Preoperative anaemia and clinical outcomes in the South African Surgical Outcomes Study

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Background. In high-income countries, preoperative anaemia has been associated with poor postoperative outcomes. To date, no large study has investigated this association in South Africa (SA). The demographics of SA surgical patients differ from those of surgical patients in the European and Northern American settings from which the preoperative anaemia data were derived. These associations between preoperative anaemia and postoperative outcomes are therefore not necessarily transferable to SA surgical patients.
Objectives. The primary objective was to determine the association between preoperative anaemia and in-hospital mortality in SA adult non-cardiac, non-obstetric patients. The secondary objectives were to describe the association between preoperative anaemia and (*i*) critical care admission and (*ii*) length of hospital stay, and the prevalence of preoperative anaemia in adult SA surgical patients.
Methods. We performed a secondary analysis of the South African Surgical Outcomes Study (SASOS), a large prospective observational study of patients undergoing inpatient non-cardiac, non-obstetric surgery at 50 hospitals across SA over a 1-week period. To determine whether preoperative anaemia is independently associated with mortality or admission to critical care following surgery, we conducted a multivariate logistic regression analysis that included all the independent predictors of mortality and admission to critical care identified in the original SASOS model.
Results. The prevalence of preoperative anaemia was 1 727/3 610 (47.8%). Preoperative anaemia was independently associated with in-hospital mortality (odds ratio (OR) 1.657, 95% confidence interval (CI) 1.055 - 2.602; p=0.028) and admission to critical care (OR 1.487, 95% CI 1.081 - 2.046; p=0.015).
Conclusions. Almost 50% of patients undergoing surgery at government-funded hospitals in SA had preoperative anaemia, which was independently associated with postoperative mortality and critical care admission. These numbers indicate a significant perioperative risk, with a clear need for quality improvement programmes that may improve surgical outcomes. Long waiting lists for elective surgery allow time for assessment and correction of anaemia preoperatively. With a high proportion of patients presenting for urgent or emergency surgery, perioperative clinicians in all specialties should educate themselves in the principles of patient blood management.

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In high-income countries, preoperative anaemia has been associated with increased postoperative morbidity and mortality.[1] Preoperative anaemia is a common problem, with three large database studies in Europe and America estimating the prevalence to be between 25% and 30%.[2-4] Anaemia is also associated with increased perioperative blood transfusions, a practice independently associated with morbidity and mortality.[5] Growing evidence supports increasingly restrictive transfusion strategies in surgical and critical care patients, and as a result allogeneic transfusions can no longer be considered an appropriate isolated management strategy for surgical patients with preoperative anaemia.[6,7] Furthermore, the demographics of the South African (SA) surgical population differ significantly from those of the populations in which the morbidity associated with preoperative anaemia has been described. SA non-cardiac surgical patients are younger, have fewer non-communicable diseases, and undergo significantly more urgent and emergency procedures than their European counterparts.[8] The prevalence of preoperative anaemia and the associated postoperative outcomes in SA patients may therefore differ from those described in the published international literature.

In SA's resource-restricted setting, it is imperative to prioritise simple interventions that are likely to be associated with improved patient outcomes. Should preoperative anaemia be independently associated with postoperative morbidity and mortality, correction of preoperative anaemia may be a simple intervention to improve surgical outcomes.

Objectives

The primary objective was to determine the association between preoperative anaemia and in-hospital mortality in SA adult non-cardiac, non-obstetric surgical patients. Secondary objectives were to describe the prevalence of preoperative anaemia in adult SA surgical patients, and to determine the association between preoperative anaemia and (*i*) length of postoperative hospital stay and (*ii*) admission to critical care units.

Methods

This study was a secondary analysis of the South African Surgical Outcomes Study (SASOS) (University of Cape Town Human Research Ethics Committee ref. no. HREC R010/2014).

