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ORIGINAL RESEARCH

Preoperative anaemia in patients undergoing open intra-abdominal surgery at a South African tertiary hospital

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Background: The prevalence of preoperative anaemia (PA) in mixed surgical populations is as high as 47.8%. PA in mixed surgical populations is associated with increased postoperative mortality (PM). It is likely that the prevalence of PA and the associated risk of PM might be higher in open intra-abdominal surgery (OIAS) populations, such as laparotomy patients, due to the underlying disease pathologies in this group. An investigation of PA in OIAS patients can inform future improvements in the perioperative management of this high-risk surgical group.
Method: This was a sub-analysis of data from a pre-existing registry of 435 laparotomy patients who attended a South African tertiary hospital. The registry collected data on preoperative haemoglobin (Hb), patient characteristics, and PM. Identified PA was graded according to World Health Organization definitions. Established mean red cell volume (MCV) thresholds were used for the morphological classification of PA.
Results: The prevalence of PA was 71.0% (95% confidence interval [CI]: 66.8–75.3%). Overall, PA was associated with a three-fold higher risk of PM (odds ratio 3.35, $p < 0.001$). Postoperative mortality was higher in patients with moderate and severe anaemia than in those without anaemia, while there was no difference in PM between patients with mild anaemia and non-anaemic patients.
Conclusion: PA is common in OIAS patients and is associated with increased PM. Identification of OIAS patients with PA, and appropriate preoperative management of these patients is recommended.

Keywords: anaemia, postoperative complications, mortality, laparotomy

Introduction

Erythrocytes are essential for maintaining adequate oxygenation of the tissues during the perioperative period.[1] These bi-concave discs possess haemoglobin (Hb) molecules that contain iron and are responsible for oxygen and carbon dioxide transport within the circulation.[2] Anaemia describes the condition when the number of erythrocytes (and as a result their oxygen-carrying capacity) is insufficient to meet physiological needs.[3] The World Health Organization (WHO) has proposed that Hb measurements of < 120 g/L in females and < 130 g/L in males be used as an indicator of anaemia.[3] The WHO grades anaemia into mild, moderate and severe categories based on a set of defined Hb thresholds (severe anaemia: Hb < 80 g/L in females and males; moderate anaemia: Hb 80–109 g/L in females and males, and mild anaemia: Hb 110–119 g/L in females, and Hb 110–129 g/L in males).[3] For many years, this same definition and grading of anaemia has been adopted in perioperative settings.[4] Anaemia affects 32.9% of the global population.[5] In South Africa, up to 22.0% of the general adult population are anaemic.[6] The prevalence of preoperative anaemia (PA) in surgical populations is reported as being much higher than that of the general population.[4] Most of these prevalence estimates, ranging between 28.7% and 47.8%, are based on observations in mixed surgical populations.[7-10] Another important finding from studies investigating PA in mixed surgical populations is the association of this condition with an increased risk of postoperative complications.[7-10] A study by Musallam et al. of 227 425 non-cardiac surgery patients (of which 30.4% had PA) found any PA to be associated with 45–77% higher risk of cardiac complications, a 33–70% higher risk of respiratory complications, a 5–16% higher risk of neurological complications, and a 24–88% higher risk of sepsis when compared with a non-anaemic patient group.[7] In a sub-analysis of the European Surgical Outcomes Study (EuSOS), Baron and colleagues reported increased hospital length of stay and postoperative admission to intensive care in patients with PA versus patients without PA ($p < 0.001$ for both postoperative outcomes).[8] The association between PA and a higher risk of postoperative critical care admission was confirmed by Marsicano and colleagues in a sub-analysis of data from the South African Surgical Outcomes Study (SASOS).[9] The authors found that SASOS patients with PA were at a 49% higher risk of requiring critical care services postoperatively when compared with non-anaemic patients.[9] Patients with PA also have a higher risk of postoperative mortality (PM) when compared with non-anaemic patients.[7-10] These studies defined PM as either 30-day mortality, or in-hospital mortality.[7-10] A meta-analysis of PA and PM by Fowler et al. found that non-cardiac surgery patients with PA were at an almost three-fold higher risk of suffering PM when compared with non-cardiac surgery patients who did not have PA (odds ratio [OR]: 2.87, 95% confidence interval [CI]: 2.10–3.93).[10] The risk of all postoperative complications in patients with PA appears to be directly correlated with the severity of PA.[7]

