Masters of Medicine in Anaesthesiology

Research Submission

The association between preoperative anaemia and surgical mortality and morbidity in South African surgical patients.

University of Cape Town

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Abstract

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. The demographics of South African surgical patients differ from those of the European and Northern American surgical patients where the preoperative anaemia data are derived. These associations between preoperative anaemia and postoperative outcomes are therefore not necessarily transferable to South African surgical patients.

Objectives: The primary objective was to determine the association between preoperative anaemia and in-hospital mortality in South African adult noncardiac, 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 to describe the prevalence of preoperative anaemia in adult South African surgical patients.

Methods: We performed a secondary analysis of the South African Surgical Outcomes Study (SASOS) – a large, prospective, observational study of patients undergoing in-patient noncardiac, non-obstetric surgery at 50 hospitals across South Africa over a one-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, which 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 1727/3610 (47.8%). Preoperative anaemia was independently associated with in-hospital mortality (odds ratio (OR) 1.66, 95% confidence interval (CI) 1.06-2.60, p=0.028) and admission to critical care (OR 1.49, 95% CI 1.08-2.05, p=0.015).

Conclusion: Almost 50% of patients undergoing surgery at government-funded hospitals in South Africa had preoperative anaemia, which was independently associated with postoperative mortality and critical care admission. These numbers indicate a significant perioperative risk, with a clear opportunity for quality improvement programmes which 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, it behoves perioperative clinicians in all specialities to educate themselves in the principles of patient blood management.

Acknowledgements and Contributions

This work is the result of a secondary analysis of data from the South African Surgical Outcomes Study (SASOS) and would therefore not have been possible without the efforts of the original study investigators, as well as the anaesthetic and surgical staff at all the participating hospitals. I thank them for their contribution to the field of perioperative medicine in South Africa and for allowing access to the database for this study.

Details of Authors Contributions

Conception of the study	Bruce Biccard
Design of the protocol and first draft of the manuscript	Daniela Marsicano
Statistical analyses	Bruce Biccard
Review of manuscript	Bruce Biccard, Daniela Marsicano, Francois Roodt, Neil Hauser
Contribution to manuscript	All authors
Editing of Manuscript	Bruce Biccard, Daniela Marsicano
Corresponding author and corrections	Daniela Marsicano

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List of abbreviations

ACS NSQIP	American College of Surgeons' National Surgical Quality Improvement Program
AIDS	Acquired immunodeficiency syndrome
ASA	American Society of Anesthesiologists
B.Sc	Bachelor of Science
BComm	Bachelor of Commerce
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
DA (SA)	Diploma in Anaesthetics of the College of Anaesthetists of South Africa
EUSOS	European Surgical Outcomes Study
FCA (SA)	Fellowship of the College of Anaesthetists of South Africa
GIT	Gastrointestinal tract
Hb	Haemoglobin concentration
HIV	Human Immunodeficiency Virus
HREC	University of Cape Town Human Research Ethics Committee
IL	Illinois
Inc.	Incorporated
IQR	Interquartile range
MBChB	Bachelor of Medicine and Bachelor of Surgery
MMed	Master of Medicine
OR	Odds ratio
p	p-value
PBM	Patient blood management
PhD	Doctor of Philosophy
Physio	Physiotherapy
Pret	University of Pretoria
ROC	Receiver operating characteristic curve
SASOS	South African Surgical Outcomes Study
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
Stell	Stellenbosch University
Surg	Surgery
TIA	Transient ischaemic attack
UCT	University of Cape Town
USA	United States of America
WHO	World Health Organisation
Wits	University of Witwatersrand

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

D. Marsicano,[1] N. Hauser,[2] F. Roodt,[3] E. Cloete,[4] I. Conradie,[5] V. Morford,[6] D. Nel,[7] D.G. Bishop,[8] TE Madiba,[9] B.M. Biccard,[10] on behalf of the SASOS Investigators.

Abstract

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. The demographics of South African surgical patients differ from those of the European and Northern American surgical patients where the preoperative anaemia data are derived. These associations between preoperative anaemia and postoperative outcomes are therefore not necessarily transferable to South African surgical patients.