Setting

SASOS was a 7-day national multicentre prospective observational cohort study. Patients aged >16 years undergoing inpatient non-cardiac, non-obstetric surgery between 07h00 on 19 May and 06h59 on 26 May 2014 in 50 participating government-funded hospitals across all nine provinces of SA were recruited into the study. Exclusions were planned day-case surgery and radiological procedures not requiring anaesthesia. Patients aged <18 years attending hospitals associated with the University of the Witwatersrand were excluded from the study because they were deemed unable to give consent. In total, 3 927 patients from 45 hospitals were included in the study. The data collected included patient demographics and comorbidities, selected preoperative blood tests (including haemoglobin concentration (Hb)), the urgency of the surgery, the surgical specialty and the anaesthetic technique. Details of the study design and procedures have been described in the primary article.[8] The primary outcome was in-hospital mortality, which was censored at 30 days for patients who were still in hospital. Data on length of stay and critical care admission were also collected. The independent risk predictors for mortality identified in SASOS were age (years), American Society of Anesthesiologists (ASA) classification ≥2, major surgery, urgent or emergency surgery, infection or injury as an indication for surgery, upper gastrointestinal tract (GIT) surgery, and the comorbidities of stroke or transient ischaemic attack and metastatic cancer.

The independent risk predictors for critical care admission were ASA classification ≥2, intermediate or major surgery, urgent or emergency surgery, injury as an indication for surgery, upper GIT surgery, head and neck surgery, neurosurgery and thoracic surgery.

Definitions

The last recorded Hb prior to surgery was recorded as the preoperative Hb. Anaemia and its subclassifications were defined as Hb <13 g/dL in males (mild 11 - 12.9, moderate 8 - 10.9, severe <8) and <12 g/dL in non-pregnant females (mild 11 - 11.9, moderate 8 - 10.9, severe <8), according to the World Health Organization sex-based criteria.[9]

Statistical analysis

Categorical variables were described as proportions and compared using χ^2 tests, Pearson's χ^2 tests and Fisher's exact tests. The continuous variables age (years), Hb (g/dL) and length of hospital stay (days) were described as means and standard deviations if normally distributed or as medians and interquartile ranges (IQRs) if not.

A multivariate logistic regression analysis was performed to determine the association between preoperative anaemia and in-hospital mortality or critical care admission. Two analyses were conducted for each outcome: (*i*) anaemia entered as a binary variable; and (*ii*) anaemia entered as mild, moderate or severe categorical data. To determine whether preoperative anaemia was independently associated with mortality or critical care admission, we forced all the independent risk factors of mortality and critical care admission identified in the primary SASOS analysis[8] into the respective anaemia models. A *post hoc* multivariate analysis for the independent predictors of anaemia in SASOS was conducted. To determine the optimal Hb cut-point for anaemia associated with mortality, a receiver operating characteristic (ROC) curve was generated.

Univariate and multivariate statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23 (SPSS Inc., USA).

Results

The study recruitment is shown in Fig. 1. Preoperative haemoglobin data were available for 3 610/3 927 (91.9%) of the SASOS patients. The patient characteristics are shown in Table 1. The prevalence of preoperative anaemia was 1 725/3 610 (47.8%), with 711 patients (19.7%) presenting with mild anaemia, 863 (23.9%) with moderate anaemia and 151 (4.2%) with severe anaemia.

In univariate analysis there was a significant association between preoperative anaemia and female gender, an ASA classification of ≥3, congestive heart failure, insulin-dependent diabetes, metastatic cancer, HIV/AIDS, urgent or emergency surgery, and gynaecological and vascular surgery.

Preoperative anaemia, in-hospital mortality and critical care admission

The incidence of mortality associated with anaemia is shown in Table 2. Anaemic patients were significantly less likely than those who were not anaemic to survive to hospital discharge.

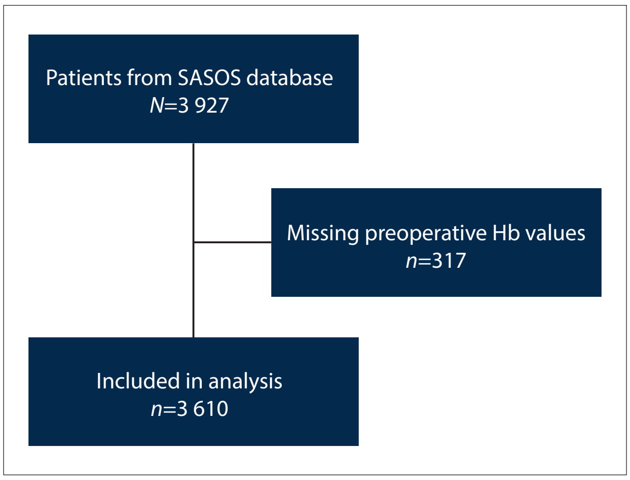

Fig. 1. Flow diagram of patient recruitment for the study. (SASOS = South African Surgical Outcomes Study; Hb = haemoglobin.)

