Statistical Analysis Plan

The impact of preoperative anaemia on hospital costs following major abdominal surgery

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Introduction

Preoperative anaemia is independently associated with an increased risk of postoperative morbidity and mortality and greater health care expenditure[1-3]. Perioperative anaemia appears to generate a substantial health burden by increasing the requirement for blood transfusions, ICU admissions, and hospital length of stay.[1, 4, 5, 6] To mitigate the putative negative impact of perioperative anaemia, health care providers are increasingly allocating resources toward the development of multidisciplinary, perioperative patient blood management programs to optimise patient haemoglobin (Hb) levels before surgery.[7]

The implementation costs of such programs can be estimated from data, which is available to policy makers. However, determining the cost-effectiveness, and therefore the sustainability of these programs, depends on accurate financial data. Such data can be used to precisely quantify the health economy burden associated with preoperative anaemia and, thereby, justify the cost effectiveness of blood management programs. In particular, a deeper understanding of these associations is imperative for health care decision makers in driving the pursuit of more efficient care for anaemic patients and improving the utilisation of financial, logistical and workforce resources. Regrettably, there is a paucity of high-quality health economics studies exploring the nature of the relationship between preoperative anaemia and the financial drivers of increased hospital costs.

To address this knowledge gap we propose to conducted a focussed and detailed health economics analysis of pre-operative anaemia at Austin Health. Our primary aim will be to quantify the burden of hospital costs attributable to preoperative anaemia in patients receiving major abdominal surgery at Austin Health. Secondary aims included estimating the associations between preoperative haemoglobin concentration ([Hb]c) and patient variables that directly relate to hospital costs, and then to determine the likely key drivers for increased hospital costs in anaemic patients. We hypothesise that increasing severity of preoperative anaemia will be independently associated with higher postoperative hospital costs and more adverse patient outcomes.

Methods:

Study design and setting

Outcome data from the financial costing records of patients undergoing major abdominal surgery at Austin Health will be collected for the time periods between July 2010 and June 2018. To more clearly appreciate the financial burden associated with preoperative anaemia, we will select four types of subspecialty surgeries, each of which being associated with significant morbidity.

These surgeries will include:

- pancreaticoduodenectomy (PD)
- major colonic resection
- major rectal resections
- liver resection surgery

We will include adult patients (age greater 18 years), who underwent surgery of greater than two hours duration and who required at least one overnight hospital stay. Due to the retrospective nature of the study and the deidentified data collected, we will request a waiver for participant consent.

The study will be registered with the Australian New Zealand Clinical Trials Registry.

Primary Outcomes

The primary outcome will the unadjusted burden of hospital costs attributable to preoperative anaemia. This will be assessed by examining relationship between [Hb]c and total hospital costs, and by investigating the association between such costs and four prespecified [Hb]c categories, namely [Hb]c <9.0 g/dL, [Hb]c 9.0 - 13.0 g/dL, [Hb]c 13.0 - 15.0 g/dL, and [Hb]c >15.0 g/dL.

Secondary Outcomes

The key secondary outcomes will be the independent relationship between [Hb]c and eight prespecified patient variables, all of are associated with anaemia. These included age, gender, ASA classification, Charlson Comorbidity Index, increased creatinine concentration, hypoalbuminemia, and type and urgency of surgery.

As additional secondary outcomes, will be to evaluate the independent relationship between [Hb]c and eleven prespecified variables that appear to directly impact on hospital costs. These include operation time, allogenic red blood cell (RBC) transfusion, number of RBC transfused, number of patients with a postoperative ICU admission, ICU admission time for patients requiring ICU, length of hospital stay, readmission within 30 days after discharge, costs incurred during readmission within 30 days after discharge, development of complications, number of complications per patient, and severity of complication.

Anaesthesia and surgery protocols
All patients have undergone standardized Austin Health enhanced recovery after surgery protocols that included preoperative multidisciplinary assessment and optimization of medical comorbidities, and optimization of exercise, and nutrition according to our local hospital policies. In addition, all patients have undergone comprehensive preoperative optimization of haemoglobin according to the National Blood Authority of Australia's patient blood management initiative[7], and glycaemic optimization according to the Australian Diabetes Society guidelines.