While the findings of these studies have contributed significantly to the understanding of PA in mixed surgical populations, the application of these findings to patients undergoing major procedures might be inappropriate. It is therefore important

that research which seeks to describe PA in patients undergoing major surgical procedures, such as elective open intra-abdominal surgery (OIAS), be conducted. This could have potentially important implications with regard to risk stratification and perioperative management of PA in this high-risk surgical group. The objectives of this study were to: 1) determine the prevalence and characteristics of PA in patients undergoing elective OIAS, more specifically laparotomy procedures; and 2) determine if PA is associated with PM in this surgical group.

Methods

Study design, study setting, and study sample

This was a sub-analysis of data from an electronic registry of 435 adult laparotomy patients who underwent their elective procedures at a tertiary South African hospital, between 1 January 2006 and 31 December 2010. Elective laparotomy was defined as non-urgent surgical abdominal access which was planned in advance.

Data collection

The pre-existing registry formed part of a larger quality improvement audit at the hospital which sought to establish tertiary surgical services utilisation, determine which were the most commonly performed elective procedures, and determine complication rates and length of stay following these procedures. All patients included in the registry had undergone elective procedures. For the purposes of this research the study sample was restricted to adult patients (aged > 18 years old). Elective procedure rates are carefully recorded on the hospital administrative system which forms the basis for establishing the expenditure attributed to various aspects of surgical services utilisation at the hospital. It is likely that we captured all elective laparotomy patients for the registry. The registry captures data related to patient characteristics (demographics and co-morbidities) and preoperative laboratory results (including Hb and mean cell volume (MCV), platelet count, creatinine, and albumin). Obesity was defined as a body mass index (BMI) > 30 kg/m^2. The most recent laboratory test results within 30 days preceding the laparotomy surgery were recorded on the registry. The strategy of using the most recent preoperative test result also accounted for changes in Hb due to interventions such as preoperative blood transfusion, as another Hb measurement would have been repeated after the preoperative intervention. The registry recorded inpatient mortality. All data included in the registry were collected via a retrospective chart review process.

Preoperative anaemia was determined from the preoperative Hb measurements using Hb thresholds recommended by the WHO.[3] Preoperative anaemia was graded by severity using WHO thresholds.[3] Conventional measurement thresholds for MCV were used to classify PA according to red cell morphology[11]: microcytic (MCV < 82 fL), normocytic (MCV 82–98 fL) or macrocytic anaemia (MCV > 98 fL).[11]

Statistical analysis

Descriptive statistics were used to present the characteristics of the study sample, and the prevalence and morphological characteristics of PA. Results are presented as frequencies and percentages or as means with standard deviation (SD). Bivariate statistics (χ^2 test) were used to test whether there was any association between PA (any PA, or PA stratified by severity) and PM. A p-value < 0.05 was considered to be a statistically significant result. We used receiver-operator characteristic curve (ROC) statistics to determine the prognostic accuracy of PA for PM. We defined prognostic accuracy according to the area under the curve (AUC) obtained as follows: < 0.500: no prognostic value; 0.500–0.600: poor; 0.600–0.700: fair; and > 0.700: good. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, USA).

Results

Description of the study sample characteristics

The characteristics of the study sample are presented in Table I. The study sample comprised 435 patients. One-third of the study sample were male. The mean age of the study sample was 44.0 (SD: 16.0) years. The most prevalent comorbidities in the study sample were obesity, hypertension, and metastatic carcinoma. Cancer was the most common indication for surgery. Just over one-third of the study sample were classified as ASA > 2.

