BMJ Open

Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty: A single centre retrospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016403
Article Type:	Research
Date Submitted by the Author:	11-Feb-2017
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Primary Subject Heading:	Health services research
Secondary Subject Heading:	Haematology (incl blood transfusion), Surgery, Anaesthesia
Keywords:	Anaesthesia in orthopaedics < ANAESTHETICS, ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic & trauma surgery < SURGERY, Anaemia < HAEMATOLOGY, Blood bank & transfusion medicine < HAEMATOLOGY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title: Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty: A single centre retrospective study
Short Title: Preoperative anaemia, total knee arthroplasty

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Key words: Anemia; Arthroplasty, knee replacement; length of stay;
Number of Tables: 3
Conflict of Interest: None to declare
Financial support: None

Cover Letter

Dear Editor-In-Chief of BMJ Open,

We are writing to resubmit an original article titled, "**Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty: A single centre retrospective study** ". We had previously submitted this article under the same title to your esteemed journal under the ID number (bmjopen-2016-015294), however it was rejected with the offer to resubmit.

We would like to thank both Dr Michael Gillies and Professor Toby Richards for their time in reviewing our original manuscript and providing invaluable comments. We have addressed their concerns in this revision. Please allow us to present a point-by-point reply to the comments in the supplementary information file at the end of our manuscript.

Our manuscript describe the results of a retrospective cohort study of 2600 patients who underwent primary Total Knee Arthroplasty in Singapore General Hospital, one of the largest public hospital in Singapore, between January 2013 and June 2014.

This study is the first study from Singapore, and from South East Asia region, that examines the relationship between preoperative anaemia and hospital length of stay, readmission and perioperative blood transfusion in patients who had undergone primary Total Knee Arthroplasty. Our study provides an estimate of the risk of preoperative anaemia on prolonged LOS and perioperative blood transfusion. These results would be helpful for health systems to analyse the cost-effectiveness of treating preoperative anemia as a prevention strategy. Our study is one of the first to control for the day of the week the surgery was done, which was recently found to be a significant predictor for LOS in arthroplasties. We believe that the results of this study would provide additional angles on perioperative anaemia and patient blood management.

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose. All authors have approved and agree with submission. Thank you for receiving our manuscript and for considering it for peer-review. We appreciate your time and look forward to hearing from you.

Best regards,

Hairil Rizal, Abdullah

Abstract

Objectives: Studies in western healthcare settings suggest that preoperative anaemia is associated with poor outcomes after elective surgery. We investigated the prevalence of preoperative anaemia among elective total knee arthroplasty patients in Singapore and its association with length of hospital stay (LOS), perioperative blood transfusion and hospital readmission rates.

Methods: Retrospective cohort study performed in a tertiary academic medical centre in Singapore. Data of patients who underwent TKA between January 2013 to June 2014, such as demographics, comorbidities, preoperative haemoglobin level, LOS and 30-day readmission data were collected. Anaemia severity was graded according to WHO classification. Multivariate logistic regression were performed to identify factors that predispose to prolonged LOS. Prolonged LOS was defined as more than 6 days, which corresponds to >75th centile LOS of the data.

Results: We analysed 2600 patients. The prevalence of anaemia was 23.5%. 434 patients (16.7%) had mild anaemia and 176 patients (6.8%) had moderate to severe anaemia. The mean LOS for all patients was 5.5±4.8 days. Based on multivariate logistic regression, preoperative anaemia significantly increased LOS (mild anaemia, aOR 1.59, p=0.001; moderate/severe anaemia, aOR 2.29, p<0.001). Transfusion of 1 unit red cell increased odds of prolonged LOS (aOR 1.98, p=0.006) and transfusion of 2 or more units had even higher odds of prolonged LOS (aOR 5.65, p<0.001). Bilateral TKR, repeat operation during hospital stay, previous CVA, general anaesthesia and age>= 65 years were associated with prolonged LOS. There were 45 (1.7%) cases of related readmission within 30 days. Due to the low number, no statistical analysis for hospital readmission was done.

Conclusion: Anaemia is common among patients undergoing elective total knee arthroplasty in Singapore and is independently associated with prolonged length of stay and increased perioperative blood transfusion.

Word count: 296

Keywords: Anaemia; Arthroplasty, knee replacement; length of stay; perioperative blood transfusion

Strengths:

- Our study provides a unique perspective from a South East Asian healthcare system on anaemia and its impact on LOS and hospital readmission rates in Singapore.
- We had minimal incomplete data (2.0%) due to the rigorous mandatory preoperative assessment database.
- Our study is one of the first to control for the day of the week the surgery was done, which was recently found to be a significant predictor for LOS in arthroplasties.

Limitations:

- This is a retrospective observational study, so it cannot establish a causal relationship between preoperative anaemia and adverse outcomes
- The selection of the 75th centile for defining prolonged LOS can be viewed as an arbitrary cut-off, although it is also used in other literature examining LOS after elective surgery.

Introduction

The prevalence of preoperative anaemia in patients undergoing non-cardiac surgery is considerably high, with rates of 30.4% and 28.7% recorded in the US and Europe respectively.[1]. This is an important health problem as even mild anemia is associated with poor outcomes post-surgery [1, 3–6], including prolonged length of hospital stay (LOS) and higher readmission rates [7, 8] .

Total knee arthroplasty (TKA) is one of the most common orthopaedic procedures worldwide [2,3]. Due to the low mortality and morbidity rates associated with TKA, improvement initiatives have mainly focused on reducing LOS and improving functional recovery after surgery [4,5]. LOS associated with TKA is directly correlated with the total procedure cost, mainly due to provision of inpatient services [6,7]. Reductions in LOS can therefore help to reduce the economic burden of TKA [8,9]. Due to the fixed bed capacity, high overhead costs, and the Diagnosis-Related Group (DRG) reimbursement system in most health systems, the economic revenue of these systems depends on an increase in patient throughput by decreasing LOS. Hence, it is important for health systems and physicians to identify modifiable risk factors that are associated with the improved recovery and discharge of these patients. However, few

studies have investigated preoperative anemia in the specific context of elective primary TKAs, with a focus on LOS and readmission rates, which are important indicators of health services outcomes. Furthermore, of the studies focusing on the association between hospital LOS after joint arthroplasties and preoperative anaemia [10–17], most were conducted within the western world healthcare settings, with different demographics and potentially varying discharge and rehabilitation policies than other regions in the world.

Therefore, in this study, we set out to investigate the relationship between preoperative anaemia and hospital LOS, perioperative blood transfusion as well as 30-day readmission rate among patients undergoing primary TKA in Singapore.

Methods

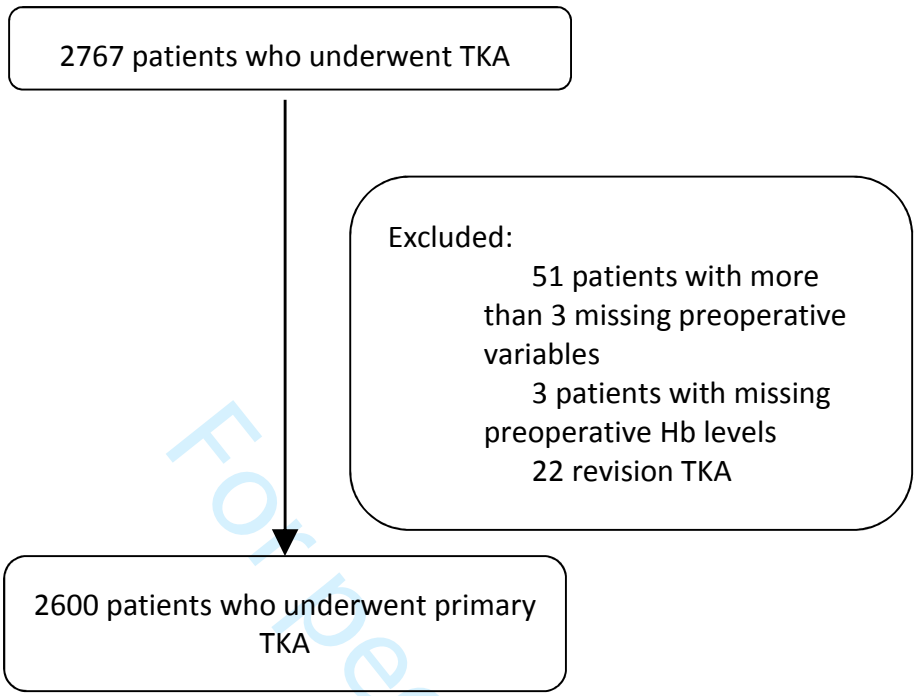
Institutional Review Board approval was obtained (Singhealth CIRB 2014/651/D) prior to the start of the study. We retrospectively analysed the electronic medical records of all 2676 patients who underwent TKA between January 2013 and June 2014 in our institution. These clinical records were sourced from our institution's clinical information system (Sunrise Clinical Manager (SCM), Allscripts, IL, USA) and stored in our enterprise data repository and analytics system (SingHealth-IHiS Electronic Health Intelligence System - eHINTS), which integrates information from multiple healthcare transactional systems including administration, clinical and ancillary systems. We generated a list of patients who underwent total knee replacements from January 2013 to June 2014 using specific surgical codes relevant to this surgery. Information from SCM included patient demographics, preoperative comorbidities such as smoking, haemoglobin level, individual components of the Revised Risk Cardiac Index [18,19], such as a history of previous cerebrovascular accidents (CVA), ischemic heart disease (IHD), congestive cardiac failure (CCF), diabetes mellitus (DM) on insulin and elevated preoperative creatinine level >2mg/dL; ASA score [20]; details of the operation such as site, duration, type of anaesthesia and day of week the surgery was done [21]; perioperative blood transfusion and repeat surgeries during hospital stay were also obtained. The length of stay (LOS) was calculated from the date of admission, to the date of discharge from hospital to their home environment. 30-day readmission data after discharge was obtained from the clinical information system database, SCM. We filtered related readmission by the ICD-10 diagnosis, and further confirmed the cause of admission by looking up the patient's electronic medical records. We defined the window for preoperative haemoglobin levels to be taken at a maximum of 14 days and a minimum of one day before the surgery. We also defined perioperative blood transfusion

to be within 2 weeks before up to 2 weeks after the date of surgery.