Notably, there will be NO CLINICAL or patient contact involved at any point. All data collected has already been collected by normal hospital anaesthesia and surgical processes.

Intraoperative anaesthesia and surgical care were managed accordingly to standard hospital practises at our institution, as were postoperative analgesic, fluid intervention, thromboembolic prophylaxis, antimicrobial and anti-emetic regimens. All patients received daily physiotherapy and postoperative analgesia via an acute pain service. Patient discharge criteria included full dietary intake, unassisted mobilisation, the absence of surgical or medical complications, and sufficient pain control.

Participants
We will identify patients from existing Austin Health Information Services database, by using International Classification of Diseases, Tenth Revision (ICD-10) codes presented below, specific to each surgical procedure.

ICD-10 Codes

Colonic resection	ICD code
Right hemicolectomy	32003-01 Right hemicolectomy with anastomosis
	32005-03 Laparoscopic extended right hemicolectomy with anastomosis
	32003-03 Laparoscopic right hemicolectomy with anastomosis
	32005-01 Extended right hemicolectomy with anastomosis
	32004-01 Extended right hemicolectomy with formation of stoma
	32000-03 Laparoscopic right hemicolectomy with formation of stoma
	32004-03 Laparoscopic extended right hemicolectomy with formation of stoma
	32000-01 Right hemicolectomy with formation of stoma
Left hemicolectomy	32006-00 Left hemicolectomy with anastomosis
	32006-02 Laparoscopic left hemicolectomy with anastomosis
	32006-03 Laparoscopic left hemicolectomy with formation of stoma
	32006-01 Left hemicolectomy with formation of stoma
Total colectomy	32009-00 Total colectomy with ileostomy
	32012-01 Laparoscopic total colectomy with ileorectal anastomosis
	32009-01 Laparoscopic total colectomy with ileostomy
	32012-00 Total colectomy with ileorectal anastomosis
Subtotal colectomy	32004-02 Laparoscopic subtotal colectomy with formation of stoma
	32005-02 Laparoscopic subtotal colectomy with anastomosis
	32005-00 Subtotal colectomy with anastomosis

	32004-00 Subtotal colectomy with formation of stoma
Other	32000-02 Laparoscopic limited excision of large intestine with formation of stoma
	32003-00 Limited excision of large intestine with anastomosis
	32003-02 Laparoscopic limited excision of large intestine with anastomosis
	32000-00 Limited excision of large intestine with formation of stoma
Liver resection	30414-00 Excision of lesion of liver 30415-00 Segmental resection of liver 30418-00 Lobectomy of liver 30421-00 Trisegmental resection of liver
Pancreaticoduodenectomy	30584-00: pancreaticoduodenectomy with formation of stoma
Rectal resection	32024-00 High anterior resection of rectum 32025-00 Low anterior resection of rectum 32026-00 Ultra low anterior resection of rectum 32028-00 Ultra low anterior resection of rectum with hand sutured coloanal anastomosis 32030-00 Rectosigmoidectomy with formation of stoma 32030-01 Laparoscopic rectosigmoidectomy with formation of stoma 32039-00 Abdominoperineal proctectomy 32047-00 Perineal proctectomy 32051-00 Total proctocolectomy with ileo-anal anastomosis 32051-01 Total proctocolectomy with ileo-anal anastomosis and formation of temporary ileostomy 32112-00 Perineal rectosigmoidectomy 92208-00 Anterior resection of rectum, level unspecified

Costing data will be provided by the Austin Health Business Intelligence Unit. The operation type will then confirmed using the operating report. Patients will be included in the study regardless of the surgical technique used (open or laparoscopic), urgency level (emergency or elective), or indication for surgery. All patients that undergo any minor concomitant procedure (e.g. appendectomy, cholecystectomy) will be included (e.g. liver resection and cholecystectomy). We will exclude patients who were admitted for a non-abdominal surgical indication who subsequently required major abdominal surgery (e.g. acute type A aortic dissection complicated by bowel ischaemia requiring emergency bowel resection). This will facilitate the comparison of a homogenous patient population, with the focus on costs directly related to the index surgical admission.

