The association between preoperative anemia and postoperative morbidity in pediatric surgical patients: A secondary analysis of a prospective observational cohort study

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Abstract

Background: The prevalence of anemia in the South African pediatric surgical population is unknown. Anemia may be associated with increased postoperative complications. We are unaware of studies documenting these findings in patients in low- and middle-income countries (LMICs). **Aim**: The primary aim of this study was to describe the association between preoperative anemia and 26 defined postoperative complications, in noncardiac pediatric surgical patients. Secondary aims included describing the prevalence of anemia and risk factors for intraoperative blood transfusion. **Method**: This was a secondary analysis of the South African Paediatric Surgical Outcomes Study, a prospective, observational surgical outcomes study. Inclusion criteria were all consecutive patients aged between 6 months and <16 years, presenting to participating centers during the study period who underwent elective and nonelective noncardiac surgery and had a preoperative hemoglobin recorded. Exclusion criteria were patients aged <6 months, undergoing cardiac surgery, or without a preoperative Hb recorded. To determine whether an independent association existed between preoperative anemia and postoperative complications, a hierarchical stepwise logistic regression was conducted. **Results**: There were 1094 eligible patients. In children in whom a preoperative Hb was recorded 46.2% had preoperative anemia. Preoperative anemia was independently associated with an increased risk of any postoperative complication (odds ratio 2.0, 95%

confidence interval: 1.3-3.1, P =.002). Preoperative anemia (odds ratio 3.6, 95% confidence interval: 1.8-7.1, P <.001) was an independent predictor of intraoperative blood transfusion. **Conclusion**: Preoperative anemia had a high prevalence in a LMIC and was associated with increased postoperative complications. The main limitation of our study is the ability to generalize the results to the wider pediatric surgical population, as these findings only relate to children in whom a preoperative Hb was recorded. Prospective studies are required to determine whether correction of preoperative anemia reduces morbidity and mortality in children undergoing noncardiac surgery.

Keywords: adverse effects; anemia; complication; pediatric surgery; perioperative period; surgery

Clinical implications

- Published studies have shown the association between preoperative anemia and increased risk of mortality in pediatric surgical patients undergoing noncardiac surgery
- This study demonstrates the association between preoperative anemia and increased risk of postoperative complications and intraoperative transfusion in a middle-income country in children aged between 6 months and 16 years undergoing noncardiac surgery

1 INTRODUCTION

Defining the prevalence of preoperative anemia plays an important role in patient optimization for surgery. Identification, and treatment of preoperative anemia represents one of the three pillars of patient blood management programs, combined with optimization of transfusion strategies, and the use of blood sparing techniques. The implementation of patient blood management programs within the adult surgical population has been clearly shown to improve outcomes and reduce costs.[1]

Since 1990, there has been a worldwide decline in anemia in children under the age of 5 years.2 The prevalence of anemia in this age group in the South Africa population has remained relatively unchanged at 37%.[2] Children in low- and middle-income countries (LMICs) are at greater threat of exposure to contributing risk factors for anemia. It would therefore be reasonable to expect that preoperative anemia would be more prevalent compared with studies from high-income countries (HICs).[3,4] The reported prevalence of preoperative anemia in adult surgical patients from African countries ranges from 38% to 47.8%.[5-7] The prevalence of anemia in the South African pediatric surgical population is unknown.

The association between increased morbidity and mortality and anemia in the adult surgical population in high-income countries has been well documented.[8-10] In adult patients undergoing noncardiac surgery, anemia was found to be an independent predictor of increased risk of cardiac, respiratory, urinary tract, and wound events, sepsis, and venous thromboembolism.[8,10] Data on anemia and morbidity in adult surgical patients from LMICs are limited. The South African Surgical Outcomes Study found that in the adult population preoperative anemia was independently associated with in-hospital mortality and admission to critical care.[8] A small retrospective observational study of adult noncardiac surgical patients in the Republic of Congo and Madagascar found that severe anemia was associated

with an increased risk of postoperative complications including unexpected ICU admission, surgical site infection, and hospital readmission.[7] In Ghana, an observational study of unselected adult noncardiac surgery patients found preoperative anemia was associated with increased length of stay.[6]