In our institution, most patients are admitted on the day of surgery and very infrequently, 1 day earlier for medical and/or social reasons. Routinely, all anti-platelets apart from Aspirin are stopped for the recommended duration before the surgery. The use of intraoperative tranexamic acid filtration to the knee joint and the placement of a drain into the joint after the surgery is not standardized. Use of cell salvage is rare. Postoperatively, all patients receive a standard hospital TKA protocol for postoperative care. This includes thromboembolism chemoprophylaxis with 40 mg once daily subcutaneous low molecular weight heparin (Clexane, Sanofi, Paris, France) on the first postoperative day, which is discontinued upon discharge. Patients also receive routine physiotherapy starting from the first postoperative day, even if it falls on the weekend. They are deemed fit for discharge when there is an agreement between the surgeon and physiotherapist that the patient is medically stable and that their functional ability is sufficient to allow discharge to their home environment. This includes being able to climb up a few steps, transfer with the aid of a walking frame and to bend their operated knee close to 90 degrees.

After excluding 51 patients with more than 3 missing variables, 3 patients who did not have pre-operative haemoglobin levels, and 22 patients who underwent revision surgery, we obtained 2600 patients in the final analysis (Figure 1). No sensitivity analysis accounting for the missing data was done due to the small number (2.0%).

Figure 1. Flowchart showing derivation of study cohort.



The primary outcome was prolonged LOS, defined as more than 6 days. This variable was selected as it represents >75th centile LOS of the whole sample. The use of 75th centile to define prolonged LOS is consistent with other studies [22]. The secondary outcome was readmission for any reason within 30 days after surgery.

Statistical analysis

We used the World Health Organisation (WHO)'s gender-based definition of anaemia severity [23]. Thus, mild anaemia was defined as haemoglobin concentration of 11-12.9g/dL in males and 11-11.9g/dL in females; moderate anaemia was defined for both genders to be haemoglobin concentration between 8-10.9g/dL and severe anaemia defined as haemoglobin concentration <8.0g/dL. Among the 610 patients (23.5%) with anaemia, 434 patients (16.7%) had mild preoperative anaemia,171 patients (6.6%) had moderate anaemia and 5 patients had severe anaemia (0.2%). Due to the small incidence of severe anaemia in the sample, we decided to group and analyse patients with moderate and severe anaemia together.

Patient demographics and clinical characteristics were compared between LOS >6 and ≤6 days (Table 1). For continuous variables, mean and standard deviation (SD) were presented and Mann-Whitney U test was used to test the mean differences between the 2 groups. For categorical variables, Chi-square test was used to compare the percentages between the 2 groups. We categorized continuous variable such as age according to their broad centile

groups, BMI according to the WHO definition of obesity, and operative duration according to <=100 minutes or > 100 minutes which corresponds to >75th centile of the data. 57 cases out

Variable	LOS ≤ 6 days N=2053	LOS > 6 days N= 547	P-value

of the final 2600 patients with incomplete data were excluded from multivariate analysis. Multivariate logistic regression was performed to determine independent predictors for increased LOS and perioperative blood transfusion while adjusting for demographic, preoperative clinical risk factors and surgical factors. All clinically relevant risk factors were used in this multivariate logistic regression. Further subgroup analysis was done for separately patients who underwent unilateral versus bilateral surgery. Analyses were performed using IBM SPSS Statistics v20.

Results

Table 1. Demographics of patients with normal Length of Stay (LOS) (≤ 6 days) versus those with prolonged LOS (> 6 days) after Total Knee Replacement (TKR)

Patient demographics				
Age – mean (sd)		65.7 (8.1)	68.5 (8.5)	<0.001
Race – n (%)	Chinese	1726 (84.1)	462 (84.5)	0.01
	Malay	161 (7.8)	26 (4.8)	
	Indian	113 (5.5)	35 (6.4)	
	Others	53 (2.6)	24 (4.4)	
Body Mass Index – n (%)	< 25	586 (29.0)	165 (32.2)	0.25
	25 – 29.9	864 (42.7)	211 (41.2)	
	30 – 34.9	434 (21.5)	95 (18.6)	
	≥ 35	138 (6.8)	41 (8.0)	
Gender – n (%)	Male	504 (24.5)	119 (21.8)	0.17
	Female	1549 (75.5)	428 (78.2)	
Details of Operation				
Type of Surgery – n (%)	Unilateral	1933 (94.2)	461 (84.3)	<0.001
	Bilateral	120 (5.8)	86 (15.7)	
Type of Anaesthesia – n (%)	GA	711 (34.6)	236 (43.1)	<0.001
	RA	1342 (65.4)	311 (56.9)	
Duration of operation – minutes (sd)		82.6 (25.2)	91.6 (32.7)	<0.001
Perioperative Blood Transfusion – n (%)	None	1988 (96.8)	461 (84.3)	<0.001
	1 unit	50 (2.4)	44 (8.0)	
	2,3 units	15 (0.7)	34 (6.2)	
	≥ 4 units	0	8 (1.5)	
Repeat Operation within Hospital Stay – n (%)	Yes	1 (0.0)	8 (1.5)	<0.001
Day of Week of Operation – n (%)	Monday	323 (15.7)	109 (19.9)	<0.001
	Tuesday	445 (21.7)	140 (25.6)	
	Wednesday	349 (17.0)	94 (17.2)	
	Thursday	513 (25.0)	80 (14.6)	
	Friday	317 (15.4)	99 (18.1)	
	Saturday	106 (5/2)	25 (4.6)	
Patient comorbidities				
Anaemia – n (%)	None	1633 (79.5)	357 (65.3)	<0.001
	Mild	313 (15.2)	121 (22.1)	
	Moderate/Severe	107 (5.2)	69 (12.6)	
DM on insulin – n (%)	Yes	32 (1.6)	12 (2.2)	0.35
Creatinine > 2mg / dL – n (%)	Yes	10 (0.5)	10 (1.8)	0.004
Previous CVA – n (%)	Yes	26 (1.3)	21 (3.8)	<0.001
IHD – n (%)	Yes	92 (4.5)	40 (7.3)	0.01
CCF – n (%)	Yes	14 (0.7)	9 (1.6)	0.04
Smoking – n (%)	Yes	194 (9.4)	53 (9.7)	0.87
ASA	1	148 (7.2)	35 (6.4)	<0.001
	2	1803 (87.8)	453 (82.8)	

3	102 (5.0)	59 (10.8)	

Table 2. Variables that predict increased Length of Stay (LOS) in Hospital after Total Knee Replacement, based on univariate and multivariate analysis.

Variable		OR (95% CI)	P-value	aOR (95% CI)*	P-value
Patient Demographics					
Age (years)	<60	REF		REF	
	60-64	1.03 (0.74 – 1.43)	0.85	1.18 (0.82 – 1.68)	0.37
	65-69	1.59 (1.17 – 2.15)	0.003	1.68 (1.19 – 2.36)	0.003
	>70	1.90 (1.45 – 2.51)	<0.001	2.04 (1.48 – 2.82)	<0.001
Race	Malay	REF		REF	
	Indian	1.92 (1.09 – 3.36)	0.02	2.61 (1.39 – 4.92)	0.003
	Others	2.80 (1.49 – 5.30)	0.001	2.92 (1.38 – 6.19)	0.005
	Chinese	1.66 (1.08 – 2.54)	0.02	2.07 (1.23 – 3.49)	0.006
Body Mass Index	<25	REF		REF	
	25 – 29.9	0.87 (0.69 – 1.09)	0.22	0.98 (0.76 – 1.25)	0.84
	30 – 34.9	0.78 (0.59 – 1.03)	0.08	0.98 (0.72 – 1.33)	0.88
	≥ 35	1.06 (0.72 – 1.56)	0.79	1.47 (0.93 – 2.32)	0.10
Gender	Male	REF		REF	
	Female	1.17 (0.93 – 1.47)	0.17	1.89 (0.89 – 1.58)	0.24
Details of Operation					
Type of Surgery	Unilateral	REF		REF	
	Bilateral	3.01 (2.24 – 4.04)	<0.001	2.76 (1.88 – 4.05)	<0.001
Type of Anaesthesia	GA	REF		REF	
	RA	0.70 (0.58 – 0.85)	<0.001	0.74 (0.60 – 0.92)	0.007
Duration of operation (minutes)	≤ 100	REF		REF	
	> 100	1.73 (1.39 – 2.15)	<0.001	1.29 (0.97 – 1.70)	0.08
Perioperative Blood Transfusion (units)	None	REF		REF	
	1	3.80 (2.50 – 5.76)	<0.001	1.98 (1.22 – 3.22)	0.006
	>= 2	12.08 (6.64 – 21.96)	<0.001	5.65 (2.92 – 10.90)	<0.001
Repeat Operation within Hospital Stay		30.46 (3.80 – 244.04)	0.001	16.29 (1.57 – 169.12)	0.02
Day of Week of Operation	Monday	2.16 (1.57 – 2.98)	<0.001	2.37 (1.66 – 3.36)	<0.001
	Tuesday	2.02 (1.49 – 2.73)	<0.001	2.41 (1.72 – 3.37)	<0.001
	Wednesday	1.73 (1.25 – 2.40)	0.001	1.99 (1.39 – 2.84)	<0.001
	Thursday	REF		REF	
	Friday	2.00 (1.45 – 2.78)	<0.001	1.93 (1.34 – 2.77)	<0.001
	Saturday	1.51 (0.92 – 2.48)	0.10	1.70 (0.99 – 2.90)	0.05
Patient comorbidities					
Anaemia	None	REF		REF	

	Mild Moderate/Severe	1.77 (1.39 – 2.25) 2.95 (2.13 – 4.08)	<0.001 <0.001	1.59 (1.22 – 2.08) 2.29 (1.57 – 3.34)	0.001 <0.001
DM on insulin		1.42 (0.73 – 2.77)	0.31	1.12 (0.51 – 2.45)	0.78
Creatinine > 2mg/dL		3.80 (1.58 – 9.19)	0.003	2.02 (0.70 – 5.82)	0.20
Previous CVA		3.11 (1.74 – 5.58) <0.001		2.84 (1.49 – 5.43)	0.002
IHD		1.68 (1.15 – 2.47)	0.008	1.46 (0.94 – 2.27)	0.09
CCF		2.44 (1.05 – 5.66)	0.04	1.52 (0.58 – 3.93)	0.39
Smoking		1.03 (0.75 – 1.42)	0.87	1.23 (0.83 – 1.81)	0.30
ASA Score	1 2 3	REF 1.06 (0.73 – 1.56) 2.45 (1.50 – 3.99)	 0.76 <0.001	REF 0.87 (0.57 – 1.31) 1.30 (0.75 – 2.26)	 0.49 0.35

Table 3. Factors associated with Perioperative Blood Transfusion after Primary TKR

Variable		aOR (95% CI)*	P-value
Type of Surgery	Unilateral Bilateral	REF 3.14 (1.73 – 5.69)	 <0.001
Type of Anaesthesia	GA RA	REF 0.62 (0.42 - .91)	 0.01
Duration of operation (minutes)	≤ 100 > 100	REF 1.58 (0.97 – 2.56)	 0.07
Repeat Operation within Hospital Stay		26.42 (4.61 – 151.56)	<0.001
Anaemia	None Mild Moderate/Severe	REF 4.00 (2.59 – 6.16) 8.15 (4.95 – 13.43)	 <0.001 <0.001
ASA Score	1 2 3	REF 1.85 (0.71 – 4.80) 3.31 (1.09 – 10.07)	 0.21 0.04
CCF		3.80 (1.21 – 12.01)	0.02

* adjusted for all the variables listed in Table 1

Demographics

Of the 2600 patients who underwent primary TKA during the study period, 23.5% were anaemic. In table 1, the mean age was higher in patients with prolonged LOS (68.5 years) compared to patients with normal LOS (65.7 years), p<0.001. There was no significant difference in BMI or

gender distribution between the two groups. However, those with prolonged LOS tended to have a higher ASA score (p<0.001), have more incidence of anaemia (p<0.001), have previous CVA (p<0.001), have repeat operation within hospital stay (p<0.001), underwent bilateral surgery compared to unilateral surgery (p<0.001), and received general anaesthesia compared to regional anaesthesia (p<0.001).