Definitions

Preoperative anaemia will be defined using the World Health Organisation criteria of [Hb]c of less than 130g/L for men and less than 120 g/L for women.(7) We will define the preoperative [Hb]c as the last Hb measurement taken before the index operation. Postoperative complications will be defined as any deviation from the normal postoperative course and will be guided by the European Perioperative Clinical Outcomes (EPCO) definitions.(11)

Complications will analysed and graded in accordance with the Clavien-Dindo (CD) classification system.(12) Patients will be stratified based on the number of complications reported (0, 1, 2, 3, 4+) and by their most severe complication (CD grades I-IV).
Length of hospital stay will be calculated as the number of days between the completion of surgery and discharge, excluding days on leave or in the hospital-in-the-home unit.

Readmissions will be defined as any unplanned admission within 30 days of discharge.
Mortality will be defined as death within 30 days of index admission.

Preoperative variables collected
Demographic data collected will include age, gender, body mass index (BMI), the American Society of Anesthesiology physical status classification (ASA),[(15)] smoking history within one year, alcohol abuse history, body mass index, Charlson comorbidity index (CCI),[(16)] principal diagnosis, presence of malignancy, and chemotherapy history within the past three months of surgery. Preoperative laboratory results collected included [Hb]c, white cell count, platelet count, serum creatinine, bilirubin and albumin concentrations, International Normalized Ratio (INR), and estimated glomerular filtration rate (eGFR).

Intraoperative and postoperative variables collected
Data collected included surgery type, emergency operation schedule, operation time, concomitant procedures, and intensive care unit (ICU) admission time (hours). Clinical variables included counts of allogeneic intra and postoperative red blood cell transfusion, the number of surgical complications, and the severity of the complication. Length of hospital stay (days), and readmission after surgery within 30 days were collected. All data was obtained using *Cerner*® electronic medical records which is an integrated, interoperable, patient-centred electronic health record platform which spans the continuum of patients care.

Cost analysis
Costs will be calculated from the day of the index operation until the day of discharge. Preoperative costs will be excluded, in order to preclude potential confounding by preoperative cost drivers. Raw costing data will be obtained from Austin Healths business intelligence unit. Costs will be allocated into a priori clinical cost "centres". These will include 'intensive care unit', 'medical', 'operative', 'pharmacy', and 'ward' cost centers. Hospital costs will be calculated using an activity-based costing methodology. All costs will be adjsuted to 30 June 2019 values based on end of fiscal quarter Australian Consumer Price Index (CPI) as reported by the Australian Tax Office.[(13)] Costs will then be converted to United States Dollar (USD) ($) based on the market rate on 30 June 2019.[(14)]

Statistical analysis
For statistical analysis, we will use IBM SPSS Statistics for Windows (version 23.0, IBM Corp., Armonk, NY, 2015) and R software 3.5.2 (R Development Core Team, Vienna, Austria, 2018). All collected data will be coded with numerical values, and names of variables will be encrypted to blind the variables' characteristics to the statistician. Data will be presented as mean ± standard deviation, median (1^{st} ~ 3^{rd} quartiles), or the number of cases (percentile) for descriptive statistics. Estimated values will be described with 95% confidence intervals. Statistical results will be presented with P-values and corresponding effect sizes. Any P-value below 0.05 will considered as statistically significant, based on the null hypothesis significance testing. The number of effects will evaluated with the estimated effect sizes.

Prior to statistical analysis, normality will assessed for continuous variables using the Shapiro-Wilk test, a visual check of the normal Q-Q plot, and frequency histograms. For skewed distributions, transformation using logarithmic or exponential scales will be applied, and normality will be re-evaluated using the normal Q-Q plot. If normality is violated post-transformation, non-parametric statistical methods will be applied for that variable. Extreme values will be managed by applying standard statistical methods and then compared to the original values from the data source. If any extreme value cannot be reconciled by interrogating the clinical notes and context of the value, they will be replaced with the Winsorization method.