Table I: Distribution of various demographic characteristics, co-morbidities, and surgery-related variables in the study sample (N = 435), expressed as a frequency (%) or mean (SD)

Characteristic	*n* (% of study sample)
Male	143 (32.9)
Mean age in years (SD)	44.0 (16.0)
Obese (BMI > 30 kg/m^2)	
Yes	152 (34.9)
No	104 (23.9)
CNBE	179 (41.1)
Indication for surgery	
Intra-abdominal bleed	12 (2.8)
Cancer	183 (42.1)
Infection	35 (8.0)
Trauma or injury	56 (12.9)
Other non-communicable disease	149 (34.3)
ASA	
ASA ≤ 2	177 (40.7)
ASA > 2	150 (34.4)
ASA CNBE	108 (24.8)
Hypertension	140 (32.2)
Diabetes	57 (13.1)
Cardiovascular disease	50 (11.5)
Metastatic carcinoma	88 (20.2)
Current smoker	44 (10.1)

SD – Standard deviation, CNBE – Could not be established (due to missing data in patient file), BMI – Body Mass Index, ASA – American Society of Anesthesiologists Physical Classification

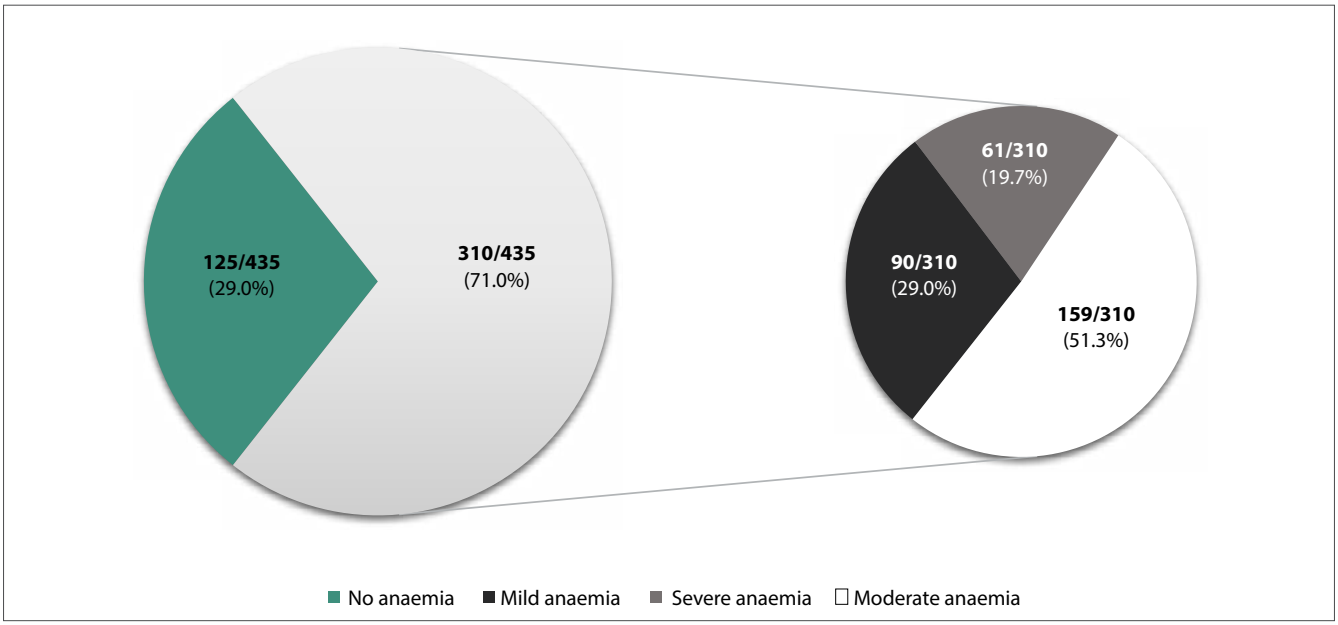

Figure 1: Pie chart showing the distribution of PA (stratified by severity) in the study sample (*N* = 435), expressed as frequencies and percentages*
*WHO grading system for Hb was used. PA – Preoperative anaemia