Objectives: The primary objective was to determine the association between preoperative anaemia and in-hospital mortality in South African adult noncardiac, 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 to describe the prevalence of preoperative anaemia in adult South African surgical patients.

Methods: We performed a secondary analysis of the South African Surgical Outcomes Study (SASOS) – a large, prospective, observational study of patients undergoing in-patient noncardiac, non-obstetric surgery at 50 hospitals across South Africa over a one-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, which 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 1727/3610 (47.8%). Preoperative anaemia was independently associated with in-hospital mortality (odds ratio (OR) 1.66, 95% confidence interval (CI) 1.06-2.60, p=0.028) and admission to critical care (OR 1.49, 95% CI 1.08-2.05, p=0.015).

Conclusion: Almost 50% of patients undergoing surgery at government-funded hospitals in South Africa had preoperative anaemia, which was independently associated with postoperative mortality and critical care admission. These numbers indicate a significant perioperative risk, with a clear opportunity for quality improvement programmes which 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, it behoves perioperative clinicians in all specialities to educate themselves in the principles of patient blood management.

Introduction

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, allogenic transfusions can no longer be considered an appropriate isolated management strategy for preoperative anaemic surgical patients.[6 ,7] Furthermore, the demographics of the South African surgical population differ significantly from those of the populations describing the morbidity associated with preoperative anaemia. South African noncardiac surgical patients are younger, with 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 South African patients may therefore differ from the published international literature.

In South Africa'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. The objective of this study was therefore to determine the prevalence of preoperative anaemia and its impact on postoperative surgical outcomes.

Methods

This study is a secondary analysis of the South African Surgical Outcomes Study (SASOS) (University of Cape Town Human Research Ethics Committee: HREC R010/2014). The aim of this study was to determine the association between preoperative anaemia and in-hospital mortality in South African adult noncardiac, non-obstetric surgical patients. Secondary aims were to describe the prevalence of preoperative anaemia in adult South African surgical patients, and to determine the association between preoperative anaemia and i) length of postoperative hospital stay, and ii) admission to critical care units.

Setting

SASOS was a 7-day national, multicentre, prospective, observational cohort study. Patients over 16 years of age, undergoing inpatient noncardiac, non-obstetric surgery between 07h00 on 19 May and 06:59 on 26 May 2014, in 50 participating government-funded hospitals across all nine provinces were recruited into the study. Exclusions were planned day case surgery and radiological procedures not requiring anaesthesia. Patients under 18 years of age attending University of the Witwatersrand hospitals were excluded from the study as they were deemed unable to give consent. In total 3927 patients were included in the study from 45 hospitals. The data collected included patient demographics and comorbidities, selected preoperative blood tests (including haemoglobin concentration (Hb)), the urgency of the surgery, the surgical speciality, 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 and critical care admission determined in the original study (see definitions) were used in this secondary analysis (see statistical analysis).

Definitions

The independent risk predictors for mortality identified in SASOS were; age (years), American Society of Anesthesiologists (ASA) classification (2 or more), major surgery, urgent or emergency surgery, infection or injury as an indication for surgery, upper GIT surgery, and the comorbidities of stroke or transient ischaemic attack, and metastatic cancer.

The SASOS independent risk predictors for critical care admission were; ASA classification 2 or more, 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.[8]

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

Statistical Analysis

Categorical variables were described as proportions and compared using chi-square tests, Pearson's chi-square tests, and Fisher's exact tests. The continuous variables age (years), haemoglobin (g/dl), and length of hospital stay (days) were described as a mean and standard deviation if normally distributed or median and interquartile range (IQR) if not normally distributed.