Variables with a missing rate of greater than 5% will be identified and evaluated to determine whether the missing values occurred at random. In such cases, imputation will be applied using the univariate imputation method of classification and regression trees, using the "mice package". Maximal iteration will be set at 250, and the number of multiple imputations will be determined appropriately.(17) We will assess the imputed values with an over-imputation diagnostic plot. For the missing analysis of categorical data, the multiple correspondence analysis will be applied with "missMDA package" in the "R" system.(18) Otherwise, statistical analysis will performed as a complete case analysis. Parametric statistical methods will be used only for the continuous, numerical variables that satisfied the normality assumption; otherwise, non-parametric methods will be applied. For parametric, statistical purposes, the homogeneity of variance assumption will be evaluated if required.

For crude estimation of relationship between [Hb]c and hospital costs, curve estimation based on the least square method will be evaluated for linear, quadratic, and cubic models. According to the curve-fit results and physiologically accepted criteria, we will divided [Hb]c into 4 categories; <9.0 g/dL, 9.0 - 13.0 g/dL, 13.0 - 15.0 g/dL, and >15.0 g/dL.

To evaluate the relationship between hospital costs and the patient's status, correlation analysis and multiple log-linear regression analysis will be used. A stepwise selection method will be applied to determine the relevant regression coefficient for this modelling. For regression, all categorical variables with more than three levels will be transformed into dummy variables. Residuals will be evaluated with the Durbin-Watson statistic test and standardised residual plots, including all partial plots. The variance inflation factor (VIF) will be used to assess collinearity, and Pearson product-moment correlation analysis will be used to evaluate the independency between selected variables. A constant will be included during estimation, in order to compensate for the unknown effect. To enhance the robustness of estimates, bootstrapping will applied to the final regression model, with 1000 samples and the simple sampling method.

To evaluate the effects of [Hb]c on the variables directly related to hospital costs, multivariate general linear modelling will be used. With Pearson's correlation analysis, the assumption of independence will be validated, and the multivariate normal distribution assumption will be tested using the "mshapiro.test" function in the "mvnormtest package", in the R system.(19) The Box test will also used for testing homogeneity of covariance matrices. Data for multivariate, general linear modelling will be trimmed using propensity score matching. This will be performed in order to adjust for other variables that may be indicative of patient status, given that they could affect the value of variables directly related to hospital costs. For propensity score matching, the nearest neighbor matching without the caliper method will be applied. Variables selected in the multiple linear regression model will be used for estimating the propensity score. Matched quality will be assessed using standardized differences with a criteria of 0.1, a propensity score distribution graph, and standardized differences density plot check.

Presentation of results

Table 1. Demographic, biochemical, and clinical data for all study patients

Variables		**Values (N=)**
Age (yrs)		
Sex (male)		
BMI (kg/m^2)		
ASA (I, II / III, IV, V)		
Charlson Comorbidity Index		
[Hb]c (g/dL)		
WHO anaemia criteria		
Creatinine concentration (µmol/L)		
Increased creatinine concentration		
Albumin (g/L)		
Hypoalbuminemia		
Surgical type (colorectal/liver/pancreatic resection)		
Emergency operation		
Operation time (mins)		
Allogenic PRBC transfusion		
Units of PRBC in patients who received transfusion during admission		
No. of patients with a postoperative ICU admission		
Duration of ICU admission for patients requiring ICU (hrs)		
Length of hospital stay (days)		
Readmission within 30 days after discharge		
Costs incurred during readmission		
No. of patients who experienced a complication		
No. of complications per patient		
No. of complications for patients experiencing a complication		
Clavien-Dindo Classification of surgical complications	I	
	II	
	III	
	IV	
	V	

Values will be expressed as mean ± standard deviation, median (1^{st} ~ 3^{rd} quartiles) or number (percentile). WHO anaemia criteria: under 130 g/dL for man, 120 g/dL for non-pregnant woman, Thrombocytopenia: Platelet count under 150×10^3, Leukopenia: white blood cell count below 4000, Leukocytosis: white blood cell count above 11000, Increased creatinine concentration: above 110 μmol/L for male, above 90 μmol/L for female, Hypoalbuminemia: below 35 g/dL, Hyperbilirubinemia: above 20 μmol/L. Hb: Haemoglobin, GFR: Glomerular filtration rate, INR: International normalized ratio, POD: Postoperative days, PRBC: Packed red blood cell, ICU: Intensive care unit.