Prevalence and grading of PA (by severity) in the study sample

The mean preoperative Hb for the study sample was 108 (SD: 27) g/L. Preoperative anaemia was present in 310/435 patients (71.0%, 95% CI: 66.8–75.3%). Figure 1 shows the number/proportion of patients in the study sample according to PA severity grade.

Morphological classification of PA in the study sample

The morphological classification of PA in the study sample is presented in Figure 2. Normocytic anaemia was the predominant morphological form.

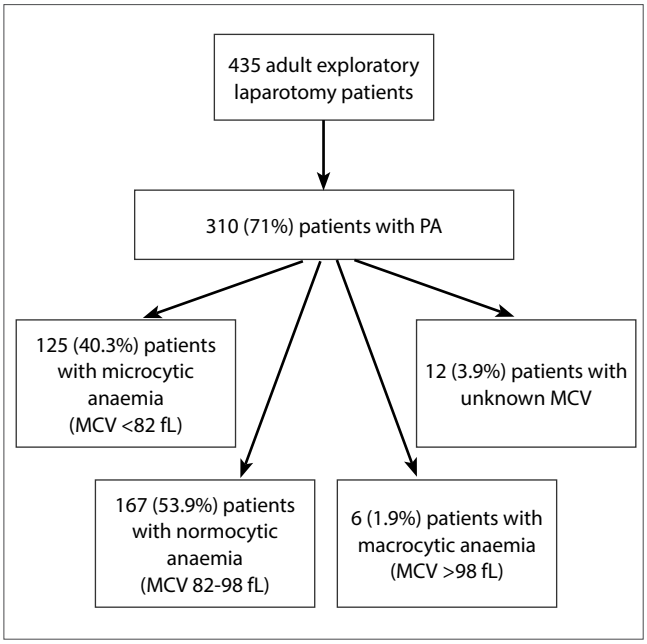

Figure 2: Flow diagram showing the frequency (%) of different morphological forms of PA in the study sample (*N* = 435)*
*PA – Preoperative anaemia, MCV – mean cell volume, fL – femtolitre

PA and PM in the study sample

As per Figure 3, the proportion of patients who suffered PM was found to be higher in the anaemic group when compared with the non-anaemic group (22.6% versus 8.0%, $p < 0.001$). PM in patients with PA was three-fold higher than that for patients without PA (OR: 3.35, 95% CI: 1.67–6.75; $p < 0.001$). This statistical association persisted when PA status was graded by severity (Figure 3). When the 95% CIs for PM estimates were taken into consideration (Figure 3), no difference in PM between patients with mild anaemia and non-anaemic patients was observed. Patients with moderate and severe anaemia appeared to be at higher risk for PM when compared with non-anaemic patients. Mortality was higher in patients with severe anaemia when compared with patients who had mild/moderate anaemia.

There was no difference in PM observed between the various morphological categories of PA that were investigated in this study (Figure 4).

Prognostic relevance of PA in the study sample

Figure 5 shows the prognostic relevance of PA for PM in the study sample. There are two ROC curves presented in Figure 5 – one for PA based on the presence or absence of anaemia by WHO criteria and one for PA based on the WHO graded severity classification. When the dichotomous classification was used (any anaemia) the AUC obtained was 0.599. When the graded severity classification was used, the AUC obtained was 0.705.

Discussion

The two most important findings from this study were that: 1) there is a high prevalence of PA (71%) in patients undergoing OIAS; and 2) moderate and severe PA are associated with increased PM, but mild PA is not.

