	2.22–3.35	<0.001	2.80	2.3–3.42	<0.001
ASA classification									
I	Reference								
II	0.92	0.77–1.10	0.37	0.89	0.47–1.69	0.72	1.00	0.55–1.81	1.0
III	1.94	1.63–2.31	<0.001	0.34	0.16–0.74	0.006	0.40	0.19–0.81	0.01
IV	9.87	8.11–12.01	<0.001	1.49	0.63–3.54	0.36	1.83	0.8–4.2	0.15
V	47.35	29.94–74.89	<0.001	4.75	0.59–38.03	0.14	5.41	0.75–39.24	0.09
Surgical speciality									
Orthopaedics	0.75	0.59–0.95	0.02	0.70	0.53–0.91	0.007	0.74	0.58–0.95	0.02
Breast	0.65	0.43–0.99	0.046	0.92	0.57–1.49	0.74	1.02	0.65–1.6	0.92
Gynaecology	0.63	0.46–0.86	0.004	0.86	0.53–1.39	0.53	0.97	0.62–1.53	0.91
Vascular	1.58	1.20–2.09	0.001	0.79	0.56–1.09	0.15	0.87	0.63–1.2	0.39
Upper GI	2.04	1.56–2.67	<0.001	1.45	1.06–1.98	0.02	1.56	1.16–2.11	0.004
Lower GI	1.53	1.20–1.96	0.001	1.06	0.82–1.38	0.65	1.13	0.88–1.45	0.34
Hepato-biliary	1.13	0.83–1.54	0.42	1.12	0.8–1.55	0.51	1.21	0.88–1.68	0.24
Plastic or cutaneous	0.80	0.56–1.12	0.20	0.81	0.53–1.23	0.31	0.84	0.57–1.22	0.36
Urology	0.75	0.57–0.99	0.04	0.68	0.46–0.99	0.05	0.74	0.52–1.06	0.10
Kidney	0.41	0.18–0.94	0.03	0.31	0.11–0.89	0.03	0.34	0.13–0.92	0.03
Head and neck	0.75	0.57–0.99	0.04	1.01	0.75–1.37	0.93	1.04	0.8–1.35	0.78
Other	Reference								
Laparoscopic surgery	0.64	0.52–0.78	<0.001	0.75	0.59–0.96	0.02	0.79	0.62–1	0.05
Comorbidities									
Cirrhosis	4.32	3.24–5.77	<0.001	2.12	1.56–2.87	<0.001	2.15	1.59–2.89	<0.001
Congestive heart failure	2.64	2.21–3.16	<0.001	1.04	0.83–1.32	0.71	1.02	0.82–1.28	0.84
COPD	1.37	1.17–1.61	<0.001	1.03	0.87–1.2	0.76	1.01	0.86–1.18	0.91
Coronary artery disease	1.82	1.60–2.09	<0.001	0.96	0.82–1.13	0.64	0.96	0.82–1.12	0.61
IDDM	2.02	1.65–2.47	<0.001	1.23	0.98–1.55	0.07	1.20	0.96–1.5	0.11
NIDDM	1.11	0.91–1.35	0.31						
Metastatic cancer	2.08	1.72–2.51	<0.001	1.27	1.04–1.56	0.02	1.26	1.03–1.54	0.03
Stroke	1.77	1.44–2.19	<0.001	0.94	0.75–1.18	0.59	0.95	0.77–1.18	0.67

predictors of in-hospital mortality. In contrast, the study performed by Saager and colleagues[10] does not differentiate between mild, moderate, and severe anaemia. Since mild anaemia patients in our study account for more than 60% of all anaemic patients, it is very likely that the overall effect of anaemia is similar to that reported by Saager and colleagues.