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. In order 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

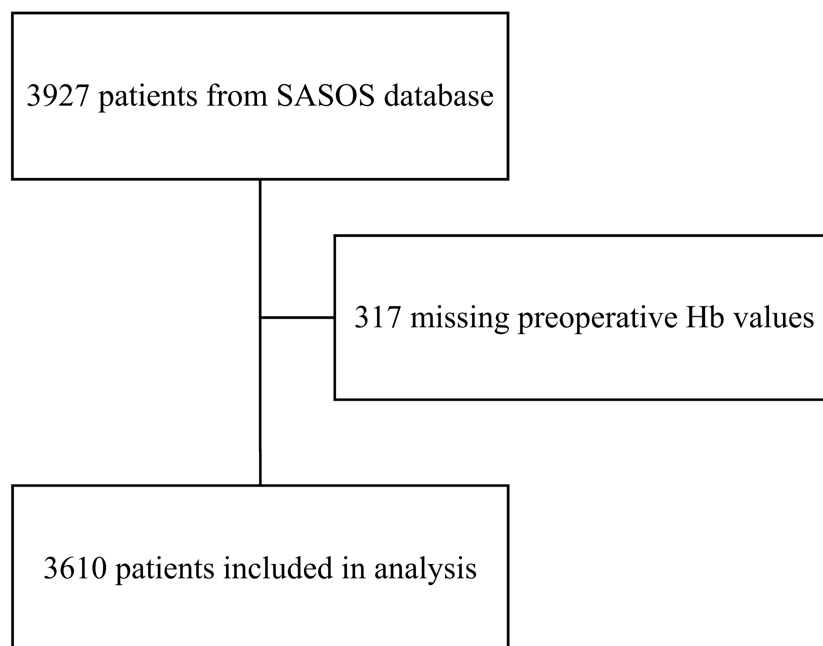
independent predictors of anaemia in SASOS was conducted. All preoperative risk factors, and risk factors describing the indication, urgency and severity of surgery were forced into the model. To determine the optimal Hb cut for anaemia associated with mortality, a receiver operating characteristic (ROC) curve was generated.

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

Results

The study recruitment is shown in Figure 1. Preoperative haemoglobin data were available in 3610/3927 (91.9%) of the SASOS patients. The patient characteristics are shown in Table 1. The prevalence of preoperative anaemia was 1725/ 3610 (47.8%), with 711 (19.7%) patients presenting with mild anaemia, 863 (23.9%) with moderate anaemia, and 151 (4.2%) with severe anaemia.

Figure 1. Flow diagram of patient recruitment for the study



Preoperative anaemia was more commonly associated with female gender, an American Society of Anesthesiologists (ASA) classification of 3 or more, congestive heart failure, insulin dependent diabetes, metastatic cancer, HIV/AIDS, urgent or emergency surgery, and gynaecological and vascular surgery.

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

Table 1. (Cont.) Baseline characteristics of patients with and without anaemia

	Total	Anaemic	Not anaemic	*p*-value
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.

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 to survive to hospital discharge.

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	35/1885 (1.9) (1.2-2.5)	Reference	
Anaemia*	84/1725 (4.9) 3.9-5.9)	2.71 (1.81-4.04)	<0.001
Anaemia subgroups			
No anaemia		Reference	
Mild anaemia	13/711 (1.8) 0.8-2.8)	0.98 (0.52-1.87)	0.96
Moderate anaemia	61/863 (7.1) 5.4-8.8)	4.02 (2.63-6.14)	<0.001
Severe anaemia	10/151 (6.6) 2.7-10.6)	3.75 (1.82-7.73)	<0.001

All but one of the risk factors independently associated with mortality and critical care admission in SASOS remained in the models when anaemia was forced into the model, as seen in Tables 3 and 4 respectively. The exception was a history of stroke in the mortality model. Anaemia was independently associated with mortality (OR 1.66, 95% CI 1.06-2.60, p 0.028) and critical care admission (OR 1.49, 95/% CI 1.08-2.05, p 0.015), in the presence of all the independent predictors of mortality and critical care admission derived in the original SASOS model.[8] Figure 2 shows the receiver operating characteristic 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).