Table 1. Baseline characteristics of patients with and without anaemia

	Total	Anaemic	Not anaemic	*p*-value
Age (years), mean (SD)	43.6 (17.6)	43.7 (18.0)	43.3 (17.0)	0.514
Hb (g/dL), mean (SD)	12.3 (2.5)	10.3 (1.7)	14.2 (1.4)	<0.001
Female, *n* (%)	1 807/3 610 (50.1)	913/1 725(52.9)	894/1 885 (47.4)	0.001
ASA, *n* (%)				<0.001
1	1 549/3 588 (43.2)	647/1 714 (37.7)	902/1 874 (48.1)	
2	1 266/3 588 (35.3)	560/1 714 (32.7)	706/1 874 (37.7)	
3	630/3 588 (17.6)	395/1 714 (23)	235/1 874 (12.5)	
4	129/3 588 (3.6)	101/1 714 (5.9)	28/1 874 (1.5)	
5	14/3 588 (0.4)	11/1 714 (0.6)	3/1 874 (0.2)	
Primary indication for surgery, *n* (%)				<0.001
Non-communicable disease	1 724/3 598 (47.9)	786/1 720 (45.7)	938/1 878 (49.9)	
Infection	686/3 598 (19.1)	378/1 720 (22.0)	308/1 878 (16.4)	
Injury	1 188/3 598 (33.0)	556/1 720 (32.3)	632/1 878 (33.7)	
History of				
Coronary artery disease	150/3 560 (4.2)	68/1 701 (4.0)	82/1 859 (4.4)	0.560
Congestive heart failure	53/3 560 (1.5)	35/1 701 (2.1)	18/1 859 (1.0)	0.008
Insulin-dependent diabetes	159/3 560 (4.5)	105/1 701 (6.2)	54/1 859 (2.9)	<0.001
Non-insulin-dependent diabetes	213/3 560 (6.0)	113/1 701 (6.6)	100/1 859 (5.4)	0.120
Metastatic cancer	94/3 560 (2.6)	63/1 701 (3.7)	31/1 859 (1.7)	<0.001
Cirrhosis	7/3 560 (0.2)	5/1 701 (0.3)	2/1 859 (0.1)	0.210
Stroke/TIA	53/3 560 (1.5)	32/1 701 (1.9)	21/1 859 (1.1)	0.072
COPD/asthma	222/3 560 (6.2)	87/1 701 (5.1)	135/1 859 (7.3)	0.008
HIV/AIDS	493/3 560 (13.8)	294/1 701 (17.3)	199/1 859 (10.7)	<0.001
Grade of surgery, *n* (%)				0.085
Minor	1 213/3 571 (34.0)	582/1 709 (34.1)	631/1 862 (33.9)	
Intermediate	1 561/3 571 (43.7)	706/1 709 (41.3)	855/1 862 (45.9)	
Major	797/3 571 (22.3)	421/1 709 (24.6)	376/1 862 (20.2)	
Urgency of surgery, *n* (%)				<0.001
Elective	1 619/3 598 (45.0)	620/1 718 (36.1)	999/1 880 (53.1)	
Urgent	1 201/3 598 (33.4)	659/1 718 (38.4)	542/1 880 (28.8)	
Emergency	778/3 598 (21.6)	439/1 718 (25.6)	339/1 880 (18.0)	
Type of surgery, *n* (%)				
Orthopaedic	1 017/3 610 (28.2)	445/1 725 (25.8)	572/1 885 (30.3)	0.003
Breast	97/3 610 (2.7)	35/1 725 (2.0)	62/1 885 (3.3)	0.023
Gynaecological	514/3 610 (14.2)	309/1 725 (17.9)	205/1 885 (10.9)	<0.001
Vascular	132/3 610 (3.7)	93/1 725 (5.4)	39/1 885 (2.1)	<0.001
Upper GIT	150/3 610 (4.2)	83/1 725 (4.8)	67/1 885 (3.6)	0.066
Lower GIT	386/3 610 (10.7)	164/1 725 (9.5)	222/1 885 (11.8)	0.031
Hepatobiliary	87/3 610 (2.4)	33/1 725 (1.9)	54/1 885 (2.9)	0.065
Plastics	228/3 610 (6.3)	119/1 725 (6.9)	109/1 885 (5.8)	0.171
Urology	193/3 610 (5.3)	83/1 725 (4.8)	110/1 885 (5.8)	0.183
Kidney	13/3 610 (0.4)	9/1 725 (0.5)	4/1 885 (0.2)	0.165
Head and neck	200/3 610 (5.5)	73/1 725 (4.2)	127/1 885 (6.7)	0.001
Neurosurgery	127/3 610 (3.5)	49/1 725 (2.8)	78/1 885 (4.1)	0.037
Thoracic	65/3 610 (1.8)	38/1 725 (2.2)	27/1 885 (1.4)	0.103
Other	396/3 610 (11.0)	190/1 725 (11.0)	206/1 885 (10.9)	0.958