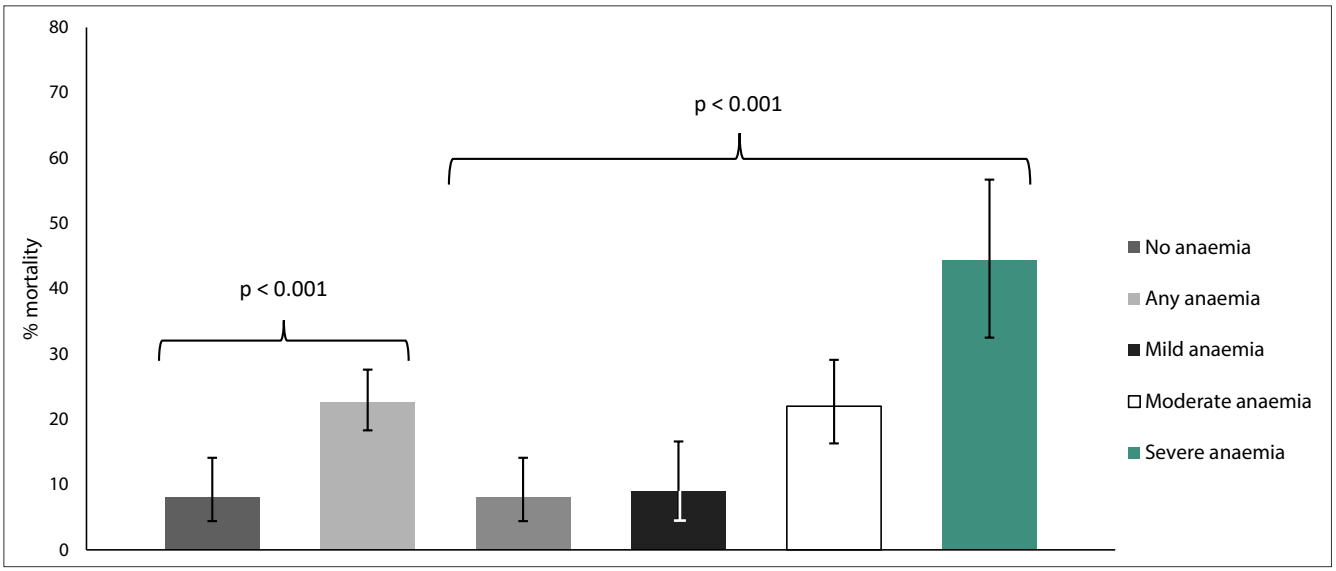

Figure 3: Bar chart showing the association between PA and PM in the study sample (*N* = 435)*
*PA – Preoperative anaemia. PM – postoperative mortality. PA graded using WHO thresholds. Error bars represent upper and lower 95% confidence intervals for PM estimates in the study sample