Recent studies in HICs have highlighted the increased risk of in-hospital mortality in neonates and children associated with preoperative anaemia.[3,4] Conflicting data exist regarding the implications of preoperative anemia on postoperative complications in pediatric surgery patients. Data from an observational study in adolescent spinal deformity surgery have shown an association between preoperative anemia and increased postoperative complications as well as increased hospital costs.[11] In comparison, a large retrospective review of the NSQIP database of patients undergoing pediatric spinal deformity surgery did not find an association between hematocrit and morbidity or mortality.[12] In pediatric cardiac surgery, higher hematocrit levels at the onset of low-flow cardiopulmonary bypass have shown to be associated with higher postoperative psychomotor development index scores.[13] In contrast, a single-centre retrospective study in infants aged <1 year undergoing pyloromyotomy found that preoperative anemia was not associated with postoperative complications.[14] Lower preoperative hemoglobin (Hb) levels have also been shown to be an independent risk predictor for allogenic blood transfusion in pediatric neurosurgical and cardiac patients.[15,16] An increased prevalence of anemia may result in increased postoperative complications in pediatric surgical noncardiac patients in LMICs. We are unaware of studies documenting these findings in this environment.

The primary objective of this study was to describe the association between preoperative anemia and postoperative complications in pediatric noncardiac surgical patients in South Africa. Secondary objectives include; (a) describing the prevalence of anemia within a pediatric surgical population in South Africa and (b) evaluating the association between preoperative anemia and intraoperative blood transfusion.

2 METHODS

Ethical approval for the study was granted by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (UCT) (HREC REF: 171/2019).

This was a secondary analysis of the South African Paediatric Surgical Outcomes Study (SAPSOS).[17] SAPSOS was a prospective observational fourteen-day South African national multicentre cohort study of pediatric patients (age <16 years) undergoing surgery. A total of 2024 patients were recruited between May 2017 and August 2017 from 43 government-funded hospitals. Outcome data were complete for 97.6% of patients for postoperative complications and 99.5% for mortality. SAPSOS is registered at https://clinicaltrials.gov/ct2/show/NCT03367832.

Inclusion criteria were all consecutive patients aged between 6 months and <16 years, presenting to participating centers during the study period who underwent elective and nonelective noncardiac surgery and had a preoperative Hb recorded. This included day case surgery and operative procedures outside operating theaters where a general anesthetic (GA) was performed. Exclusion criteria were patients without a preoperative Hb recorded, cardiac surgery, and age <6 months. Anemia (g/d) was defined according to the WHO criteria.[18]

- Children 6-59 months of age (Mild, 10.0-10.9; Moderate, 7.0-9.9; Severe, <7.0)

- Children 5-11 years of age (Mild, 11.0-11.4; Moderate, 8.0-10.9; Severe, <8.0)
- Children 12-14 years of age (Mild, 11.0-11.9; Moderate, 8.0-10.9; Severe, <8.0)
- Nonpregnant women aged 15 years and above (Mild, 10.0-10.9; Moderate, 7.0-9.9; Severe, <7.0)
- Men aged 15 years of age and above (Mild, 11.0-12.9; Moderate, 8.0-10.9; Severe, <8.0)

Definitions for severity of surgery were adapted from the definitions used in the African Surgical Outcomes Study (ASOS)[19] (See Supporting Information).

2.1 Sample size

We intended to recruit as many eligible patients as possible from the SAPSOS, in order to establish a representative sample from all participating South African centers. Based on the SAPSOS study results, excluding patients aged <6 months (n = 189), patients who underwent cardiac surgery (n = 39), and estimating that 48%20 (629/1 311) of children presenting for elective surgery will have had a preoperative Hb recorded, and assuming 95% of children presenting for urgent and emergency surgery will have a preoperative Hb recorded, we calculated an estimated sample size of 1098 patients. The overall postoperative complication rate of 9.7% in the principal SAPSOS study, given the estimated the sample size of 1098 patients, should yield approximately 107 postoperative events.

To detect an odds ratio of 1.89 with an 80% power, a two-sided significance level of 0.05 and a 1:1 ratio in the numbers of subjects would require a sample size of 550 observations per arm. The sample size should therefore be able to detect a clinically meaningful effect size of a minimum of 20% regarding the presence of preoperative anemia and the primary outcome of any postoperative complication.