Length of stay (LOS)

The mean LOS for all TKA patients, including both unilateral and bilateral cases, was 5.5 ± 4.8 days, with a median of 4 days and 75th centile of 6 days. This result is similar to previous published LOS rates of primary unilateral TKA in our institution[24].

547 patients (21.0%) had LOS more than six days (i.e prolonged LOS). Based on the multivariate analysis presented in table 2, the variables associated with independent elevated risk of prolonged LOS include older age > 70years (aOR 2.04, p<0.001), bilateral TKA (aOR 2.76, p <0.001), repeat surgery within LOS (aOR 16.20, p=0.02), having mild anaemia (aOR 1.59, p=0.001) or moderate/severe anaemia (aOR 2.29, p<0.001), and previous cerebrovascular accidents (CVA) (aOR 2.84, p=0.002). Perioperative blood transfusion of 1 unit independently increased risk of prolonged LOS by 1.98 (p=0.006), while transfusion of 2 or more units independently increased risk by 5.65 (p<0.001). Variables that reduced LOS include having regional anaesthesia (aOR 0.74, p=0.007), having surgery on Thursday and being of Malay race. BMI, gender, presence of DM on insulin, previous diagnosis of ischemic heart disease, previous history of congestive heart failure or smoking, and elevated ASA scores were not associated with higher risks of prolonged LOS.

We did further subgroup analysis to establish whether the effect of anaemia on LOS is consistent in across both types of primary TKR - unilateral and bilateral. For patients who underwent unilateral TKR only (2394 cases), mild anaemia had an independent aOR of 1.71 (p<0.001) and moderate/severe anaemia had an independent aOR of 2.29 (p<0.001) for prolonged LOS. For patients who underwent bilateral TKR (206 cases), anaemia was not associated with a significant impact on LOS. We postulate that the lack of significance is due to the small number of cases of patients who had anaemia who underwent bilateral TKR, of which 31 had mild anaemia and only 12 had moderate/severe anaemia.

Perioperative blood transfusion

Factors that increased risk of perioperative blood transfusion (Table 3) included bilateral surgery (aOR 3.14, p<0.001), repeat operation during hospital stay (aOR 26.42, p<0.001), presence of mild anaemia (aOR 4.00, p<0.001) and moderate/severe anaemia (aOR 8.00, p<0.001), ASA score of 3 (aOR 3.31, p=0.04, and history of CCF (aOR 3.80, p=0.02). Regional anaesthesia was found to reduce risk of perioperative blood transfusion (aOR 0.62, p=0.01).

Hospital readmission within 30 days

We had 45 cases of related readmission within 30 days of discharge out of 2600 cases (1.7%). 14 were due to infection, 12 due to pain, swelling and/or stiffness after surgery, 4 due to discharge from the wound that is non-infected, 5 due to non-infected wound discharge, 4 due to DVT in the operative leg, 3 due to periprosthetic fractures, 3 due to hematoma/bleeding from the wound, 2 due to wound erythema, 1 due to wound dehiscence and 1 from contact dermatitis of the wound. Due to the low rates of readmission, no further statistical analysis was done.

Discussion

In this retrospective cohort study of 2600 consecutive patients who underwent elective primary TKA in our center, the prevalence of preoperative anaemia, as defined by the WHO gender-based classification, was found to be at 23.5%. Patients with mild preoperative anaemia had an adjusted Odd Ratio of prolonged LOS (> 6 days) of 1.57, while patients with moderate/severe anemia had an adjusted Odds Ratio of 2.29. Our findings are consistent with previous studies which explored the relationship between preoperative anaemia and LOS in elective primary knee arthroplasties. For example, Jans et al. found preoperative anaemia to be an independent predictor of prolonged LOS among patients undergoing “fast-track” knee arthroplasty [11]. This is similar with another observational study, conducted in the “traditional pathway” environment for elective primary knee arthroplasty [25]. As these studies were done in the western world health systems and a wide disparity in postoperative hospital stays after TKA has been documented due to the [26–29] variations in practice and rehabilitation protocols between countries, our study provided a perspective from a South East Asian healthcare system. In countries with advanced healthcare systems and an ageing population, the exponentially increasing number of TKAs performed yearly [3] importunes that more effort is needed to identify modifiable risk factors for delayed hospital discharges. This is an important

health care cost containment strategy, especially as TKAs are elective procedures that can be postponed to allow optimization of risk factors for suboptimal outcomes.

Recent publications have highlighted the need for improved patient blood management in anaemic patients and our study strengthens this argument for elective arthroplasty cases [30–32]. With the potential cost and hospital bed savings, it may be justified to delay this elective surgery to treat any underlying reversible causes of anaemia, such as iron-deficiency anaemia. In a recent RCT by Froessler, preoperative intravenous iron treatment of iron deficiency anaemia among patients who underwent major abdominal surgery resulted in reduction of median LOS by three days [33].

Other studies have found preoperative anaemia to be a strong predictor for perioperative allogeneic blood transfusion in knee surgeries[34,35], which is associated with poorer outcomes and prolonged LOS [11,36]. In our study, we found that even mild anemia was an independent risk factor for perioperative blood transfusion (aOR 4.00; p<0.001). Furthermore, there is an incremental effect as patients with moderate/severe anemia are at an even higher risk (aOR 8.00; p<0.001) for perioperative blood transfusion. This has a direct impact on LOS as the presence of anaemia (both mild and moderate/severe), and perioperative transfusion of even 1 unit of blood independently increases the risk of prolonged LOS.

One of the aims of our study was to identify the risk factors for 30-day hospital readmission in our study population. However, we were unable to do so due to the small incidence of 45 readmissions out of 2600 cases, which precludes any meaningful analysis. Our 30-day related readmission rates are similar to previous published rate in our institution, which is between 1.7-2.9% for primary unilateral TKR.[24]. This is lower than the 30-day all-cause readmission rates in literature of 4.0 -5.5% [37–39], because it only looks at readmission that is related to complications attributable to the surgery. Nevertheless, our readmission rates are similar to Schairer et al's 30-day surgical readmission rate of 2.4%, of which cellulitis and surgical site infection are the most common causes. In our study, surgical site infection was also the most common cause of readmission (31.1%).

Strengths of study

One of the strengths of our study was that it is amongst the first few to control for the day of the week the surgery was done, which has recently been shown to affect LOS in TKA and total hip arthroplasty [21]. We found that having surgery on Thursday is significantly associated with the lowest odds of prolonged LOS. We postulate that this is because patients would have

received standard physiotherapy for at least two days, on Friday and Saturday, and may be inclined to go home on Sunday where there is more familial support at home.

Another strength of our study is that we included both subjective measures of clinical risk estimates such as the ASA score [27,43], as well as the components of the RCRI which comprise of diagnosis of specific conditions. This allowed us to find that out of the 5 clinical conditions within the RCRI score, only a history of previous CVA was significantly associated with increased LOS (aOR 2.84, p=0.002). Furthermore, a history of CCF was found to be associated with increased risk of perioperative blood transfusion (aOR 3.80, p=0.02).

Finally, we focused our study on patients who underwent primary total knee arthroplasty rather than combining hip and knee arthroplasty together, which is more commonly done in literature, as we wanted a more homogenous study population. We excluded revision TKA as it is known in literature to be associated with increased need for blood transfusion.[40,41]

Limitations of study

Our study recruitment occurred over 1.5 years. Our recruitment period is similar to another study published on this topic, which recruited over a 2 year period[11]. We also had a modest study cohort of 2600 patients which is comparable to other studies [11,37]. While our study was performed retrospectively, it had minimal missing data (2.0%). This may be due to the fact that our clinical data, such as the preoperative variables, were collected electronically in a mandatory, prospective manner during routine preoperative anaesthesia assessment. Due to the observational nature of the study, a causal relationship between preoperative anaemia and adverse outcomes is difficult to establish. In addition, while our selection of the 75th centile for defining prolonged LOS can be viewed as an arbitrary cut-off in the absence of a universal definition of prolonged LOS, the use of 75th centile has been done in literature before for a similar study [22]. We do not have data on whether drains were placed by the surgeons during the surgery, however, a recent study done in the same institution showed that while drains were associated with a larger drop in Hb level and greater total blood loss, it did not significantly impact blood transfusion rate, LOS or 30-day readmission rates[24].

Conclusion

In conclusion, we found the prevalence of preoperative anaemia to be 23.5% among patients who underwent primary total knee arthroplasty in Singapore. It was an independent risk

factor for prolonged length of hospital stay after the surgery and perioperative blood transfusion. We suggest measures to correct anaemia prior to surgery should be considered.

Acknowledgements

We would like to thank Ms Serene Ong, Academic Medicine Research Institute, Duke-NUS Medical School, for her help in manuscript preparation. We also like to thank Ms Sudha Harikrishnan, from the Department of Anaesthesiology, for her invaluable help in data extraction. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Lastly, we would also like to thank Dr Chan Yiong Huak, Head, Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore for his invaluable help in data analysis and interpretation.

Contributorship statement

Abdullah HR - Contributed to the study conception and design, data acquisition, analysis and interpretation, drafting and final approval of the manuscript.

Sim YE – Contributed to data analysis and interpretation, drafting, revision and final approval of the manuscript

Y Hao – Contributed to data analysis and interpretation, drafting of the manuscript and final approval

Lin GY – Contributed to data acquisition, analysis and interpretation, drafting of the manuscript and final approval

Liew GHC - Contributed to the study conception and design, data analysis, revision of the manuscript and final approval

EL Lamoureux – Contributed to data analysis and critical appraisal, revision and final approval of the manuscript.