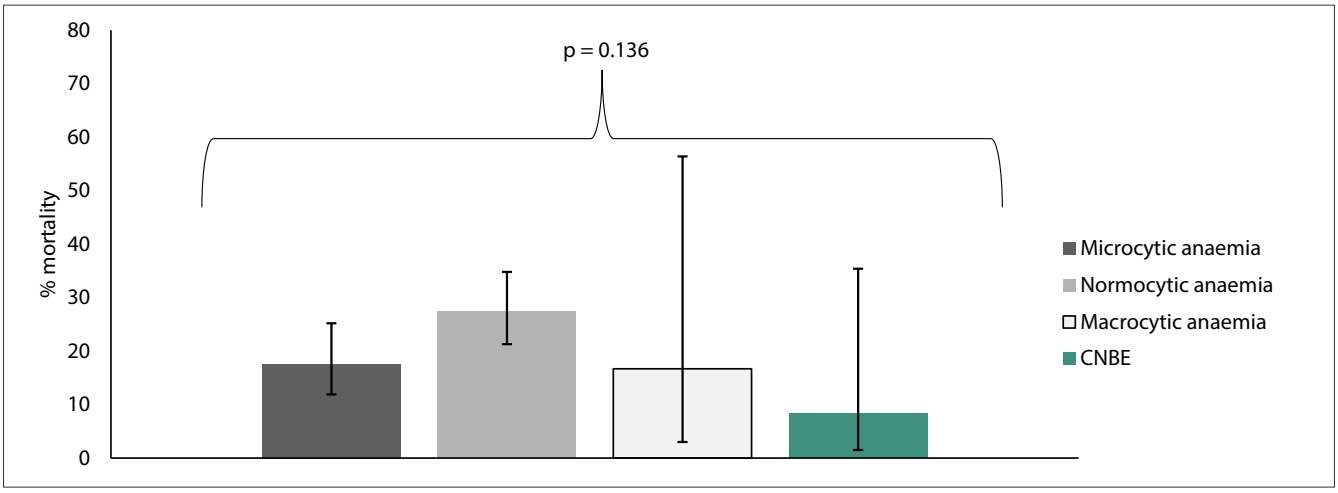

Figure 4: Bar graph showing the association between morphological classification of PA and PM in the study sample (*N* = 435)*
*PA – Preoperative anaemia. PM – postoperative mortality. Morphological classification based on widely accepted threshold for mean cell volume. Error bars represent upper and lower 95% confidence intervals for PM estimates in the study sample

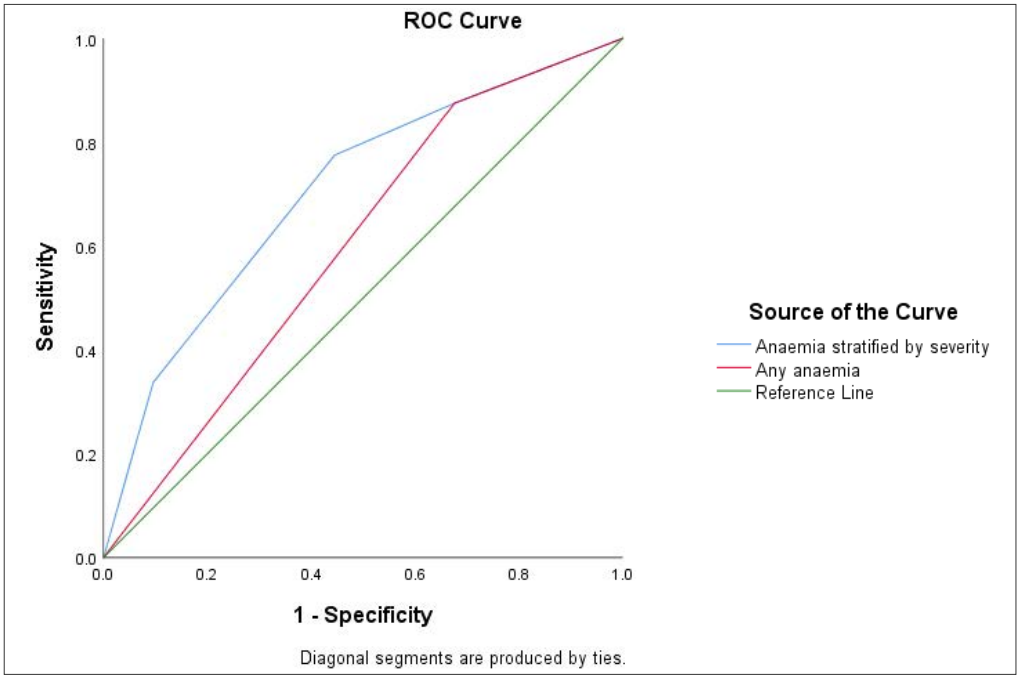

Figure 5: Prognostic relevance of PA for PM in the study sample (*N* = 435), shown as two ROC curves*
*PA – Preoperative anaemia, PM – postoperative mortality, ROC – receiver-operator-characteristic