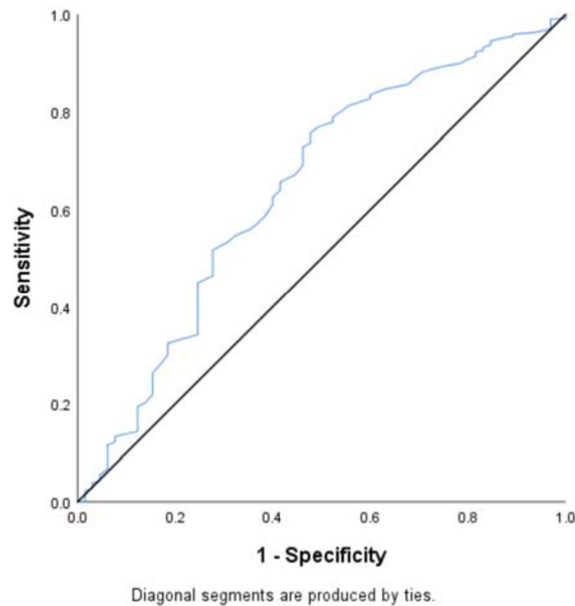
Table 3. Multivariate analysis of risk factors associated with mortality

	OR (95% CI)	p-value
Age (mortality)	1.02 (1.01-1.03)	0.005
Anaemia	1.66 (1.06-2.60)	0.028
ASA		
1	Reference	
2	2.89 (1.34-6.21)	0.007
3	5.80 (2.69-12.49)	<0.001
4	24.21 (10.64-55.07)	<0.001
5	15.07 (3.42-66.45)	<0.001
History of		
Stroke/ TIA (mortality model)	2.36 (0.97-5.78)	0.060
Metastatic cancer (mortality model)	2.97 (1.40-6.32)	0.005
Grade of surgery		
Minor	Reference	
Intermediate	1.67 (0.87-3.20)	0.123
Major	3.22 (1.67-6.22)	0.001
Urgency of surgery		
Elective	Reference	
Urgent	1.88 (1.06-3.33)	0.032
Emergency	2.90 (1.61-5.24)	<0.001
Type of Surgery		
Upper GIT	2.92 (1.57-5.41)	0.001
Primary indication for surgery recorded		
Non-communicable	Reference	
Infection	1.66 (0.93-2.96)	0.085
Injury	2.12 (1.26-3.55)	0.005

Table 4. Multivariate analysis of risk factors associated with critical care admission

	OR (95% CI)	**p-value**
Anaemia	1.49 (1.08-2.05)	0.015
ASA		
1	Reference	
2	1.40 (0.90-2.20)	0.140
3	4.90 (3.24-7.41)	<0.001
4	12.11 (7.09-20.69)	<0.001
5	7.56 (2.24-25.54)	0.001
Grade of surgery		
Minor	Reference	
Intermediate	2.23 (1.31-3.81)	0.003
Major	8.74 (5.19-14.70)	<0.001
Urgency of surgery		
Elective	Reference	
Urgent	2.34 (1.55-3.52)	
Emergency	3.09 (2.05-4.66)	<0.001
Indication for surgery		
Non-communicable	Reference	
Infection	1.01 (0.65-1.58)	0.952
Injury	1.52 (1.06-2.17)	0.023
Type of Surgery		
Upper GIT	2.91 (1.76-4.82)	<0.001
Head and neck	4.55 (2.53-8.17)	<0.001
Neurosurgery	7.52 (4.66-12.15)	<0.001
Thoracic	4.43 (2.22-8.83)	<0.001

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



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) versus 2.5 days (IQR 1-5) respectively, $p<0.001$).

Predictors of Anaemia

Patients with an ASA classification of 3 and 4 and those with insulin dependent diabetes, coronary artery disease, metastatic cancer, and HIV were significantly more likely to be anaemic. Urgent and emergency surgery were associated with preoperative anaemia.