MH Tan – Contributed to the study conception and design, drafting of manuscript and final approval.

Competing interests

No conflicts of interest to declare.

Funding

This research was funded by the hospital department funds.

Data Sharing

Full dataset can be downloaded from http://dx.doi.org/10.5061/dryad.73250/1

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Page where Item can be found	Recommendation
Title	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
Abstract	3	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		Introduction
Background/rationale	4	Explain the scientific background and rationale for the investigation being reported
Objectives	5	State specific objectives, including any prespecified hypotheses
		Methods
Study design	5-6	Present key elements of study design early in the paper
Setting	5-6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5-6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
	NA	(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	5-7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	*5-6*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	NA	Describe any efforts to address potential sources of bias
Study size	NA	Explain how the study size was arrived at
Quantitative variables	7	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	7	(*a*) Describe all statistical methods, including those used to control for confounding
	7	(*b*) Describe any methods used to examine subgroups and interactions
	6	(*c*) Explain how missing data were addressed
	NA	(*d*) If applicable, explain how loss to follow-up was addressed
	6	(*e*) Describe any sensitivity analyses
		Results
Participants	6	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	6	(b) Give reasons for non-participation at each stage
	6	(c) Consider use of a flow diagram
Descriptive data	6-7	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	7	(b) Indicate number of participants with missing data for each variable of interest
	NA	(c) Summarise follow-up time (eg, average and total amount)
Outcome data	7-10	Report numbers of outcome events or summary measures over time
Main results	9-10	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
	NA	(*b*) Report category boundaries when continuous variables were categorized
	NA	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	11	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	12-13	Summarise key results with reference to study objectives
Limitations	14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	12-13	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	NA	Discuss the generalisability (external validity) of the study results
Other information		
Funding	16	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

BMJ Open

Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty in Singapore: A single centre retrospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016403.R1
Article Type:	Research
Date Submitted by the Author:	22-Mar-2017
Complete List of Authors:	abdullah, hairil; Singapore General Hospital, Department of Anesthesiology Sim, Eileen; Singapore General Hospital, Department of Anaesthesiology Ying, Hao; Singapore General Hospital, Health Services Research Unit Lin, Gengyu; National University Singapore Yong Loo Lin School of Medicine Liew, Geoffrey ; Singapore General Hospital, Department of Anaesthesiology Lamoureux, Ecosse; Singapore Eye Research Institute Tan, Mann Hong; Singapore General Hospital, Department of Orthopaedic Surgery
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Haematology (incl blood transfusion), Surgery, Anaesthesia
Keywords:	Anaemia < HAEMATOLOGY, ORTHOPAEDIC & TRAUMA SURGERY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Blood bank & transfusion medicine < HAEMATOLOGY, Anaesthesia in orthopaedics < ANAESTHETICS

Title: Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty in Singapore: A single centre retrospective study
Short Title: Preoperative anaemia, total knee arthroplasty

Running Head:
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Key words: Anemia; Arthroplasty, knee replacement; length of stay;
Number of Tables: 3

Conflict of Interest: None to declare
Financial support: None

Abstract

Objectives: Studies in western healthcare settings suggest that preoperative anaemia is associated with poor outcomes after elective orthopaedic surgery. We investigated the prevalence of preoperative anaemia among primary unilateral total knee arthroplasty patients in Singapore and its association with length of hospital stay (LOS), perioperative blood transfusion and hospital readmission rates.

Methods: Retrospective cohort study performed in a tertiary academic medical centre in Singapore. Data of patients who underwent primary unilateral TKA between January 2013 to June 2014, such as demographics, comorbidities, preoperative haemoglobin level, LOS and 30-day readmission data were collected. Anaemia severity was graded according to WHO classification. Multivariate logistic regression were performed to identify factors that predispose to prolonged LOS. Prolonged LOS was defined as more than 6 days, which corresponds to >75th centile LOS of the data.

Results: We analysed 2394 patients. The prevalence of anaemia was 23.7%. 403 patients (16.8%) had mild anaemia and 164 patients (6.8%) had moderate to severe anaemia. The mean LOS for all patients was 5.4±4.8 days. Based on multivariate logistic regression, preoperative anaemia significantly increased LOS (mild anaemia, aOR 1.71, p<0.001; moderate/severe anaemia, aOR 2.29, p<0.001). Transfusion of 1 unit red cell increased odds of prolonged LOS (aOR 2.12, p=0.006) and transfusion of 2 or more units had even higher odds of prolonged LOS (aOR 6.71, p<0.001). Repeat operation during hospital stay, previous cerebrovascular accidents, general anaesthesia and age>70 years were associated with prolonged LOS. There were 42 (1.7%) cases of related readmission within 30 days. Due to the low number, no statistical analysis for hospital readmission was done.

Conclusion: Anaemia is common among patients undergoing elective total knee arthroplasty in Singapore and is independently associated with prolonged length of stay and increased perioperative blood transfusion.

Word count: 286

Keywords: Anaemia; Arthroplasty, knee replacement; length of stay; perioperative blood transfusion, patient blood management

Strengths:

- Our study provides a unique perspective from a South East Asian healthcare system on anaemia and its impact on LOS and hospital readmission rates after unilateral, primary total knee arthroplasty.
- We had minimal incomplete data (2.0%) due to the rigorous mandatory preoperative assessment database.
- Our study is one of the first to control for the day of the week the surgery was done, which was recently found to be a significant predictor for LOS in arthroplasties.

Limitations:

- This is a retrospective observational study, so it cannot establish a causal relationship between preoperative anaemia and adverse outcomes
- The selection of the 75th centile for defining prolonged LOS can be viewed as an arbitrary cut-off, although it is also used in other literature examining LOS after elective surgery.

Introduction

The prevalence of preoperative anaemia in patients undergoing non-cardiac surgery is considerably high, with rates of 30.4% and 28.7% recorded in the US and Europe respectively.[1]. This is an important health problem as even mild anemia is associated with poor outcomes post-surgery [1, 3–6], including prolonged length of hospital stay (LOS) and higher readmission rates [7, 8] .

Total knee arthroplasty (TKA) is one of the most common orthopaedic procedures worldwide [2,3]. Due to the low mortality and morbidity rates associated with TKA, improvement initiatives have mainly focused on reducing LOS and improving functional recovery after surgery [4,5]. LOS associated with TKA is directly correlated with the total procedure cost, mainly due to provision of inpatient services [6,7]. Reductions in LOS can therefore help to reduce the economic burden of TKA [8,9]. Due to the fixed bed capacity, high overhead costs, and the

Diagnosis-Related Group (DRG) reimbursement system in most health systems, the economic revenue of these systems depends on an increase in patient throughput by decreasing LOS. Additionally, unexpected prolonged LOS could negatively impact the patient's perspective of a good surgical outcome. Hence, it is important for health systems and physicians to identify modifiable risk factors that are associated with the improved recovery and discharge of these patients. Most studies examining the association between hospital LOS after joint arthroplasties and preoperative anaemia [10–17] were conducted within the western healthcare settings, with different demographics, potentially diverse discharge and rehabilitation policies from other regions in the world.

Therefore, in this study, we set out to investigate the relationship between preoperative anaemia and hospital LOS, perioperative blood transfusion as well as 30-day readmission rate among patients undergoing primary unilateral TKA in Singapore.

Methods

Institutional Review Board approval was obtained (Singhealth CIRB 2014/651/D) prior to the start of the study. The electronic medical records of all 2676 patients who underwent TKA between January 2013 and June 2014 in our institution were analysed. These clinical records were sourced from our institution's clinical information system (Sunrise Clinical Manager (SCM), Allscripts, IL, USA) and stored in our enterprise data repository and analytics system (SingHealth-IHiS Electronic Health Intelligence System - eHINTS), which integrates information from administration, clinical and ancillary healthcare systems. We generated a list of patients who underwent total knee replacements from January 2013 to June 2014 using specific surgical codes relevant to this surgery. Information from SCM included patient demographics, preoperative comorbidities such as smoking, haemoglobin level, individual components of the Revised Risk Cardiac Index [18,19], such as a history of previous cerebrovascular accidents (CVA), ischemic heart disease (IHD), congestive cardiac failure (CCF), diabetes mellitus (DM) on insulin and elevated preoperative creatinine level >2mg/dL; ASA score [20]; details of the operation such as site, duration, type of anaesthesia and day of week the surgery was done [21]; perioperative blood transfusion and repeat surgeries during hospital stay were also obtained. The length of stay (LOS) was calculated from the date of admission, to the date of discharge from hospital to their home environment. 30-day readmission data after discharge

was obtained from the clinical information system database, SCM. We filtered related readmission by the ICD-10 diagnosis, and further confirmed the cause of admission by looking up the patient's electronic medical records. We defined the window for preoperative haemoglobin levels to be taken at a maximum of 14 days and a minimum of one day before the surgery. We also defined perioperative blood transfusion to be within 2 weeks before up to 2 weeks after the date of surgery.

In our institution, most patients are admitted on the day of surgery and very infrequently, 1 day earlier for medical and/or social reasons. Routinely, all anti-platelet medications apart from Aspirin are stopped for the recommended duration before the surgery. The use of intraoperative tranexamic acid infiltration to the knee joint, intravenous tranexamic acid and the placement of a drain into the joint after the surgery is not standardized. Use of cell salvage is rare. Postoperatively, all patients receive a standard hospital TKA protocol for postoperative care and discharge. This includes thromboembolism chemoprophylaxis with 40 mg once daily subcutaneous low molecular weight heparin (Clexane, Sanofi, Paris, France) on the first postoperative day, which is discontinued upon discharge. Patients also receive routine physiotherapy starting from the first postoperative day, even if it falls on the weekend. They are deemed fit for discharge when there is an agreement between the surgeon and physiotherapist that the patient is medically stable and that their functional ability is sufficient to allow discharge to their home environment. This includes being able to climb up a few steps, transfer with the aid of a walking frame and to bend their operated knee close to 90 degrees.

After excluding 51 patients with more than 3 missing variables, 3 patients who did not have pre-operative haemoglobin levels, 22 patients who underwent revision surgery and 206 patients who underwent bilateral surgery, we obtained 2394 patients in the final analysis (Figure 1). No sensitivity analysis accounting for the missing data was done due to the small number (2.0%).

The primary outcome was prolonged LOS, defined as more than 6 days. This cutoff was selected as it represents >75th centile LOS of the whole sample. The use of 75th centile to define prolonged LOS is consistent with other studies [22]. The secondary outcome was readmission for any reason within 30 days after surgery.