Hb = haemoglobin; ASA = American Society of Anesthesiologists; TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease; GIT = gastrointestinal tract.

The risk factors independently associated with mortality and critical care admission in SASOS are shown in Tables 3 and 4, respectively. Anaemia was independently associated with mortality (odds ratio (OR) 1.657, 95% confidence interval (CI) 1.055 - 2.602; p=0.028) and critical care admission (OR 1.487, 95% CI 1.081 - 2.046; p=0.015) in the presence of all the independent predictors of mortality and critical care admission derived in the original SASOS model.[8] All the original independent predictors for mortality and critical care admission remained in the models when anaemia was forced into the model, with the exception of a history of stroke in the mortality model. Fig. 2 shows the ROC curve for anaemia and survival to hospital discharge. The optimal Hb cut-point was 10.95 g/dL, with an area under the curve of 0.662 CI (0.608 - 0.716).

Preoperative anaemia and length of hospital stay

Patients with preoperative anaemia remained in hospital significantly longer than those with a normal preoperative Hb (median 4 days (IQR 1 - 10) v. 2.5 days (IQR 1 - 5), respectively) (p<0.001).

Table 2. In-hospital mortality of patients with and without anaemia, and by subgroups

	In-hospital mortality, *n* (%) (95% CI)	OR (95% CI)	*p*-value
No anaemia	35/1 885 (1.9) (1.2 - 2.5)	Ref	
Anaemia	84/1 725 (4.9) (3.9 - 5.9)	2.706 (1.814 - 4.036)	<0.001
Anaemia subgroups			
None		Ref	
Mild	13/711 (1.8) (0.8 - 2.8)	0.984 (0.518 - 1.872)	0.962
Moderate	61/863 (7.1) (5.4 - 8.8)	4.020 (2.632 - 6.142)	<0.001
Severe	10/151 (6.6) (2.7 - 10.6)	3.749 (1.819 - 7.727)	<0.001

CI = confidence interval: OR = odds ratio.

Table 3. Independent predictors of mortality

	OR (95% CI)	*p*-value
Age	1.018 (1.005 - 1.030)	0.005
Anaemia	1.657 (1.055 - 2.602)	0.028
ASA		
1	Ref	
2	2.887 (1.342 - 6.209)	0.007
3	5.802 (2.694 - 12.493)	<0.001
4	24.206 (10.640 - 55.065)	<0.001
5	15.069 (3.417 - 66.453)	<0.001
History of		
Stroke/TIA (mortality model)	2.361 (0.965 - 5.778)	0.060
Metastatic cancer (mortality model)	2.973 (1.399 - 6.319)	0.005
Grade of surgery		
Minor	Ref	
Intermediate	1.669 (0.871 - 3.200)	0.123
Major	3.218 (1.666 - 6.216)	0.001
Urgency of surgery		
Elective	Ref	
Urgent	1.878 (1.057 - 3.334)	0.032
Emergency	2.900 (1.607 - 5.235)	<0.001
Type of surgery		
Upper GIT	2.915 (1.570 - 5.411)	0.001
Primary indication for surgery recorded		
Non-communicable disease	Ref	
Infection	1.661 (0.932 - 2.961)	0.085
Injury	2.115 (1.261 - 3.547)	0.005

OR = odds ratio; CI = confidence interval; ASA = American Society of Anesthesiologists; TIA = transient ischaemic attack; GIT = gastrointestinal tract.

Predictors of anaemia

There was an independent association between preoperative anaemia and ASA classification of 3 and 4, insulin-dependent diabetes, metastatic cancer, HIV, and urgent and emergency surgery (Table 5).

Discussion

Statement of principal findings

The study showed a high prevalence of preoperative anaemia (47.8%) in SA patients presenting for non-cardiac and non-obstetric surgery. Preoperative anaemia was independently associated with in-hospital mortality, increased admission to critical care units and a longer hospital stay.