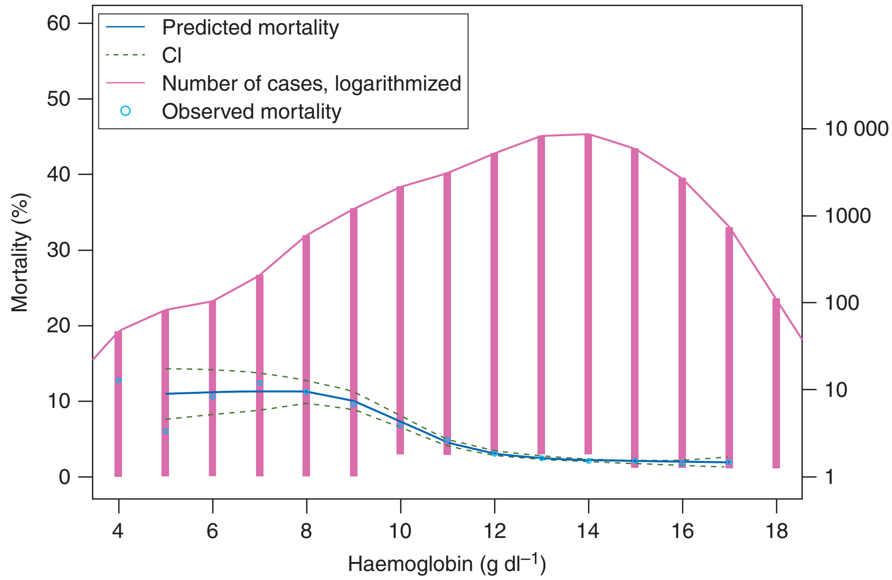

Fig 1 Predicted mortality according to preoperative Hb concentrations.

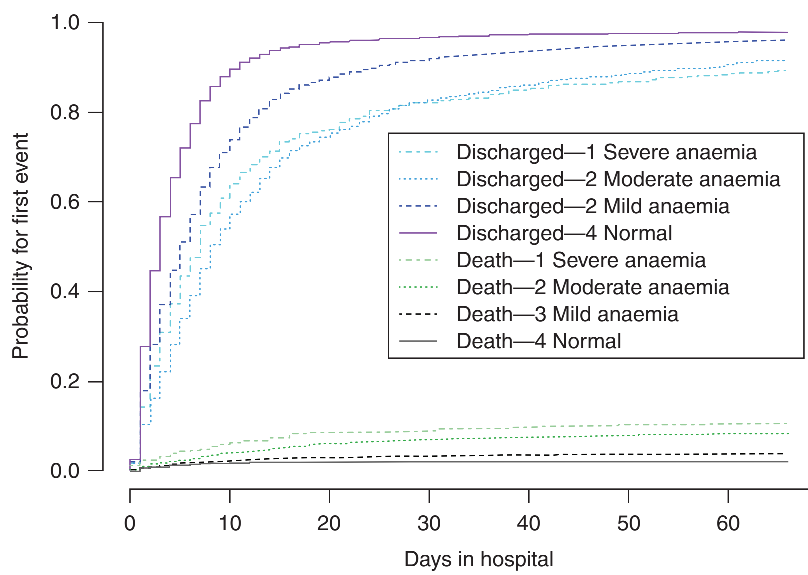

Fig 2 Cumulative incidence of hospital discharge and in-hospital death distributed among groups with different preoperative Hb concentrations.

Additionally, our results suggest that anaemia is associated with greater admission to ICUs and increased intensive care resource use. Anaemic patients required MV and inotropes more frequently compared with patients with normal preoperative Hb concentrations. Furthermore, the use of central venous catheters and cardiac output monitoring was greater in anaemic patients. However, factors other than anaemia contribute to intensive care admissions and resource use.[22–24] The use of invasive monitoring is multifactorial and probably institutionally driven. The data reported in this article suggest that anaemia is associated with increased perioperative morbidity, but factors such as regional differences in patient care and centre policies have to be considered when interpreting these data.