Table 5. Independent Predictors of Anaemia

	OR (95% CI)	p-value
Age	1.00 (1.00-1.01)	0.244
Gender (female)	1.08 (0.92-1.28)	0.358
ASA		
1	Reference	
2	1.13 (0.93-1.37)	0.207
3	2.41 (1.87-3.10)	<0.001
4	5.02 (3.06-8.22)	<0.001
5	2.80 (0.72-10.86)	0.136
History of		
Coronary artery disease	0.53 (0.36-0.78)	0.001
Congestive heart failure	1.36 (0.71 – 2.58)	0.351
Insulin dependent diabetes	1.75 (1.20-2.56)	0.004
Non-insulin dependent diabetes	1.15 (0.84-1.58)	0.380
Metastatic cancer	1.98 (1.23-3.21)	0.005
Cirrhosis	2.64 (0.44-15.78)	0.286
Stroke/TIA	1.20 (0.65-2.23)	0.560
COPD/Asthma	0.53 (0.38-0.73)	<0.001
HIV positive/AIDS	1.58 (1.26-1.98)	<0.001
Grade of surgery		
Minor	Reference	
Intermediate	0.90 (0.76-1.07)	0.220
Major	1.14 (0.92-1.40)	0.230
Urgency of surgery		
Elective	Reference	
Urgent	1.84 (1.54-2.19)	<0.001
Emergency	1.84 (1.49-2.26)	<0.001
Primary indication for surgery recorded		
Non-communicable	Reference	
Infection	0.78 (0.63-0.98)	0.030
Injury	1.12 (0.89-1.42)	0.340

Discussion

Statement of principal findings

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

Strengths and weaknesses of the study

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 South Africa 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 South Africa.[8] These data therefore have generalisability for these surgical populations in South Africa.

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

Due to the original study design, we could not distinguish patients presenting with anaemia due to acute blood loss, from those with chronic anaemia. Acute anaemia, as may be caused by trauma or gastrointestinal bleeding, 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 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 trauma associated acute anaemia.

We could also not control for perioperative blood transfusions as this information was not collected during the original study. While transfusions can be lifesaving in certain situations, it is likely, that blood administration and anaemia are both independently associated with postoperative mortality.[10] 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, due 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. It is for these reasons, that the data presented here, should be considered hypothesis generating at best.

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 less than that reported in EuSOS.[4 ,8] A

higher prevalence of anaemia, but with less comorbidities suggests that a nutritional iron deficiency anaemia may be a proportionately larger contributor to the aetiology of anaemia in South Africa when compared to the other studies. It is possible therefore, that a larger proportion of preoperative anaemia may be reversible in South Africa, compared to other published cohorts. This is important, considering 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 of perioperative anaemia to a more holistic patient blood management (PBM) strategy.[11] PBM is an evidence-based approach that aims to identify and address the three pillars of haematological risk that face surgical patients through; i) identification and treatment of preoperative anaemia, ii) minimisation of perioperative blood loss, and iii) the management of postoperative anaemia by optimising the patient's physiological reserve together with the adoption of restrictive haemoglobin transfusion triggers.[12,13] 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.[14] Indeed, in recognition of these benefits, in 2010 the World Health Assembly urged member states to promote, where appropriate, patient blood management as a transfusion alternative.[15]

Our study suggests that preoperative anaemia is common in South Africa, and it provides impetus to actively adopt a PBM approach in South Africa. We believe this has the potential to improve surgical outcomes in South Africa. Future local research should attempt to determine the types of preoperative anaemia, the time required and the response to therapy prior to surgery, as well as the surgical outcomes in patients who have been optimised prior to surgery.

Conclusions

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

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Appendices

Ethics approval letter

Instructions to Authors: South African Medical Journal (SAMJ)

Reviewer comments from the journal

Response to reviewer’s queries

Ethics approval

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
29 JAN 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.1.2019
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	29/1/2018

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	22/01/2018		
HREC REF Number	HREC 878/2016	Current Ethics Approval was granted until	30/12/2017
Protocol title	The Association Between Preoperative Anaemia and Surgical Mortality and Morbidity in South African Surgical Patients		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ **No**		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof Bruce Biccard		
Department / Office Internal Mail Address	Department of Anaesthesia and Perioperative Medicine		

28 June 2017 Page 1 of 6 FHS016

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates.	☐ Yes	☑ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes	
1.3 Annual Approval for **full committee** review	- R 3420 (inclusive of vat)
For invoicing purposes, please provide:	
Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

2. List of documentation for approval

3. Protocol status (tick ✓)

☐	Open to enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☑	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	
Number of participants enrolled, since last HREC Progress report (continuing review)	
Additional number of participants still required	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	

6. Cumulative summary of participants

Total number of participants who provided consent	
Number of participants determined to be ineligible (i.e. after screening)	
Number of participants currently active on the study	
Number of participants completed study (without events leading to withdrawal)	
Number of participants withdrawn at participants' request (i.e. changed their mind)	
Number of participants withdrawn by PI due to toxicity or adverse events	
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

This study is a sub-study linked to R010/2014. Data collected in study R010/2014 has no patient identifying information. Data analysis for study HREC 878/2016 was completed last year, and the findings of the study are ready to submit in the form of an article.