Context

Our study findings of an association between preoperative anaemia and postoperative mortality are in keeping with similar large studies of the American College of Surgeons National Surgical Quality Improvement Program database (ACS NSQIP) and the European Surgical Outcomes Study (EuSOS) database.[2-4] However, our study presents data from a middle-income country, while the others present data from predominantly high-income countries. Furthermore, it was observed that the burden of comorbidities in SASOS was significantly lower than that reported in EuSOS.[4,8] A higher prevalence of anaemia, but with fewer comorbidities, suggests that a nutritional iron deficiency anaemia may be a proportionately larger contributor to the aetiology of anaemia in SA than in the other studies. It is therefore possible that a larger proportion of preoperative anaemia may be reversible in SA compared with other published cohorts. This is important in view of the fact that preoperative anaemia is associated with significant perioperative morbidity and mortality.

Internationally, increasing awareness of the risks and expenses associated with allogeneic blood transfusions has resulted in a shift of focus from transfusion as a treatment for perioperative anaemia to a more holistic patient blood management (PBM) strategy.[10] PBM is an evidence-based approach that aims to identify and address the three pillars of haematological risk that face surgical patients

Table 4. Independent predictors of critical care admission

	OR (95% CI)	*p*-value
Anaemia	1.487 (1.081 - 2.046)	0.015
ASA		
1	Ref	
2	1.403 (0.895 - 2.201)	0.140
3	4.895 (3.236 - 7.405)	<0.001
4	12.110 (7.086 - 20.694)	<0.001
5	7.564 (2.240 - 25.538)	0.001
Grade of surgery		
Minor	Ref	
Intermediate	2.230 (1.307 - 3.805)	0.003
Major	8.735 (5.192 - 14.696)	<0.001
Urgency of surgery		
Elective	Ref	
Urgent	2.335 (1.550 - 3.520)	<0.001
Emergency	3.090 (2.049 - 4.660)	<0.001
Indication for surgery		
Non-communicable disease	Ref	
Infection	1.014 (0.652 - 1.575)	0.952
Injury	1.515 (1.059 - 2.169)	0.023
Type of surgery		
Upper GIT	2.910 (1.756 - 4.824)	<0.001
Head and neck	4.550 (2.533 - 8.174)	<0.001
Neurosurgery	7.523 (4.659 - 12.149)	<0.001
Thoracic	4.431 (2.224 - 8.828)	<0.001

OR = odds ratio; CI = confidence interval; ASA = American Society of Anesthesiologists; TIA = transient ischaemic attack; GIT = gastrointestinal tract.

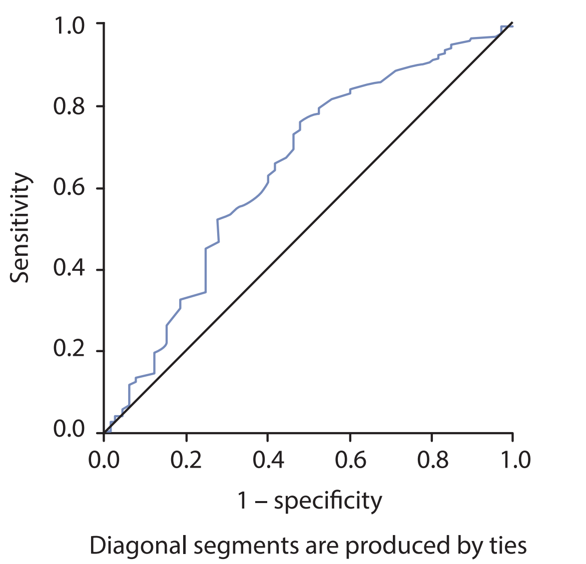

Fig. 2. Receiver operating characteristic curve for preoperative anaemia and survival to hospital discharge.

through: (*i*) identification and treatment of preoperative anaemia; (*ii*) minimisation of perioperative blood loss; and (*iii*) management of postoperative anaemia by optimising the patient's physiological reserve together with the adoption of restrictive haemoglobin transfusion triggers.[11,12] This approach has been associated with a reduction in: (*i*) perioperative morbidity and mortality; (*ii*) perioperative blood loss and transfusions; (*iii*) length of hospital stay; and (*iv*) costs.[13] Indeed, in recognition of these benefits, in 2010 the World Health Assembly urged member states to promote PBM as a transfusion alternative where appropriate.[14]

Our study suggests that preoperative anaemia is common in SA, and it provides impetus to actively adopt a PBM approach in SA. We believe that this has the potential to improve surgical outcomes in this country. Future local research should attempt to determine the types of preoperative anaemia and appropriate treatment regimens.