Statistical analysis

We used the World Health Organisation (WHO)'s gender-based definition of anaemia severity [23]. Thus, mild anaemia was defined as haemoglobin concentration of 11-12.9g/dL in males and 11-11.9g/dL in females; moderate anaemia was defined for both genders to be haemoglobin concentration between 8-10.9g/dL and severe anaemia defined as haemoglobin concentration <8.0g/dL. Among the 567 patients (23.7%) with anaemia, 403 patients (16.8%) had mild preoperative anaemia,159 patients (6.6%) had moderate anaemia and 5 patients had severe anaemia (0.2%). Due to the small incidence of severe anaemia in the sample, patients with moderate and severe anaemia were analyzed together.

Patient demographics and clinical characteristics were compared between LOS >6 and ≤6 days (Table 1). For continuous variables, mean and standard deviation (SD) were presented and Mann-Whitney U test was used to test the mean differences between the 2 groups. For categorical variables, Chi-square test was used to compare the proportions between the 2 groups. We categorized continuous variable such as age according to their broad centile groups, BMI according to the WHO definition of obesity, and operative duration according to ≤100 minutes or > 100 minutes which corresponds to >75th centile of the data. Multivariate logistic regression was performed to determine independent predictors for increased LOS (Table 2) and perioperative blood transfusion (Table 3) while adjusting for demographic, preoperative clinical risk factors and surgical factors. We repeated the logistic regression for LOS with non-gender based cutoffs for anemia to see if it yielded significantly different results from the WHO definition of anaemia. No anemia was defined as Hb ≥ 13.0g/dL, mild anemia as Hb 11.0-12.9 g/dL and moderate/severe anemia as Hb < 11.0g/dL. Finally, we also constructed General Linear Model (GLM) with our data, taking LOS and hemoglobin as continuous variables, to assess the effect size of every unit rise in Hb on LOS. We found little presence of collinearity between hemoglobin level and perioperative blood transfusion and their effect on LOS based on linear regression. However, in our GLM model, the addition of perioperative blood transfusion as a variable reduced the significance and effect size of preoperative hemoglobin level, hence both models with and without perioperative blood transfusion were performed and presented. All analyses were performed using IBM SPSS Statistics v21.

Results

Table 1. Demographics of patients with normal Length of Stay (LOS) (≤ 6 days) versus those with prolonged LOS (> 6 days) after Primary Unilateral Total Knee Replacement (TKR)

Variable		Length of stay ≤ 6 days N=1933	Length of stay > 6 days N= 461	P-value
Patient demographics				
Age – mean (sd)		65.9 (8.0)	69.2 (8.6)	<0.001
Race – n (%)	Chinese	1628 (84.2)	385 (83.5)	0.02
	Malay	148 (7.7)	23 (5.0)	
	Indian	106 (5.5)	31 (6.7)	
	Others	51 (2.6)	22 (4.8)	
Body Mass Index – n (%)	< 25	555 (29.2)	138 (31.8)	0.16
	25 – 29.9	812 (42.7)	182 (41.9)	
	30 – 34.9	410 (21.5)	77 (17.7)	
	≥ 35	126 (6.6)	37 (8.5)	
Gender – n (%)	Male	477 (24.7)	102 (22.1)	0.25
	Female	1456 (75.3)	359 (77.9)	
Details of Operation				
Type of Anaesthesia – n (%)	GA	649 (33.6)	184 (39.9)	0.01
	RA	1284 (66.4)	277 (60.1)	
Duration of operation – minutes (sd)		79.6 (21.6)	84.9 (27.5)	<0.001
Perioperative Blood Transfusion – n (%)	None	1879 (97.2)	394 (85.5)	<0.001
	1 unit	43 (2.2)	37 (8.0)	
	≥ 2units	11 (0.6)	30 (6.5)	
Repeat Operation within Hospital Stay – n (%)	Yes	1 (0.1)	6 (1.3)	<0.001
Day of Week of Operation – n (%)	Monday	307 (15.9)	90 (19.5)	<0.001
	Tuesday	424 (21.9)	119 (25.8)	
	Wednesday	326 (16.9)	84 (18.2)	
	Thursday	472 (24.4)	63 (13.7)	
	Friday	301 (15.6)	86 (18.7)	
	Saturday	103 (5.3)	19 (4.1)	
Patient comorbidities				
Anaemia – n (%)	None	1537 (79.5)	290 (62.9)	<0.001
	Mild	294 (15.2)	109 (23.6)	
	Moderate/Severe	102 (5.3)	62 (13.4)	

DM on insulin – n (%)	Yes	30 (1.6)	11 (2.4)	0.22
Creatinine > 2mg / dL – n (%)	Yes	9 (0.5)	9 (2.0)	0.001
Previous CVA – n (%)	Yes	26 (1.3)	20 (4.3)	<0.001
IHD – n (%)	Yes	89 (4.6)	39 (8.5)	0.001
CCF – n (%)	Yes	12 (0.6)	6 (1.3)	0.128
Smoking – n (%)	Yes	184 (9.5)	43 (9.3)	0.90
ASA	1 2 3	137 (7.1) 1699 (87.9) 97 (5.0)	26 (5.6) 382 (82.9) 53 (11.5)	<0.001

Table 2. Variables that predict increased Length of Stay (LOS) in Hospital after Primary Unilateral Total Knee Replacement, based on univariate and multivariate analysis.

Variable		OR (95% CI)	P-value	aOR (95% CI)	P-value
Patient Demographics					
Age (years)	<60	REF		REF	
	60-64	0.95 (0.66, 1.37)	0.78	1.08 (0.73, 1.59)	0.71
	65-69	1.37 (0.98, 1.92)	0.07	1.42 (0.98, 2.06)	0.06
	>70	2.04 (1.51, 2.75)	<0.001	1.94 (1.38, 2.73)	<0.001
Race	Malay	0.66 (0.42, 1.03)	0.07	0.53 (0.31, 0.92)	0.02
	Indian	1.24 (0.82, 1.87)	0.32	1.34 (0.85, 2.11)	0.21
	Others	1.82 (1.09, 3.04)	0.02	1.49 (0.83, 2.68)	0.19
	Chinese	REF		REF	
Body Mass Index	<25	REF		REF	
	25 – 29.9	0.90 (0.71, 1.15)	0.41	1.02 (0.78, 1.32)	0.91
	30 – 34.9	0.76 (0.56, 1.03)	0.07	0.92 (0.65, 1.28)	0.61
	≥ 35	1.18 (0.78, 1.78)	0.43	1.56 (0.96, 2.53)	0.07
Gender	Male	REF		REF	
	Female	1.15 (0.90, 1.47)	0.25	1.20 (0.89, 1.63)	0.23
Details of Operation					
Type of Anaesthesia	GA	REF		REF	
	RA	0.76 (0.62, 0.94)	0.01	0.75 (0.59, 0.95)	0.02
Duration of operation (minutes)	≤ 100	REF		REF	
	> 100	1.41 (1.09, 1.84)	0.01	1.37 (1.03, 1.84)	0.03
Perioperative Blood Transfusion (units)	None	REF		REF	
	1	4.10 (2.61, 6.45)	<0.001	2.12 (1.24, 3.60)	0.006
	>= 2	13.01 (6.46, 26.17)	<0.001	6.71 (3.14, 14.33)	<0.001

Repeat Operation within Hospital Stay		25.48 (3.06, 212.14)	0.003	15.22 (1.38, 167.59)	0.03
Day of Week of Operation	Monday	2.20 (1.54, 3.13)	<0.001	2.38 (1.62, 3.49)	<0.001
	Tuesday	2.10 (1.51, 2.93)	<0.001	2.42 (1.68, 3.49)	<0.001
	Wednesday	1.93 (1.35, 2.76)	<0.001	2.21 (1.50, 3.24)	<0.001
	Thursday	REF		REF	
	Friday	2.14 (1.50, 3.06)	<0.001	1.99 (1.35, 2.94)	0.001
	Saturday	1.38 (0.79, 2.41)	0.25	1.46 (0.80, 2.67)	0.22
Patient comorbidities					
Anaemia	None	REF		REF	
	Mild	1.97 (1.53, 2.53)	<0.001	1.71 (1.29, 2.27)	<0.001
	Moderate/Severe	3.22 (2.29, 4.53)	<0.001	2.29 (1.54, 3.39)	<0.001
DM on insulin		1.55 (0.77, 3.12)	0.22	1.20 (0.53, 2.76)	0.66
Creatinine > 2mg/dL		4.26 (1.68, 10.78)	0.002	2.35 (0.78, 7.11)	0.13
Previous CVA		3.33 (1.84, 6.01)	<0.001	2.89 (1.50, 5.55)	0.001
IHD		1.92 (1.30, 2.83)	0.001	1.50 (0.95, 2.36)	0.08
CCF		2.11 (0.79, 5.66)	0.14	1.19 (0.38, 3.75)	0.77
Smoking		0.98 (0.69, 1.39)	0.90	1.15 (0.76, 1.75)	0.50
ASA Score	1	REF		REF	
	2	1.19 (0.77, 1.83)	0.44	0.96 (0.61, 1.52)	0.86
	3	2.88 (1.68, 4.92)	<0.001	1.40 (0.77, 2.56)	0.27

Legend: REF = reference

Table 3. Factors associated with Perioperative Blood Transfusion after Primary Unilateral TKR

Variable		aOR (95% CI)*	P-value
Type of Anaesthesia	GA	REF	
	RA	0.57 (0.37, 0.87)	0.009
Duration of operation (minutes)	≤ 100	REF	
	> 100	1.89 (1.14, 3.14)	0.014
Repeat Operation		16.51 (2.22, 123.04)	0.006

within Hospital Stay			
Anaemia	None	REF	
	Mild	4.13 (2.54, 6.71)	<0.001
	Moderate/Severe	9.13 (5.34, 15.61)	<0.001
ASA Score	1	REF	
	2	2.08 (0.63, 6.90)	0.23
	3	4.00 (1.05,15.21)	0.042
CCF		7.71 (2.24, 26.53)	0.001

* adjusted for all the variables listed in Table 1

Legend: REF = reference

Demographics

Of the 2394 patients who underwent primary TKA during the study period, 23.7% were anaemic. 403 patients (16.8%) had mild preoperative anaemia, 159 patients (6.6%) had moderate anaemia and 5 patients had severe anaemia (0.2%). In table 1, patients with prolonged LOS had higher mean age (69.2 years) compared to patients with normal LOS (65.9 years), p<0.001. There was no significant difference in BMI or gender distribution between the two groups. However, those with prolonged LOS tended to have a higher ASA score (p<0.001), higher incidence of anaemia (p<0.001), previous CVA (p<0.001), undergo repeat operation within their hospital stay (p<0.001) and received general anaesthesia compared to regional anaesthesia (p<0.01).