2.2 Statistical analysis

Categorical variables are reported as number and percentage. All patient and surgical characteristics were compared between anemic and nonanemic children using Pearson's chi-squared or Fisher's exact tests as appropriate. Continuous variables were calculated and presented as mean and standard deviation, or as median and interquartile range (IQR). A *t* test for normally distributed data or Mann-Whitney *U*-test for nonnormally distributed data was used to compare differences in continuous variables.

A hierarchical forward stepwise regression analysis was used to determine the independent predictors for all postoperative complications (Infective complications: superficial surgical site infection (SSI), deep SSI, body cavity infection, pneumonia, urinary tract infection, bloodstream infection; Cardiovascular complications: arrhythmia, pulmonary edema, pulmonary embolism, cardiac arrest; Other complications: gastrointestinal bleed, acute kidney injury, postoperative bleed, acute respiratory distress syndrome (ARDS), anastomotic breakdown, other) and intraoperative blood transfusion using a cutoff of $P > .01$ for removal. The results are expressed as regression coefficient and standard error, the odds ratio (OR) as a measure of risk, the 95% confidence interval (CI), and *P* values obtained from the Wald test. Possible independent preoperative risk factors for postoperative complications were included based on clinical plausibility and known independent preoperative risk factors for postoperative complications in the South African Paediatric Surgical Outcomes Study

cohort.21 The number of potential risk factors included in the intraoperative transfusion model was limited by the number of outcomes.

Receiver operating curves (ROC) were constructed for the models for all postoperative complications and intraoperative blood transfusion.

Statistical analyses were performed using ncss 2019 Statistical Software (2019). NCSS, LLC.

3 RESULTS

Among the 2024 patients included in the SAPSOS cohort, after exclusion of all children aged <6 months and undergoing cardiac surgery, 1094 had a preoperative Hb recorded (54.1%; Figure 1). About 505/1 094 (46.2%) of patients who had a preoperative Hb recorded had preoperative anemia (36.9% mild, 60.0% moderate, and 3.1% severe anemia). The median preoperative Hb in the anemic group was 10.2 g/dL (IQR 9.4-10.8) vs 12.4 g/dL (IQR 11.9-13.5) in the nonanemic group. Children with anemia had higher ASA physical status classification ($P < .001$) were younger ($P < .001$) and had higher incidence of HIV/AIDS ($P = .013$), but no significant difference in other major comorbidities, urgency of surgery, indication for surgery, or grade of surgery (Table 1).