Table 2. Correlation analysis between variables of patient status, as directly related to costs and categorized [Hb]c (below 9.0 g/dL vs. 9.0 ~ 13.0 g/dL), and total hospital costs.

Category	**Variables**	**[Hb]c (N=)**		**Total hospital costs (N=)**	
		Correlation coefficient	**P value**	**Correlation coefficient**	**P value**
Patient status	Age (yrs)				
	Sex (Female)				
	BMI (kg/m^2)				
	ASA (I, II / III, IV, V)				
	Charlson Comorbidity Index				
	[Hb]c				
	Increased creatinine concentration				
	Hypoalbuminemia				
	Surgical type (colorectal/liver/pancreatic resection)				
	Emergency operation				
Directly related to costs	Operation time (min)				
	Allogenic PRBC transfusion				
	No of PRBC transfused				
	No. of patients with a postoperative ICU admission				
	Duration of ICU admission for patients requiring ICU (hrs)				
	Length of hospital stay (days)				
	Readmission within 30 days after discharge				
	Costs incurred during readmission				
	Patients who experienced complication				
	No. of complications in one patient				
	Clavien-Dindo Classification				

Pearson's correlation analysis will be used for continuous variables, Spearman's rank correlation analysis will be used for categorical variables. Increased creatinine concentration: above 110 μmol/L for male, above 90 μmol/L for female, Hypoalbuminemia: below 35 g/dL, Hb: Haemoglobin, POD: Postoperative days, PRBC: Packed red blood cell, ICU: Intensive care unit. *: indicates P<.

Table 3. Log-linear regression modelling results between total hospital costs and variables related to the patient's status in [Hb]c below 13.0 g/dL. surgery.

Variables	**Univariable model (R2 =, F() = , P=)**		**Multiple model, stepwise selection**† **(R2 =, F(), = , P=)**	
	Regression coefficient†	**P value**	**Regression coefficient**†	**P value**
(Constant)				
[Hb]c below 9.0 g/dL				
Age (yrs)				
Sex (Female)				
BMI (kg/m2)				
ASA (I, II / III, IV, V)				
Charlson Comorbidity Index				
Increased creatinine concentration				
Hypoalbuminemia				
Surgical type: Hepatic‡				
Surgical type: Pancreatic‡				
Emergency operation				

Increased creatinine concentration: above 110 µmol/L for male, above 90 µmol/L for female, Hypoalbuminemia: below 35 g/dL. Hb: Haemoglobin. *: indicates P<, †: 95% confidence intervals will be bootstrapped, ‡: Dummified variables of "Surgical types": Colorectal (reference category), Hepatic and Pancreatic resection. The coefficients of "Surgical types of hepatic and pancreatic operation" will be estimated based on the reference value of "Surgical types of Colorectal

Table 4. The effects of [Hb]c ([Hb]c 9.0 - 13.0 g/dL vs. below 9.0 g/dL) on total hospital costs.

Dependent variables	Before PSM (N =)			After PSM (N =)		
	Multivariate analysis					
	F() = , P= , partial η2 =			F() = , P= , partial η2 =		
	Univariate analysis					
	F()	P value	Partial η^2	F()	P value	Partial η^2
Operation time (hrs)†						
No of PRBC transfused†						
ICU admission time (hrs) †						
Length of hospital stay (days) †						
Costs incurred during readmission†						
No. of complications in one patient†						
Clavien-Dindo Classification						

To control the effects of variables related to the patient's status except [Hb]c, propensity score matching method will be applied. PSM: Propensity score matching, PRBC: Packed red blood cells, *: indicates P<, †: logarithmic transformed variables. This table is the multivariate general linear model.