8. Protocol violations and exceptions (tick ✓ all that apply)

☑	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☑	No prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
None.

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	☑ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. MCC, FDA)?		
☐ Yes	☐ No	☑ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	☑ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☑ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☑	Shown no change
If there has been a change, please explain:	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☑ No
If yes, please explain and if necessary attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	22/01/2018

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

02 December 2016

HREC REF: 878/2016

Prof B Biccard
Anaesthesia & Perioperative Medicine
D23, NGSH

Dear Prof Biccard

PROJECT TITLE: THE ASSOCIATION BETWEEN PREOPERATIVE ANAEMIA AND SURGICAL MORTALITY AND MORBIDITY IN SOUTH AFRICAN SURGICAL PATIENTS-(MMed-candidate-Dr D Marsicano) sub-study linked to R010/2014

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Dr D Marsicano will be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 878/2016

his serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 878/2016

Instructions to Authors: South African Medical Journal (SAMJ)

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out

    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.

- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies

- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Reviewer comments from the journal

Please comment on your General impression of this manuscript - bear the following in mind:

Is the article relevant?
Does it offer anything new?
Are there similar studies in our region/outside the region?
Does it add to the existing medical body of knowledge?
On first glance, are the methods, results and conclusions reasonable?
Do the conclusions actually draw on the results?
Does the article have a clear message?
Will it help SAMJ readers make better clinical decisions and, if so, how?
Is a general medical journal the right place for it?
Reviewer #1: The article is relevant, adds new information, no similar studies in the region, adds to existing knowledge, all sections reasonable, conclusions correctly drawn, message clear, SAMJ readers understand the relevance of preoperative anaemia better, yes SAMJ is the best journal for this article.

Reviewer #2: The article is relevant to the South African context having been derived from an large South African observational study. It provides the first form description of the role of anaemia in patients undergoing surgery and suggests that this is a significant factor in poor outcomes. The message is clear, the methodology is sound and if the recommendations are adopted I believe this would improve outcomes. I think that this message extends beyond the boundaries of surgery and anaesthesia and would be well suited for a general medical journal.

Please comment on the Methods and analysis presented in this manuscript

Study design

Is the research question and planned outcomes clearly defined?
Was the sample adequate and sufficiently described?
Are the methods adequately described and appropriate to the study objectives?

Statistical considerations

Are simple statistical methods applied appropriately?

Reviewer #1: (No Response)

Reviewer #2: The study design and outcomes are appropriate. The methodology references a study called SASOS when speaking about the candidate variables but these are not listed in the paper. I think it is important to add these variables into the main paper - the casual reader is unlikely to find the source study. If this is a secondary analysis, and two additional regression analyses were also run - how were steps taken to correct for multiple testing? Surely with a prevalence as high as 40% steps should be taken to avoid drawing incorrect inferences?

I am not sure if this sample included emergency surgery. Where the patient was bleeding from an acute cause - such as trauma or bleeding DUI, or had previously been in surgery or in ICU the cause of the anemia cannot be directly linked to their preoperative state. Has this been considered and if so, how was it adjusted for or explored? Does the signal remain when you take out the emergency / acute bleed / ICU group?

There does not seem to be signal in the mild anemia group - rather it all seems to be coming from the moderate anemia group. The wide CI in the severe anemia group suggests that this threshold may not be appropriate for the perioperative environment. Would it be possible to graph the risk relationship between Hb and

mortality?

Please comment on the Results, Discussion and Conclusions presented in this manuscript

Results

Is the population/sample adequately described?
Are the results clearly presented?
Are they credible and do they answer the research question?
Are tables clear and useful, not simply mirroring data discussed in the Results text?

Reviewer #1: (No Response)

Reviewer #2: Population and sample well described. Results are clear.