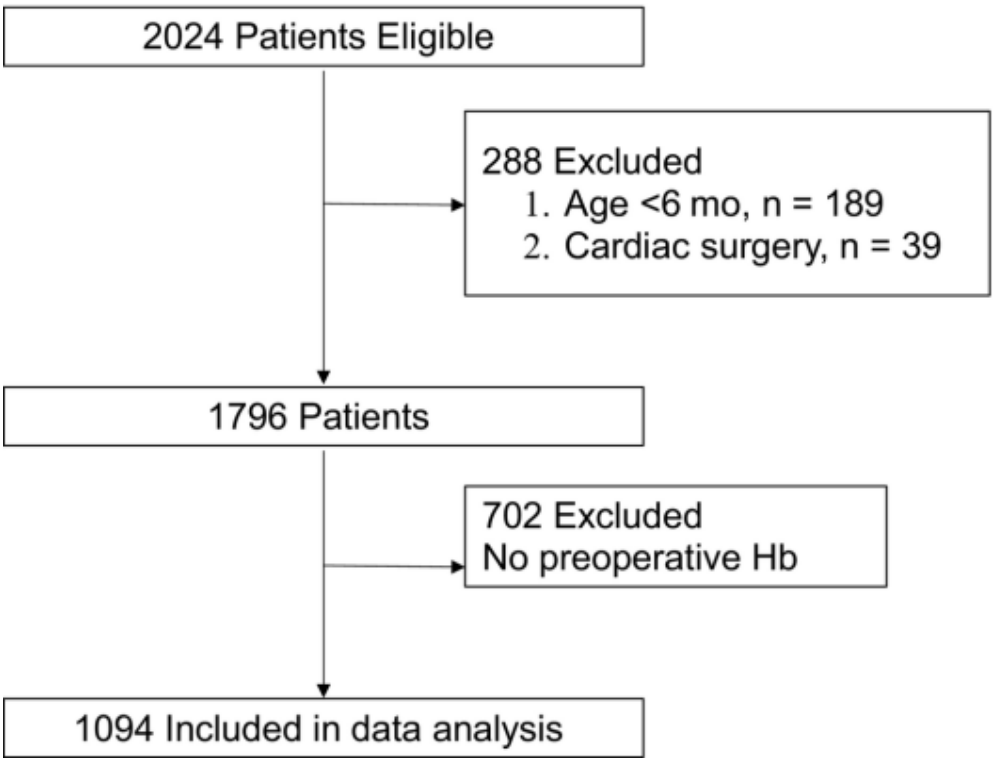

Figure 1. Flowchart

Table1. Demographic characteristics and comorbidities in children with and without preoperative anemia

Variables	Anemic (n = 505)	Nonanemic (n = 589)	P value
Hemoglobin (median, IQR)	10.2 (9.4-10.8)	12.4 (11.9-13.5)	<.001
Males, n/N (%)	325/681 (47.7)	356/681 (52.3)	.154
Age group (y), n/N (%)			
≥0.5-1	29/53 (54.7)	24/53 (45.3)	
≥1-4	147/262 (56.1)	115/262 (43.9)	
≥4-13	279/669 (41.7)	390/669 (58.3)	
≥13-16	50/110 (45.5)	60/110 (54.5)	.001
ASA physical status, n/N (%)			
1	310/720 (43.1)	410/720 (56.9)	
2	105/228 (46.1)	123/228 (53.9)	
≥3	87/141 (61.7)	54/141 (38.3)	<.001
Comorbidity, n/N (%)			
Heart disease	14/32 (43.8)	18/32 (56.3)	.781
Cancer	26/50 (52.0)	24/50 (48.0)	.398
Neurological disorder	21/49 (43.8)	28/49 (56.3)	.732
HIV/AIDS	23/34 (67.6)	11/34 (32.4)	.013
Respiratory disease	44/97 (45.4)	53/97 (54.6)	.869
Congenital syndrome	36/66 (54.5)	30/66 (45.5)	.161
Sleep Disordered Breathing	17/43 (39.5)	26/43 (60.5)	.375
Any Comorbidity	205/404 (50.7)	199/404 (49.3)	.540
Primary indication, n/N (%)			
Noncommunicable disease	137/306 (44.8)	169/306 (55.2)	
Infective	111/247 (44.9)	136/247 (55.1)	
Trauma	160/317 (50.5)	157/317 (49.5)	
Congenital	97/223 (43.5)	126/223 (56.5)	.335
Grade of surgery, n/N (%)			
Minor	244/529 (48.5)	285/529 (53.9)	
Intermediate	227/491 (45.0)	264/491 (53.8)	
Major	31/71 (43.7)	40/71 (56.3)	.199
Urgency of surgery, n/N (%)			
Elective	279/647 (43.1)	368/647 (56.9)	
Urgent	134/261 (51.3)	127/261 (48.7)	
Emergency	92/186 (49.5)	94/186 (50.5)	.918

Complete complications data were available for 1074 patients (98.2%). About 108/1 073 (9.9%) of patients experienced postoperative complications. Hierarchical forward stepwise regression analysis showed an association between preoperative anemia and an increased risk of 'all postoperative complications' (OR 1.99, 95% CI: 1.28-3.10, *P* = .002; Table 2).

Table2. Multivariable analysis of factors associated all complications [a]

Variables	OR	CI	P-value
Orthopedic Surgery	0.36	0.19-0.67	.001
Intermediate Surgery	1.90	1.17-3.08	.010
Anemia	1.99	1.28-3.10	.002
Major Surgery	2.69	1.27-5.70	.010
Urgent Surgery	3.06	1.80-5.20	<.001
ASA-PS ≥ 3	3.65	2.17-6.14	<.001
Emergency Surgery	4.21	2.47-7.18	<.001

[a] All complication includes; infective, cardiovascular, and other complications

About 58/1 095 (5.3%) of patients received an intraoperative blood transfusion. Hierarchical forward stepwise regression analysis showed an association between preoperative anemia and an increased risk of intraoperative blood transfusion (OR 3.60, 95% CI: 1.83-7.05, $P < .001$; Table 3). The ROC curve operating curve for intraoperative blood transfusion representing the proportion of correct classifications for different probability cutoff points based on the variables in the equation is shown in Figure 2.