The prevalence of preoperative anaemia in the EuSOS cohort was similar to that reported previously (28.7% *vs* 26.3%,[6] 30.4%,[8] and 25.3%).[10] These results confirm the high prevalence of preoperative anaemia, and validate a timely

Table 2 Perioperative outcomes according to preoperative Hb concentrations. ICU, intensive care unit; MV, mechanical ventilation; NIV, non-invasive ventilation

	Severe anaemia		Moderate anaemia		Mild anaemia		Normal haemoglobin		Normal *vs* anaemia
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***P*-value**
Number of patients	637	1.6	3427	8.7	7231	18.4	27 439	69.8	
Age (yr)	60 (18)		65 (17)		63 (19)		56 (18)		
In-hospital mortality		11.3		8.6		4.0		2.2	<0.001
Admitted to ICU		25.6		22.0		11.2		5.4	<0.001
NIV within 24 h		1.1		2.2		1.4		0.7	<0.001
MV within 24 h		17.6		12.1		5.0		1.8	<0.001
Inotrope/vasopressor use		13.0		9.6		4.4		1.4	<0.001
Central venous catheter		22.1		19.7		11.5		4.5	<0.001
Cardiac output monitor		12.9		9.4		7.5		4.3	<0.001

assessment of Hb concentrations before elective procedures. However, our data do not differentiate between the varying causes of anaemia. Acute and chronic forms of anaemia have different underlying conditions, and often require targeted and specific therapeutic approaches. Recent publications have highlighted the need for improved patient blood management in anaemic patients.[17 25] Furthermore, the European Society of Anaesthesiology has recently published guidelines for the management of severe perioperative bleeding.[26] In these guidelines, the authors recommend that patients at risk of bleeding be assessed for anaemia 4–8 weeks before elective surgery.[27] They further recommend to identify the cause of anaemia, and to treat iron deficiency with either oral or i.v. iron supplementation.[28–33] If iron deficiency has been ruled out, the authors suggest treating patients with erythropoietin-stimulating agents.[29 34–36] These methods, however, are not without risk themselves, and if applied inappropriately, could increase morbidity and be as costly as transfusion of red blood cells.[37] Thus, each patient should be assessed individually in order to balance the risks and benefits of any therapy.

Significant blood loss is common during surgery, and many patients have depressed bone marrow function after surgery.[38 39] Normal or increased haematocrit might confer an advantage by reducing red blood cell transfusions, which have been shown to be independently associated with increased perioperative in-hospital mortality.[11–15] The need for blood transfusion with all its side-effects can also be regarded as a secondary effect of anaemia. In this cohort, patients with severe or moderate anaemia were probably transfused more often than those with mild or moderate anaemia. In addition, perioperative outcome could have been influenced by factors such as reduced oxygen transport capacity, reduced microcirculatory function, and impaired tissue and organ perfusion. This interaction between anaemia and mortality has to be kept in mind when interpreting data sets as complex as the one at hand.

To our knowledge, this is the first multinational prospective study evaluating the effect of abnormal preoperative Hb concentrations on in-hospital morbidity and intensive care resource use. All consecutive patients were included in the study, limiting this bias in case selection. Furthermore, prospective data acquisition minimized errors associated with data detection and reporting.

One limitation of our study is that Hb concentrations were determined within 28 days of surgery. Thus, the actual values on the day of surgery might differ from those included in the analysis. The fact that only laboratory results obtained within 28 days of surgery were included in the study may account for some missing Hb values. Moreover, recent guidelines for preoperative patient evaluation from the European Society of Anaesthesiology do not recommend lab testing (e.g. full blood count) in all patients, especially before minor or intermediate surgery.[40] Patients with missing data points in this study were significantly younger, underwent minor surgery more frequently, and exhibited lower ASA scores than those with a complete data set. Thus, missing Hb values might be a result of adherence to guidelines for perioperative patient management. Including these patients with missing Hb values to calculate the prevalence of preoperative anaemia might have slightly reduced the prevalence of anaemia reported in this study (28.7%).

In conclusion, we report that abnormal preoperative Hb concentrations are highly prevalent, and that anaemia is associated with increased in-hospital mortality and worse outcome in patients undergoing non-cardiac and non-neurological surgery. Preoperative assessment and correction of Hb concentrations to normal values might reduce mortality and reduce the intensive care resource use in these patients.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

D.M.B. assisted in the design and statistical analysis of the study, wrote the manuscript, and approved the final manuscript as submitted. H.H., M.P., and B.M. performed statistical analysis, assisted in the writing of the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. A.R., R.P.M., R.M.P., and P.M. designed the study, supervised the study, assisted in the writing of the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Declaration of interest

None declared.

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