Study strengths and weaknesses

A major strength of this study is that it was possible to control for other independent predictors of mortality and critical care admission using the full SASOS data set. The finding that anaemia is associated with mortality and critical care admission in SA is therefore robust. A further strength is that this study included all the government-funded tertiary hospitals and 55.4% of the government-funded regional and tertiary hospitals in SA.[8] These data therefore have generalisability for these surgical populations in SA.

A potential weakness of the study is that surgical populations attending private hospitals were not included, and the results may therefore not be generalisable to this population. Similarly, government-funded district hospitals were poorly represented, and these data may therefore not be generalisable to these hospitals. However, the finding that anaemia is independently associated with perioperative mortality in SA is consistent with other surgical studies,[1] and would suggest that our data are probably generalisable to the entire SA surgical population.

Owing to the original study design, we could not distinguish acute from chronic anaemia. Acute anaemia is associated with morbidity, and chronic anaemia negatively affects the outcome associated with acute anaemia. While emergency surgery was independently associated with anaemia, injury as an indication for surgery was

Table 5. Independent predictors of anaemia

	OR (95% CI)	*p*-value
Age	1.003 (0.998 - 1.008)	0.244
Gender (female)	1.082 (0.915 - 1.279)	0.358
ASA		
1	Ref	
2	1.131 (0.934 - 1.368)	0.207
3	2.408 (1.873 - 3.096)	<0.001
4	5.019 (3.063 - 8.223)	<0.001
5	2.802 (0.724 - 10.855)	0.136
History of		
Coronary artery disease	0.531 (0.360 - 0.783)	0.001
Congestive heart failure	1.357 (0.714 – 2.578)	0.351
Insulin-dependent diabetes	1.749 (1.197 - 2.556)	0.004
Non-insulin-dependent diabetes	1.152 (0.840 - 1.580)	0.380
Metastatic cancer	1.982 (1.226 - 3.205)	0.005
Cirrhosis	2.644 (0.443 - 15.779)	0.286
Stroke/TIA	1.202 (0.647 - 2.230)	0.560
COPD/asthma	0.527 (0.384 - 0.725)	<0.001
HIV/AIDS	1.580 (1.258 - 1.983)	<0.001
Grade of surgery		
Minor	Ref	
Intermediate	0.900 (0.760 - 1.065)	0.220
Major	1.136 (0.922 - 1.399)	0.230
Urgency of surgery		
Elective	Ref	
Urgent	1.835 (1.537 - 2.191)	<0.001
Emergency	1.837 (1.490 - 2.264)	<0.001
Primary indication for surgery recorded		
Non-communicable disease	Ref	
Infection	0.784 (0.629 - 0.976)	0.030
Injury	1.122 (0.885 - 1.423)	0.340

OR = odds ratio; CI = confidence interval; ASA = American Society of Anesthesiologists; TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease.

not. We therefore conclude that it is unlikely that the entire signal of morbidity and mortality associated with anaemia in this study was due to acute anaemia.

We could also not control for perioperative blood transfusions. It is likely, however, that blood administration and anaemia are both independently associated with postoperative mortality,[15] and we therefore believe that this weakness should not compromise the interpretation of our findings. Furthermore, it is also possible that the prevalence and severity of preoperative anaemia may have been underestimated in this study, owing to preoperative transfusions.

A major limitation of this work is the potential role of multiple testing on the significance of these findings, as this is a secondary analysis of the SASOS dataset. Should one correct for a second analysis for mortality and a second analysis for critical care admission, an adjusted two-sided significance level of 0.05/2 = 0.025 could be considered appropriate. If one applies this approach, anaemia remains independently associated with critical care admission but not mortality. For these reasons, the data presented here should be considered hypothesis generating at best.

Conclusions

SA patients have a higher prevalence of preoperative anaemia than reported in other international cohorts, and this is associated with surgical mortality. Simply transfusing patients perioperatively can no longer be considered an acceptable solution, owing to the morbidity associated with blood transfusion. Education and institution of PBM programmes in SA are important to reduce the morbidity and mortality associated with preoperative anaemia.

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Conflicts of interest. None.

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