Table3. Multivariable analysis of factors associated transfusion

Variables	OR	CI	P-Value
ASA-PS 2	2.38	1.09-5.18	.030
Intermediate Surgery	2.41	1.16-5.02	.019
Anemia	3.60	1.83-7.05	<.001
Trauma Indication	5.65	2.37-13.47	<.001
ASA-PS ≥3	6.90	3.20-14.85	<.001
Major Surgery	15.26	6.19-37.59	<.001

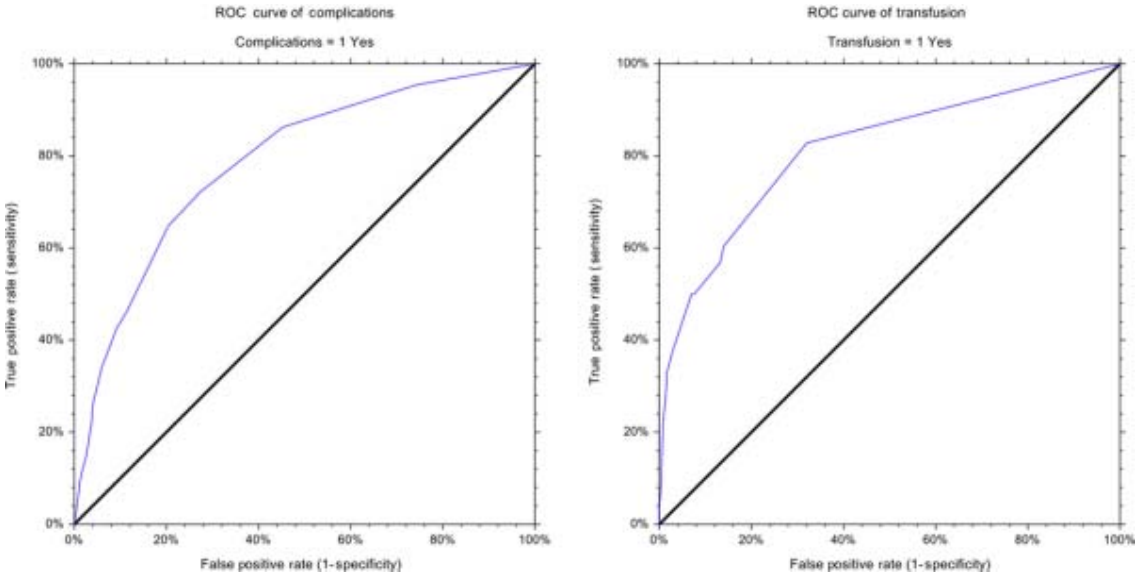

Figure 2*. Receiver Operating Curves*

4 DISCUSSION

The principal finding of this study is that preoperative anemia is independently associated with an increased risk of postoperative complications in children undergoing noncardiac surgery in whom a preoperative Hb was documented (OR 1.99, 95% CI 1.28-3.10, $P = .002$). These findings are similar to those reported from a large database study of 36,335 patients undergoing adolescent spinal deformity surgery which found and an association between preoperative anemia and increased risk of postoperative complications (OR 2.10, 95% CI 1.51-2.91, $P < .001$),11 although their reported overall complication rate was lower (7.6%, 95% CI 6.3%–8.9%). Mussallam et al have also described the association between preoperative anemia and postoperative morbidity from 227 425 adult patients undergoing noncardiac surgery.8 They describe higher rates of certain morbidities in the anemic compared with nonanemic patients including, cardiac, respiratory, urinary tract, and wound events, sepsis, and venous thromboembolism. They found the composite postoperative morbidity at 30 days was higher in patients with anemia than in those without anemia (adjusted OR 1.35, 1.30-1.40).