Table 5. Correlation analysis between variables of patient status, as related to Hbc and total hospital costs among patients with a [Hb]c 13.0 ~ 15.0 g/dL vs. those above 15.0 g/dL.

Category	**Variables**	**[Hb]c (N =)**		**Total hospital costs (N=)**	
		Correlation coefficient	P value	Correlation coefficient	P value
Patients' status	Age (yrs)				
	Sex (Female)				
	BMI (kg/m^2)				
	ASA (I, II / III, IV, V)				
	Charlson Comorbidity Index				
	[Hb]c				
	Increased creatinine concentration				
	Hypoalbuminemia				
	Surgical types (Colorectal/Liver/Pancreatic)				
	Emergency operation				
Directly related to costs	Operation time (hrs)				
	Allogenic PRBC transfusion				
	No of PRBC transfused				
	No. of patients with a postoperative ICU admission				
	ICU admission time for patients requiring ICU (hrs)				
	Length of hospital stay (days)				
	Readmission within 30 days after discharge				
	Costs incurred during readmission				
	Patients who experienced complication				
	No. of complications in one patient				
	Clavien-Dindo Classification				

Pearson's correlation analysis will be used for continuous variables, Spearman's rank correlation analysiswill be used for categorical variables. Increased creatinine concentration: above 110 μmol/L for male, above 90 μmol/L for female, Hypoalbuminemia: below 35 g/dL. Hb: Haemoglobin, POD: Postoperative days, PRBC: Packed red blood cell, ICU: Intensive care unit. *: indicates P <

Table 6. Log-linear regression modelling results for total hospital costs and variables related to patient status in those with a [Hb]c above 13.0 g/dL.

Variables	**Univariable model (R^2 =, F() = , P=)**		**Multiple model, stepwise selection† (R^2 =, F() = , P=)**	
	Regression coefficient†	**P value**	**Regression coefficient†**	**P value**
Constant				
Age (yrs)				
Sex (male)				
BMI (kg/m^2)				
ASA (I, II / III, IV, V)				
Charlson Comorbidity Index				
[Hb]c				
Increased creatinine concentration				
Hypoalbuminemia				
Surgical type: Hepatic‡				
Surgical type: Pancreatic‡				
Emergency operation				

Increased creatinine concentration: above 110 µmol/L for male, above 90 µmol/L for female, Hypoalbuminemia: below 35 g/dL. Hb: Haemoglobin. *: indicates P <1, †: 95% confidence intervals will be bootstrapped, ‡: Dummified variables of "Surgical types": Colorectal (reference category), Hepatic and Pancreatic resection. The coefficients of "Surgical types of hepatic and pancreatic operation" will be estimated based on the reference value of "Surgical type of Colorectal surgery".

Table 7. The effects of [Hb]c ([Hb]c 13.0 ~ 15.0 g/dL vs. above 15.0 g/dL) on total hospital costs.

Dependent variables	**Before PSM (N =)**			**After PSM (N =)**		
	Multivariate analysis					
	F() =, P=, Partial η2 =			F() =, P=, Partial η2 =		
	Univariate analysis					
	F()	P value	Partial η^2	F()	P value	Partial η^2
Operation time (hrs)†						
No of PRBC transfused†						
Duration of ICU admission (hrs) †						
Length of hospital stay (days) †						
Costs incurred during readmission†						
No. of complications in one patient†						
Clavien-Dindo Classification						

To control the effects of variables related to the patient's status except [Hb]c, propensity score matching method will be applied. PSM: Propensity score matching, PRBC: Packed red blood cells. *: indicates P <, †: logarithmic transformed variable. This table is the multivariate general linear model.

Figure 1. Curve- fit modelling with linear, quadratic, and cubic models.

Figure 2. Total hospital costs of each level of [Hb]c*. *Data will be presented as median and 1st ~ 3rd quartiles. *: [Hb]c below 9.0 g/dL, [Hb]c between 9.0 ~ 13.0 g/dL.

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