Length of stay (LOS)

The mean LOS for all TKA patients, was 5.4 days (± 4.8 days), with a median of 4 days and 75th centile of 6 days. This result is similar to previous published LOS rates of primary unilateral TKA in our institution[24].

461 patients (19.3%) had LOS more than six days (i.e prolonged LOS). Based on the multivariate analysis presented in table 2, the variables associated with independent elevated risk of prolonged LOS include older age > 70years (aOR 1.94, p<0.001), repeat surgery within LOS (aOR 15.22, p=0.03), having mild anaemia (aOR 1.71, p<0.001) or moderate/severe

anaemia (aOR 2.29, p<0.001), and previous cerebrovascular accidents (CVA) (aOR 2.89, p=0.001). Perioperative blood transfusion of 1 unit independently increased risk of prolonged LOS by 2.12 (p=0.006), while transfusion of 2 or more units independently increased risk by 6.71 (p<0.001). Variables that reduced LOS include having regional anaesthesia (aOR 0.74, p=0.02), having surgery on Thursday and being of Malay race. BMI, gender, presence of DM on insulin, previous diagnosis of ischemic heart disease, previous history of congestive heart failure or smoking, and elevated ASA scores were not associated with higher odds of prolonged LOS.

We repeated multivariate logistic regression for LOS with the non-gender based hemoglobin cutoffs as described earlier. Compared to no anemia, mild anemia (Hb 11.0-12.9g/dL) had an aOR 1.39 (1.09, 1.76, p=0.007) while moderate/severe anemia (Hb < 11.0 g/dL) had an aOR of 2.35 (1.56, 3.54, p<0.001) of prolonged LOS (> 6 days). These results were comparable to the findings generated with WHO definition of anemia.

Perioperative blood transfusion

Factors that increased risk of perioperative blood transfusion (Table 3) included repeat operation during hospital stay (aOR 16.51, p=0.006), presence of mild anaemia (aOR 4.13, p<0.001) and moderate/severe anaemia (aOR 9.13, p<0.001), ASA score of 3 (aOR 4.00, p=0.04, and history of CCF (aOR 7.71, p=0.001). Regional anaesthesia was found to reduce risk of perioperative blood transfusion (aOR 0.57, p=0.009).

Effect size of Hemoglobin on LOS

As shown in Table 4, when perioperative transfusion was excluded, every 1g increase in preoperative hemoglobin reduced LOS by 0.2 days (95% CI 0.08,0.34, p=0.002). However, after including perioperative transfusion, every 1g increase in preoperative hemoglobin reduced LOS minimally by 0.07 days (95% CI -0.20, 0.06, p=0.28).

Table 4. Effect size of every 1g increase in Hb, with and without factoring effect of perioperative blood transfusion based on General Linear Model

Without adjusting for Perioperative Transfusion *		
Hb Increase	Incr in LOS in days (95% CI)	P-value

1g	-0.21 (-0.34, -0.08)	0.002
2g	-0.42 (-0.68, -0.16)	0.002
3g	-0.63 (-1.01, -0.24)	0.002
After adjusting for Perioperative Transfusion [+]		
Perioperative Transfusion 0 units	REF	
1 unit	4.02 (3.01, 5.03)	<0.001
≥ 2 units	8.35 (6.97, 9.73)	<0.001
Per unit increase in Hb by 1g	-0.07 (-0.20, 0.06)	0.28

* R^2 =0.114, adjusted R^2=0.103

[+] R^2 = 0.182, adjusted R^2=0.171

Legend: REF=reference

Hospital readmission within 30 days

Table 5. Causes of related admission within 30-days of discharge after primary unilateral TKR

Causes of readmission	N
Surgical site infection	13
Pain/Swelling/Stiffness	11
Non-infective Wound Discharge	5
Deep Vein Thrombosis	4
Periprosthetic Fracture	3
Hematoma/bleeding	2
Erythema	2
Contact Dermatitis	1
Wound Dehiscence	1
Grand Total	**42**

We had 42 cases of related readmission within 30 days of discharge out of 2394 cases (1.7%) (Table 5). Due to the low rates of readmission, no further statistical analysis was done.

Discussion

In this retrospective cohort study of 2394 consecutive patients who underwent elective primary TKA in our center, the prevalence of preoperative anaemia, as defined by the WHO gender-based classification, was found to be at 23.7%. Patients with mild preoperative anaemia had an adjusted Odd Ratio of prolonged LOS (> 6 days) of 1.71, while patients with

moderate/severe anemia had an adjusted Odds Ratio of 2.29. Our findings are consistent with previous studies which explored the relationship between preoperative anaemia and LOS in elective primary knee arthroplasties. For example, Jans et al. found preoperative anaemia to be an independent predictor of prolonged LOS among patients undergoing “fast-track” knee arthroplasty [11]. This is similar with another observational study, conducted in the “traditional pathway” environment for elective primary knee arthroplasty [25]. As these studies were done in the western world health systems and a wide disparity in postoperative hospital stays after TKA has been documented due to the [26–29] variations in practice and rehabilitation protocols between countries, our study provided a perspective from a South East Asian healthcare system. In countries with advanced healthcare systems and an ageing population, the exponentially increasing number of TKAs performed yearly [3] importunes that more effort is needed to identify modifiable risk factors for delayed hospital discharges.

In addition, we have also found that every 1g increase in preoperative Hb reduces the patient’s LOS in hospital by 0.2 days. While this number is small, when we consider that the presence of preoperative anemia is one of the strongest independent predictor of perioperative blood transfusion (mild anemia is associated with aOR of blood transfusion of 4.13, $p<0.001$; moderate severe anemia with aOR of transfusion of 9.13, $p<0.001$), which on its own has a strong independent influence on prolonging LOS, preoperative anemia becomes clinically important. Thus, optimizing preoperative anemia becomes an important health care cost containment strategy, especially since TKAs are elective procedures that can be postponed to allow optimization of risk factors for suboptimal outcomes. Other studies have also found preoperative anaemia to be a strong predictor for perioperative allogeneic blood transfusion in knee surgeries[30,31], which is associated with poorer outcomes and prolonged LOS [11,32]. In our study, the transfusion of 1unit of blood is associated with aOR of prolonged LOS of 2.12, $p=0.006$, while transfusion of 2 or more units has an aOR of 6.71, $p<0.001$.

Our study adds to the growing body of publications from Asian countries on the negative impact of preoperative anemia on postoperative outcomes in orthopaedic and non-orthopaedic surgeries[33,34]. International guidelines now recommend patient blood management programs with early detection of preoperative anaemia to identify the cause and treat any underlying reversible causes, such as iron-deficiency anaemia[35]. Such intervention can reduce postoperative blood transfusion, LOS and readmission. In particular, iron deficiency anemia is

amenable to administration of IV iron treatment. Froessler et al demonstrated that preoperative intravenous iron treatment of iron deficiency anaemia among patients who underwent major abdominal surgery resulted in reduction of median LOS by three days [36]. In the UK, preoperative iron supplementation prior to elective hip/knee arthroplasty has reduced transfusion rates, 90-day readmission rates and halved median hospital LOS[37]. In Australia, transfusion rates have also been reduced since similar interventions for the same surgeries[38]. Unfortunately in our institution, further evaluation and management of anaemia is often left to the ordering physician's discretion, and a more systematic approach to the detection and management of preoperative anaemia is timely.

One of the aims of our study was to identify the risk factors for 30-day hospital readmission in our study population. However, we were unable to do so due to the small incidence of 42 readmissions out of 2349 cases, which precludes any meaningful analysis. Our 30-day related readmission rates are similar to previous published rate in our institution, which is between 1.7-2.9% for primary unilateral TKR.[24]. This is lower than the 30-day all-cause readmission rates in literature of 4.0 -5.5% [39–41], because it only looks at readmission that is related to complications attributable to the surgery. Nevertheless, our readmission rates are similar to Schairer et al's 30-day surgical readmission rate of 2.4%, of which cellulitis and surgical site infection are the most common causes. In our study, surgical site infection was also the most common cause of readmission (31.1%).

Strengths of study

One of the strengths of our study was that it is amongst the first few to control for the day of the week the surgery was done, which has recently been shown to affect LOS in TKA and total hip arthroplasty [21]. We found that having surgery on Thursday is significantly associated with the lowest odds of prolonged LOS. We postulate that this is because patients would have received standard physiotherapy for at least two days, on Friday and Saturday, and may be inclined to go home on Sunday where there is more familial support at home.

Another strength of our study is that we included both subjective measures of clinical risk estimates such as the ASA score [27,43], as well as the components of the RCRI which comprise of diagnosis of specific conditions. This allowed us to find that out of the 5 clinical conditions within the RCRI score, only a history of previous CVA was significantly associated

with increased LOS (aOR 2.89, p=0.001). Furthermore, a history of CCF was found to be associated with increased risk of perioperative blood transfusion (aOR 7.71, p=0.001).

Finally, we focused our study on patients who underwent primary total knee arthroplasty rather than combining hip and knee arthroplasty together, which is more commonly done in literature, as we wanted a more homogenous study population. We excluded revision and bilateral TKA as they are known in literature to be associated with increased need for blood transfusion and LOS.[42,43].

Our study recruitment occurred over 1.5 years. Our recruitment period is similar to another study published on this topic, which recruited over a 2 year period[11]. We feel that this is an advantage as no major changes in health care and discharge policy occurred during this short time frame that would influence our primary outcome of LOS.

Limitations of study

We also had a modest study cohort of 2349 patients which is comparable to other studies [11,39]. While our study was performed retrospectively, it had minimal missing data (2.0%). This may be due to the fact that our clinical data, such as the preoperative variables, were collected electronically in a mandatory, prospective manner during routine preoperative anaesthesia assessment. Due to the observational nature of the study, a causal relationship between preoperative anaemia and adverse outcomes is difficult to establish. In addition, while our selection of the 75th centile for defining prolonged LOS can be viewed as an arbitrary cut-off in the absence of a universal definition of prolonged LOS, the use of 75th centile has been done in literature before for a similar study [22]. We do not have data on whether drains were placed by the surgeons during the surgery, however, a recent study done in the same institution showed that while drains were associated with a larger drop in Hb level and greater total blood loss, it did not significantly impact blood transfusion rate, LOS or 30-day readmission rates[24]. We also did not have data on the prevalence of the use of intraoperative tranexamic acid infiltration into the joint, administration of IV tranexamic acid by the anesthesiologists, or use of leucodepleted blood products for transfusion. Non-leucodepleted blood has been postulated to reduce transfusion related immunomodulatory (TRIM) effects including mortality[44], although clinical studies in cardiac surgery have not proven to be conclusive so far[45,46].