This study also raises concern regarding the significant burden of anemia among children undergoing noncardiac surgery in South Africa. The prevalence of anemia within our study cohort was much higher than reported from large database studies from North America which found the prevalence of anemia in children presenting for noncardiac surgery to be 24% in children aged >1 year3 and 21.7% within the neonatal surgical population.4 In comparison, data from a small retrospective study from India noted that a third of children who presented for cleft lip and palate surgery were anemic (Hb < 10.0 g/dL).21 The prevalence of preoperative anemia in our study is consistent with the prevalence of preoperative anemia reported from the SASOS study, a prospective observational study of adult surgical patients across 50 public hospitals in South Africa (47.8%).5 This supports the finding that the prevalence of anemia in the surgical population in South Africa is higher than HICs. The relatively high prevalence of preoperative anemia, even present in almost half of the children classified as ASA PS 1, or presenting for elective surgery, or undergoing minor and intermediate surgery, is likely indicative of the overall population of children presenting for surgery in South Africa being exposed to risk factors including; poor nutrition and poor health, and intestinal parasitic infestations.22 Malaria is not an endemic disease within the majority of South Africa.

Within our study cohort preoperative anemia was associated with an increased risk of receiving an intraoperative blood transfusion (OR 3.60, 95% CI 1.83-7.05, $P < .001$). The indications for transfusion were not recorded, but the threshold for transfusion is influenced by the initial Hb, which will affect the maximum allowable blood loss.23 Identification and treatment of preoperative anemia is a pillar of perioperative patient blood management and is particularly relevant when other risk factors for intraoperative transfusion are present.

4.1 Limitations

The main limitation of our study is the inability to generalize the results to the wider pediatric surgical population, as this study only included patients in whom a preoperative Hb was done. This results in a selection bias, as is reflected in the findings that the majority of patients in whom preoperative Hb was performed had higher ASA scores and were more likely to have major surgery, urgent or emergent surgery, and/or surgery for traumatic or infective indications. Although our findings highlight the importance of anemia negatively

impacting on patient outcomes in these patients, to understand whether these findings are generalizable across all pediatric surgical patients, a systematic screening for anemia would be required across all surgical patients. Although, the true prevalence of anemia with the general pediatric surgical population in South Africa is likely to be lower than reported in our study (46.2%), the prevalence of anemia in children under 5 years in South Africa has been reported as 37%2; therefore, the findings are unlikely to be substantially different across the entire pediatric surgical cohort in South Africa.

The study cohort were represented from 43 government-funded hospitals, primarily treating patients from a low socioeconomic background and may not reflect the prevalence of anemia in the patient population treated at private hospitals. It is also difficult to directly compare the reported prevalence of preoperative anemia due to the variability in the cutoff levels used to define anemia (See Supporting Information). We chose to use the WHO criteria for defining anemia, but other studies quoted within this article have used similar, but different definitions (See Supporting Information). Uniformity of definitions in perioperative outcomes in pediatric surgical patients is required to enable direct comparisons between studies and ultimately enable evidence-based change in practice.

Another limitation of this study is that it is not possible to ascertain the cause of anemia as iron studies were not routinely conducted in this study. It would be of value to further investigate the causes of anemia within this patient population to allow a better understanding of preoperative interventions needed to optimize the hemoglobin in these children prior to surgery.

The timing of the preoperative Hb was also not recorded, although it was limited to the period 1 month prior to surgery. It is possible that an immediate preoperative Hb may have differed from the recorded result, if the patient had for example received a blood transfusion or iron supplementation preceding surgery.

Another limitation is that the pragmatic nature of the study, resulted in a very simple classification of surgical severity. We are therefore unable to document the impact of anemia on outcomes according to complexity of surgery. There are more robust measures now to adjust for the surgical complexity, which would be desirable in future work on the impact of anemia outcomes in pediatric surgery.24

5 CONCLUSION

Anemia is a common preoperative comorbidity within the South African pediatric surgical population, and it is associated with increased postoperative complications. Surgery may be the first point of access to healthcare for children at risk of anemia and therefore represent an important opportunity for the detection and treatment of anemia in children in LMICs. Instituting management of preoperative anemia within a patient blood management program has the potential to reduce postoperative complications, intraoperative blood transfusion, and mortality in pediatric surgical patients. Prospective interventional studies are required to ascertain whether correction of preoperative anemia reduces morbidity and mortality in children undergoing noncardiac surgery.

CONFLICT OF INTEREST

No conflict of interest.

ETHICAL APPROVAL

Ethical approval for the study was granted on the 18/03/2019 by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC REF:171/2019).

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