The 71% of patients in the study sample that presented with PA is much higher than prevalence estimates for PA reported in studies from mixed surgical populations.[7-10] The age of our study population is younger with a higher proportion of females and patients with cancer when compared with other studies.[8] The impact of iron deficiency anaemia is most severe in younger premenopausal women, such as the majority of our study sample, who will have low iron status and reduced Hb because of iron loss in menstrual blood.[12] Chronic disease pathologies such as cancer, which was the indication for surgery in 42.1% of our study sample, can also contribute to functional iron deficiency. Chronic conditions can cause a combination of hypo-activity of the bone marrow, reduced erythropoietin production or a blunted response to erythropoietin, and a reduction in the lifespan of circulating erythrocytes.[13] The chronic inflammation associated with cancer induces hepcidin (an iron-regulatory peptide) production, which reduces the availability of iron for red cell maturation resulting in anaemia.[14,15]

The overall observed association between PA and increased PM in this study is in agreement with a recent meta-analysis of surgical studies conducted by Fowler and colleagues, that reported an almost three-fold higher risk of suffering PM.[10] We noted that PM was similar in patients with mild anaemia and non-anaemic patients, and that the overall association between PA and PM was being driven by significantly higher levels of PM in patients with moderate and severe anaemia. The similar incidence of PM in patients with mild PA and non-anaemic patients might be due to our smaller sample size, as the bulk of the published literature suggests that even mild PA is associated with worse clinical outcomes when compared to a non-anaemic group.[7] The physiological response to surgery includes a catabolic component,[16] which can last for three to eight days following surgery.[17] Oxygen plays an important role in catabolic reactions and the physiological requirement for oxygen may therefore be increased in the context of the surgical insult.[16,17] If one considers the important role of erythrocytes in maintaining oxygenation during the perioperative period, patients with moderate or severe anaemia suffer more substantial hypoxia and subsequent ischaemic injury in important organ systems as in the case of myocardial and acute kidney injury,[18,19] which then predisposes these patients to PM. The link between inadequate oxygenation of tissues during the perioperative period and postoperative complications has been described in interventional and observational studies. A randomised controlled trial conducted by Wilson et al., found that enhancement of oxygen delivery (through adrenaline or dopexamine) in major surgery patients was associated with significantly lower PM in the adrenaline/dopexamine group versus the control group (3% versus 17%, $p = 0.007$).[20] An observational study by Abdelmalak and colleagues reported that tissue oxygenation was inversely associated with thirty-day mortality and serious in-hospital complications ($p = 0.02$) in patients undergoing major surgery.[21] In the same study, the risk of major postoperative morbidity had declined by 18% for a 5% increase in the minimum tissue oxygen saturation.[21] Improving perioperative oxygen delivery may lead to improved postoperative outcomes in major surgery patients.

A 2013 meta-analysis reported that iron supplementation (intravenous or oral) could raise Hb by 6.5 (95% CI: 5.1–7.9) g/L.[22] Although there is limited high-quality evidence of reduced PM in elective major surgery patients with PA who receive iron therapy, a meta-analysis of studies involving acute major surgery patients reported a 50% reduction in PM when PA was treated preoperatively with iron supplementation.[23] It is likely that there would also be some protective effect against PM in elective surgery patients who receive iron therapy.