Discussion

Are the results well discussed in light of previous evidence and the literature?
Are the limitations of the study sufficiently discussed?/ Are the strengths and weakness discussed?
Is the meaning and relevance of the study discussed?

Reviewer #1: (No Response)

Reviewer #2: I would like to see more comment on the other factors driving anemia - particularly because this study included emergency patients. At the moment the discussion leaves one with the impression that this issue is only because of preoperative anemia and intraoperative blood loss. A few lines to avoid this simplification should be sufficient.

Response to reviewer's queries

Revision: Manuscript SAMJ13148 'Preoperative anaemia and clinical outcomes in the South African Surgical Outcomes Study (SASOS)'

Thank you for the opportunity to submit a revised version of our manuscript for possible publication in *SAMJ*.

We have itemised the queries with a written description of our changes in blue text for ease of reading. We have submitted two versions of the manuscript, one with tracked changes and the other with accepted changes in red text. A few minor errors have been corrected for example, Mmed to MMed and a missing closing bracket under *Definitions*, these were also highlighted,

Query 1: Study design and statistical considerations

Reviewer #1: (No Response)

Reviewer #2:

1. The study design and outcomes are appropriate. The methodology references a study called SASOS when speaking about the candidate variables but these are not listed in the paper. I think it is important to add these variables into the main paper - the casual reader is unlikely to find the source study.

We have included the following two sentences under *Setting*:

"The independent risk predictors for mortality identified in SASOS were; age (years), American Society of Anesthesiologists (ASA) classification (2 or more), major surgery, urgent and emergency surgery, infection or injury as an indication for surgery, upper GIT surgery, and the comorbidities of stroke or transient ischaemic attack, or metastatic cancer.
The independent risk predictors for critical care admission were; ASA classification 2 or more, intermediate or major surgery, urgent and emergency surgery, injury as an

indication for surgery, upper GIT surgery, head and neck surgery, neurosurgery, thoracic surgery."

2. If this is a secondary analysis, and two additional regression analyses were also run - how were steps taken to correct for multiple testing? Surely with a prevalence as high as 40% steps should be taken to avoid drawing incorrect inferences?

We have added the following paragraph to *Strengths and weaknesses of the study*
"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. It is for these reasons, that the data presented here, should be considered hypothesis generating at best."

3. I am not sure if this sample included emergency surgery. Where the patient was bleeding from an acute cause - such as trauma or bleeding DUI, or had previously been in surgery or in ICU the cause of the anemia cannot be directly linked to their preoperative state. Has this been considered and if so, how was it adjusted for or explored? Does the signal remain when you take out the emergency / acute bleed / ICU group?

We conducted a post hoc analysis of the predictors for anaemia and added the results (text and table 5) and the following:

Statistical analysis
"A post hoc multivariate analysis for the independent predictors of anaemia in SASOS was conducted."

Results

"Patients with an ASA classification of 3 and 4 and those with insulin dependent diabetes, metastatic cancer, and HIV were significantly more likely to be anaemic. Urgent and emergency surgery were associated with preoperative anaemia."

Strengths and weaknesses of the study

*"*Due 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 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."

4. There does not seem to be signal in the mild anemia group - rather it all seems to be coming from the moderate anemia group. The wide CI in the severe anemia group suggests that this threshold may not be appropriate for the perioperative environment. Would it be possible to graph the risk relationship between Hb and mortality?

We generated a ROC curve and added it (figure 2) and the following to the article.

Statistical Analysis

"To determine the optimal Hb cut for anaemia associated with mortality, a receiver operating characteristic (ROC) curve was generated."

Preoperative anaemia, in-hospital mortality, and critical care admission

"Figure 2 shows the receiver operating characteristic 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)."

Query 2: Discussion

Reviewer #1: (No Response)

Reviewer #2:

1. I would like to see more comment on the other factors driving anemia - particularly because this study included emergency patients. At the moment the discussion leaves one with the impression that this issue is only because of preoperative anemia and intraoperative blood loss. A few lines to avoid this simplification should be sufficient.

We hope that the paragraph added to *Strengths and weaknesses of the study* (for Query 1 point 3) addresses this concern.