Conclusion

In conclusion, we found the prevalence of preoperative anaemia to be 23.7% among patients who underwent primary total knee arthroplasty in Singapore. It was an independent risk factor for prolonged length of hospital stay and perioperative blood transfusion. We suggest measures to correct anaemia prior to surgery should be considered.

Acknowledgements

We would like to thank Ms Serene Ong, Academic Medicine Research Institute, Duke-NUS Medical School, for her help in manuscript preparation. We also like to thank Ms Sudha Harikrishnan, from the Department of Anaesthesiology, for her invaluable help in data extraction. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Lastly, we would also like to thank Dr Chan Yiong Huak, Head, Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore for his invaluable help in data analysis and interpretation.

Contributorship statement

Abdullah HR - Contributed to the study conception and design, data acquisition, analysis and interpretation, drafting and final approval of the manuscript.

Sim YE – Contributed to data analysis and interpretation, drafting, revision and final approval of the manuscript

Y Hao – Contributed to data analysis and interpretation, drafting of the manuscript and final approval

Lin GY – Contributed to data acquisition, analysis and interpretation, drafting of the manuscript and final approval

Liew GHC - Contributed to the study conception and design, data analysis, revision of the manuscript and final approval

EL Lamoureux – Contributed to data analysis and critical appraisal, revision and final approval of the manuscript.

MH Tan – Contributed to the study conception and design, drafting of manuscript and final

approval.

Competing interests

No conflicts of interest to declare.

Funding

This research was funded by the hospital department funds.

Data Sharing

Full dataset can be downloaded from http://dx.doi.org/10.5061/dryad.73250/1

Figure Legends

Figure 1. TKA – total knee arthroplasty

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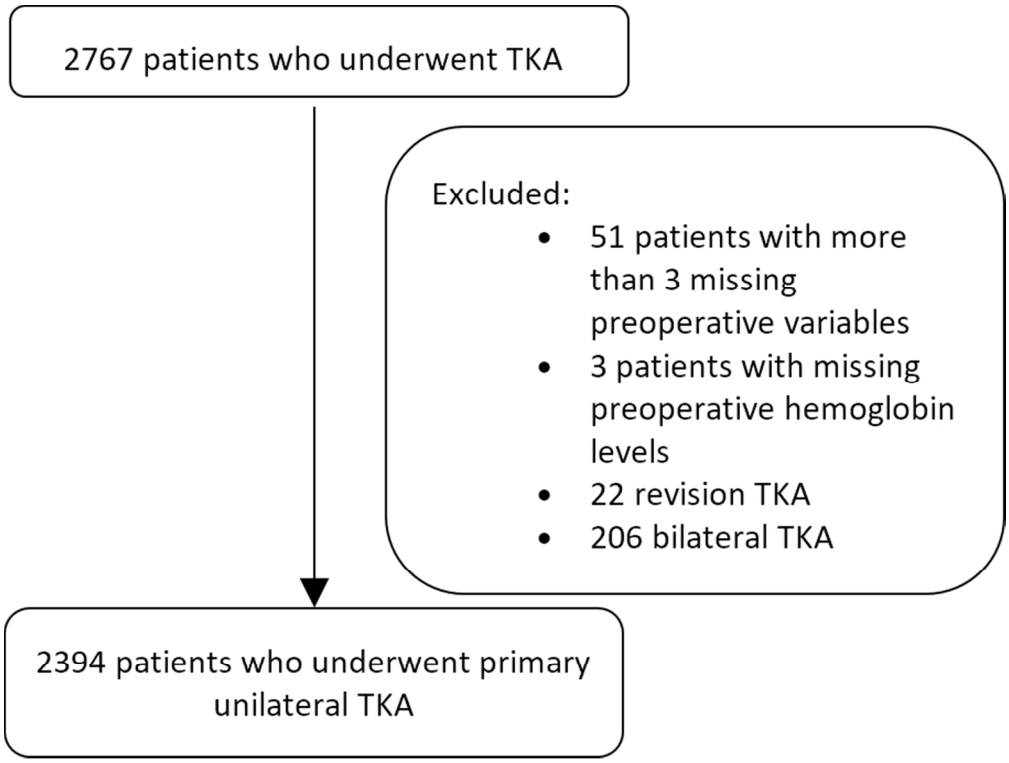

Figure 1. Flowchart of study cohort derivation

76x57mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Page where Item can be found	Recommendation
Title	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
Abstract	5	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		Introduction
Background/rationale	7-8	Explain the scientific background and rationale for the investigation being reported
Objectives	8	State specific objectives, including any prespecified hypotheses
		Methods
Study design	8-9	Present key elements of study design early in the paper
Setting	8-9	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	8-9	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
	NA	(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	8-10	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	*8-9*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	NA	Describe any efforts to address potential sources of bias
Study size	NA	Explain how the study size was arrived at
Quantitative variables	10-11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	10-11	(*a*) Describe all statistical methods, including those used to control for confounding
	10-11	(*b*) Describe any methods used to examine subgroups and interactions
	9	(*c*) Explain how missing data were addressed
	NA	(*d*) If applicable, explain how loss to follow-up was addressed
	11	(*e*) Describe any sensitivity analyses
		Results
Participants	9	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	9	(b) Give reasons for non-participation at each stage
	10	(c) Consider use of a flow diagram
Descriptive data	9	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	9	(b) Indicate number of participants with missing data for each variable of interest
	NA	(c) Summarise follow-up time (eg, average and total amount)
Outcome data	11-12	Report numbers of outcome events or summary measures over time
Main results	12-14	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
	NA	(*b*) Report category boundaries when continuous variables were categorized
	NA	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	15	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	14-17	Summarise key results with reference to study objectives
Limitations	20	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	17-18	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	NA	Discuss the generalisability (external validity) of the study results
Other information		
Funding	21	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

BMJ Open

Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty in Singapore: A single centre retrospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016403.R2
Article Type:	Research
Date Submitted by the Author:	13-Apr-2017
Complete List of Authors:	abdullah, hairil; Singapore General Hospital, Department of Anesthesiology Sim, Eileen; Singapore General Hospital, Department of Anaesthesiology Ying, Hao; Singapore General Hospital, Health Services Research Unit Lin, Gengyu; National University Singapore Yong Loo Lin School of Medicine Liew, Geoffrey ; Singapore General Hospital, Department of Anaesthesiology Lamoureux, Ecosse; Singapore Eye Research Institute Tan, Mann Hong; Singapore General Hospital, Department of Orthopaedic Surgery
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Haematology (incl blood transfusion), Surgery, Anaesthesia
Keywords:	Anaemia < HAEMATOLOGY, ORTHOPAEDIC & TRAUMA SURGERY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Blood bank & transfusion medicine < HAEMATOLOGY, Anaesthesia in orthopaedics < ANAESTHETICS

Title: Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty in Singapore: A single centre retrospective study
Short Title: Preoperative anaemia, total knee arthroplasty

Running Head:
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1 Key words: Anemia; Arthroplasty, knee replacement; length of stay;
2 Number of Tables: 3
3 Conflict of Interest: None to declare
4 Financial support: None

Abstract

Objectives: Studies in western healthcare settings suggest that preoperative anaemia is associated with poor outcomes after elective orthopaedic surgery. We investigated the prevalence of preoperative anaemia among primary unilateral total knee arthroplasty patients in Singapore and its association with length of hospital stay (LOS), perioperative blood transfusion and hospital readmission rates.

Methods: Retrospective cohort study performed in a tertiary academic medical centre in Singapore, involving patients who underwent primary unilateral TKA between January 2013 to June 2014. Demographics, comorbidities, preoperative haemoglobin level (Hb), LOS and 30-day readmission data were collected. Anaemia was classified according to WHO definition. Prolonged LOS was defined as more than 6 days, which corresponds to >75th centile LOS of the data.

Results: We analysed 2394 patients. The prevalence of anaemia was 23.7%. 403 patients (16.8%) had mild anaemia and 164 patients (6.8%) had moderate to severe anaemia. Overall mean LOS was 5.4±4.8 days. Based on multivariate logistic regression, preoperative anaemia significantly increased LOS (mild anaemia, aOR 1.71, p<0.001; moderate/severe anaemia, aOR 2.29, p<0.001). Similar effects were seen when preoperative anemia was defined by haemoglobin level below 13 g/dL, regardless of gender. Transfusion proportionately increased prolonged LOS (1 unit - aOR 2.12, p=0.006; 2 or more units - aOR 6.71, p<0.001). Repeat operation during hospital stay, previous cerebrovascular accidents, general anaesthesia and age>70 years were associated with prolonged LOS. Our 30-day related readmission rate was 1.7% (42) cases.

Conclusion: Anaemia is common among patients undergoing elective total knee arthroplasty in Singapore and is independently associated with prolonged length of stay and increased perioperative blood transfusion. We suggest measures to correct anaemia prior to surgery, including the use of non-gender based haemoglobin cut-off for establishing diagnosis.

Word count: 278

Keywords: Anaemia; Arthroplasty, knee replacement; length of stay; perioperative blood transfusion, patient blood management

Strengths:

- Our study provides a unique perspective from a South East Asian healthcare system on anaemia and its impact on LOS and hospital readmission rates after unilateral, primary total knee arthroplasty.
- We had minimal incomplete data (2.0%) due to the rigorous mandatory preoperative assessment database.
- We found comparable aOR of prolonged LOS using the WHO gender based definition of anaemia, which defines mild anemia in men to be hemoglobin concentration (Hb) between 11.0-12.9g/dL and in women to be 11.0-11.9g/dL, and a non-gender based definition which defines mild anemia as Hb 11.0-12.9 g/dL for both genders. Therefore, this lends weight to the recent proposition for a non-gender based cutoff of < 13.0g/dL in defining preoperative anaemia.
- Our study is one of the first to control for the day of the week the surgery was done, which was recently found to be a significant predictor for LOS in arthroplasties.

Limitations:

- This is a retrospective observational study, so it cannot establish a causal relationship between preoperative anaemia and adverse outcomes
- The selection of the 75th centile for defining prolonged LOS can be viewed as an arbitrary cut-off, although it is also used in other literature examining LOS after elective surgery.

Introduction

The prevalence of preoperative anaemia in patients undergoing non-cardiac surgery is considerably high, with rates of 30.4% and 28.7% recorded in the US and Europe

respectively.[1]. This is an important health problem as even mild anemia is associated with poor outcomes post-surgery [1, 3–6], including prolonged length of hospital stay (LOS) and higher readmission rates [7, 8] .