Patient blood management strategies such as optimising surgical technique and the use of anti-fibrinolytic agents (tranexamic acid) can reduce intraoperative blood loss in OIAS patients. Glance and colleagues reported that surgical cases involving less-skilled trainee surgeons were 56–78% more likely to require a blood transfusion than cases involving experienced surgeons.[24] In a randomised controlled trial investigating the effectiveness of tranexamic acid in hepatectomy patients, Wu et al. reported that patients in the tranexamic acid group experienced significantly lower overall levels of perioperative blood loss when compared with a placebo group (300 mL versus 600 mL, $p < 0.001$).[25] Blood transfusion is another strategy which can be used to address anaemia during the perioperative period. However, this approach should be carefully considered as large cohort studies have reported a 29–32% higher risk of PM in surgical patients who receive perioperative transfusions.[26,27]

Preoperative anaemia displayed fair-to-good prognostic accuracy for PM in this study. The difference in AUC between the dichotomous classification and the graded classification is likely due to differences in risk for PM between the various grades of PA. Sub-analyses of the EuSOS and SASOS datasets,[8,9] wherein potential confounders were accounted for, have identified PA as an independent risk factor for PM. In the EuSOS sub-analysis, PA (graded by severity) was independently associated with a 1.2–2.8-fold higher risk of PM.[8] In the SASOS sub-analysis, PA was independently associated with a 1.6-fold higher risk of PM.[9] It must be noted however, that PM is multifactorial. It is therefore possible that PA might be more useful if it is included within a multifactorial risk stratification index, rather than being used as a prognostic indicator on its own.

A strength of this study is that it explores a less frequently reported population rather than the European or North American populations investigated in most of the existing literature. The younger, predominately female study population is also a useful group to assess if the association between preoperative anaemia and poor postoperative outcome is still seen. There were limitations to this study. Data was sourced from a single, tertiary public sector hospital questioning generalisability to other facilities. The type of diseases, comorbidities, prior health status and hence prevalence of PA may differ in private sector hospitals or other public sector hospitals. This study is limited to patients presenting between 2006 and 2010, which may limit the range of diseases seen, as the patient profile and range of conditions may change in a population over time. Iron studies are not performed routinely for surgical patients at our facility, and we were unable to determine the impact of iron deficiency in our study population. As this was a retrospective study,

variables such as nutritional status, iron studies, inflammatory markers and the cause of death were not noted, and hence we were unable to investigate these aspects. In 2017, a consensus statement was released recommending the use of Hb < 130 g/L as the cut-point for PA in both males and females.[28] Our study used the 2011 WHO Hb thresholds to define PA rather than the 2017 Hb thresholds for two main reasons. Firstly, our use of the 2011 WHO Hb thresholds allowed us to directly compare our findings to those findings reported from the EuSOS and SASOS sub-analyses,[8,9] which also defined PA according to the 2011 WHO Hb thresholds.[3] Secondly, the 2017 Hb thresholds were still not fully adopted in our specific setting and the 2011 WHO Hb threshold was more widely used. We propose that research be performed to assess the relevance of using the 2017 Hb threshold versus the 2011 WHO Hb threshold to define PA in our setting. The registry did not collect information on preoperative interventions for anaemia, and there is a possibility that if there were any interventions, these could have affected patient outcomes following surgery.

We report a much higher prevalence of PA in this sample of OIAS/major surgery patients than that reported in studies comprised of a mix of minor, intermediate, and major surgical procedures. In keeping with the findings from studies of mixed surgical populations, PA was associated with increased PM. Moderate and severe PA are associated with increased PM, but mild PA is not. Preoperative anaemia displays a fair-to-good prognostic accuracy for PM in patients undergoing OIAS, however it is possible that it would be more useful if it were included within a multifactorial risk stratification index. A recent international consensus statement has put forward recommendations for best clinical practice in the perioperative management of anaemia and iron deficiency, of which early diagnosis of PA and preoperative optimisation of Hb are important themes.[28] Such recommendations are highly relevant to study populations such as ours. We recommend that further research, which also seeks to address the limitations of the current study, be conducted to confirm our findings.

Conflict of interest

The authors declare that there are no financial or personal relationships which may have inappropriately influenced the writing of this paper.

Ethical approval

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, SA (Protocols: BE674/18 and BCA208/18).

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