Total knee arthroplasty (TKA) is one of the most common orthopaedic procedures worldwide [2,3]. Due to the low mortality and morbidity rates associated with TKA, improvement initiatives have mainly focused on reducing LOS and improving functional recovery after surgery [4,5]. LOS associated with TKA is directly correlated with the total procedure cost, mainly due to provision of inpatient services [6,7]. Reductions in LOS can therefore help to reduce the economic burden of TKA [8,9]. Due to the fixed bed capacity, high overhead costs, and the Diagnosis-Related Group (DRG) reimbursement system in most health systems, the economic revenue of these systems depends on an increase in patient throughput by decreasing LOS. Additionally, unexpected prolonged LOS could negatively impact the patient's perspective of a good surgical outcome. Hence, it is important for health systems and physicians to identify modifiable risk factors that are associated with the improved recovery and discharge of these patients. Most studies examining the association between hospital LOS after joint arthroplasties and preoperative anaemia [10–17] were conducted within the western healthcare settings, with different demographics, potentially diverse discharge and rehabilitation policies from other regions in the world.

Therefore, in this study, we set out to investigate the relationship between preoperative anaemia and hospital LOS, perioperative blood transfusion as well as 30-day readmission rate among patients undergoing primary unilateral TKA in Singapore.

Methods

Institutional Review Board approval was obtained (Singhealth CIRB 2014/651/D) prior to the start of the study. The electronic medical records of all 2676 patients who underwent TKA between January 2013 and June 2014 in our institution were analysed. These clinical records were sourced from our institution's clinical information system (Sunrise Clinical Manager (SCM), Allscripts, IL, USA) and stored in our enterprise data repository and analytics system (SingHealth-IHiS Electronic Health Intelligence System - eHINTS), which integrates information

from administration, clinical and ancillary healthcare systems. We generated a list of patients who underwent total knee replacements from January 2013 to June 2014 using specific surgical codes relevant to this surgery. Information from SCM included patient demographics, preoperative comorbidities such as smoking, haemoglobin level, individual components of the Revised Risk Cardiac Index [18,19], such as a history of previous cerebrovascular accidents (CVA), ischemic heart disease (IHD), congestive cardiac failure (CCF), diabetes mellitus (DM) on insulin and elevated preoperative creatinine level >2mg/dL; ASA score [20]; details of the operation such as site, duration, type of anaesthesia and day of week the surgery was done [21]; perioperative blood transfusion and repeat surgeries during hospital stay were also obtained. The length of stay (LOS) was calculated from the date of admission, to the date of discharge from hospital to their home environment. 30-day readmission data after discharge was obtained from the clinical information system database, SCM. We filtered related readmission by the ICD-10 diagnosis, and further confirmed the cause of admission by looking up the patient's electronic medical records. We defined the window for preoperative haemoglobin levels to be taken at a maximum of 14 days and a minimum of one day before the surgery. We also defined perioperative blood transfusion to be within 2 weeks before up to 2 weeks after the date of surgery.

In our institution, most patients are admitted on the day of surgery and very infrequently, 1 day earlier for medical and/or social reasons. Routinely, all anti-platelet medications apart from Aspirin are stopped for the recommended duration before the surgery. The use of intraoperative tranexamic acid infiltration to the knee joint, intravenous tranexamic acid and the placement of a drain into the joint after the surgery is not standardized. Use of cell salvage is rare. Postoperatively, all patients receive a standard hospital TKA protocol for postoperative care and discharge. This includes thromboembolism chemoprophylaxis with 40 mg once daily subcutaneous low molecular weight heparin (Clexane, Sanofi, Paris, France) on the first postoperative day, which is discontinued upon discharge. Patients also receive routine physiotherapy starting from the first postoperative day, even if it falls on the weekend. They are deemed fit for discharge when there is an agreement between the surgeon and physiotherapist

that the patient is medically stable and that their functional ability is sufficient to allow discharge to their home environment. This includes being able to climb up a few steps, transfer with the aid of a walking frame and to bend their operated knee close to 90 degrees.

After excluding 51 patients with more than 3 missing variables, 3 patients who did not have pre-operative haemoglobin levels, 22 patients who underwent revision surgery and 206 patients who underwent bilateral surgery, we obtained 2394 patients in the final analysis (Figure 1). No sensitivity analysis accounting for the missing data was done due to the small number (2.0%).

The primary outcome was prolonged LOS, defined as more than 6 days. This cutoff was selected as it represents >75th centile LOS of the whole sample. The use of 75th centile to define prolonged LOS is consistent with other studies [22]. The secondary outcome was readmission for any reason within 30 days after surgery.

Statistical analysis

We used the World Health Organisation (WHO)'s gender-based definition of anaemia severity [23]. Thus, mild anaemia was defined as haemoglobin concentration of 11-12.9g/dL in males and 11-11.9g/dL in females; moderate anaemia was defined for both genders to be haemoglobin concentration between 8-10.9g/dL and severe anaemia defined as haemoglobin concentration <8.0g/dL. Among the 567 patients (23.7%) with anaemia, 403 patients (16.8%) had mild preoperative anaemia,159 patients (6.6%) had moderate anaemia and 5 patients had severe anaemia (0.2%). Due to the small incidence of severe anaemia in the sample, patients with moderate and severe anaemia were analyzed together.

Patient demographics and clinical characteristics were compared between LOS >6 and ≤6 days (Table 1). For continuous variables, mean and standard deviation (SD) were presented and Mann-Whitney U test was used to test the mean differences between the 2 groups. For categorical variables, Chi-square test was used to compare the proportions between the 2 groups. We categorized continuous variable such as age according to their broad centile groups, BMI according to the WHO definition of obesity, and operative duration according to

≤100 minutes or > 100 minutes which corresponds to >75th centile of the data. Multivariate logistic regression was performed to determine independent predictors for increased LOS (Table 2) and perioperative blood transfusion (Table 3) while adjusting for demographic, preoperative clinical risk factors and surgical factors. We repeated the logistic regression for LOS with non-gender based cutoffs for anemia to see if it yielded significantly different results from the WHO definition of anaemia. No anemia was defined as Hb ≥ 13.0g/dL, mild anemia as Hb 11.0-12.9 g/dL and moderate/severe anemia as Hb < 11.0g/dL. Finally, we also constructed General Linear Model (GLM) with our data, taking LOS and hemoglobin as continuous variables, to assess the effect size of every unit rise in Hb on LOS. We found little presence of collinearity between hemoglobin level and perioperative blood transfusion and their effect on LOS based on linear regression. However, in our GLM model, the addition of perioperative blood transfusion as a variable reduced the significance and effect size of preoperative hemoglobin level, hence both models with and without perioperative blood transfusion were performed and presented. All analyses were performed using IBM SPSS Statistics v21.

Results

Table 1. Demographics of patients with normal Length of Stay (LOS) (≤ 6 days) versus those with prolonged LOS (> 6 days) after Primary Unilateral Total Knee Replacement (TKR)

Variable		Length of stay ≤ 6 days N=1933	Length of stay > 6 days N= 461	P-value
Patient demographics				
Age – mean (sd)		65.9 (8.0)	69.2 (8.6)	<0.001
Race – n (%)	Chinese	1628 (84.2)	385 (83.5)	0.02
	Malay	148 (7.7)	23 (5.0)	
	Indian	106 (5.5)	31 (6.7)	
	Others	51 (2.6)	22 (4.8)	
Body Mass Index – n (%)	< 25	555 (29.2)	138 (31.8)	0.16
	25 – 29.9	812 (42.7)	182 (41.9)	
	30 – 34.9	410 (21.5)	77 (17.7)	
	≥ 35	126 (6.6)	37 (8.5)	
Gender – n (%)	Male	477 (24.7)	102 (22.1)	0.25

	Female	1456 (75.3)	359 (77.9)	
Details of Operation				
Type of Anaesthesia – n (%)	GA	649 (33.6)	184 (39.9)	0.01
	RA	1284 (66.4)	277 (60.1)	
Duration of operation – minutes (sd)		79.6 (21.6)	84.9 (27.5)	<0.001
Perioperative Blood Transfusion – n (%)	None	1879 (97.2)	394 (85.5)	<0.001
	1 unit	43 (2.2)	37 (8.0)	
	≥ 2units	11 (0.6)	30 (6.5)	
Repeat Operation within Hospital Stay – n (%)	Yes	1 (0.1)	6 (1.3)	<0.001
Day of Week of Operation – n (%)	Monday	307 (15.9)	90 (19.5)	<0.001
	Tuesday	424 (21.9)	119 (25.8)	
	Wednesday	326 (16.9)	84 (18.2)	
	Thursday	472 (24.4)	63 (13.7)	
	Friday	301 (15.6)	86 (18.7)	
	Saturday	103 (5.3)	19 (4.1)	
Patient comorbidities				
Anaemia – n (%)	None	1537 (79.5)	290 (62.9)	<0.001
	Mild	294 (15.2)	109 (23.6)	
	Moderate/Severe	102 (5.3)	62 (13.4)	
DM on insulin – n (%)	Yes	30 (1.6)	11 (2.4)	0.22
Creatinine > 2mg / dL – n (%)	Yes	9 (0.5)	9 (2.0)	0.001
Previous CVA – n (%)	Yes	26 (1.3)	20 (4.3)	<0.001
IHD – n (%)	Yes	89 (4.6)	39 (8.5)	0.001
CCF – n (%)	Yes	12 (0.6)	6 (1.3)	0.128
Smoking – n (%)	Yes	184 (9.5)	43 (9.3)	0.90
ASA	1	137 (7.1)	26 (5.6)	<0.001
	2	1699 (87.9)	382 (82.9)	
	3	97 (5.0)	53 (11.5)	

Table 2. Variables that predict increased Length of Stay (LOS) in Hospital after Primary Unilateral Total Knee Replacement, based on univariate and multivariate analysis.

Variable	OR (95% CI)	P-value	aOR (95% CI)	P-value

Patient Demographics					
Age (years)	<60	REF		REF	
	60-64	0.95 (0.66, 1.37)	0.78	1.08 (0.73, 1.59)	0.71
	65-69	1.37 (0.98, 1.92)	0.07	1.42 (0.98, 2.06)	0.06
	>70	2.04 (1.51, 2.75)	<0.001	1.94 (1.38, 2.73)	<0.001
Race	Malay	0.66 (0.42, 1.03)	0.07	0.53 (0.31, 0.92)	0.02
	Indian	1.24 (0.82, 1.87)	0.32	1.34 (0.85, 2.11)	0.21
	Others	1.82 (1.09, 3.04)	0.02	1.49 (0.83, 2.68)	0.19
	Chinese	REF		REF	
Body Mass Index	<25	REF		REF	
	25 – 29.9	0.90 (0.71, 1.15)	0.41	1.02 (0.78, 1.32)	0.91
	30 – 34.9	0.76 (0.56, 1.03)	0.07	0.92 (0.65, 1.28)	0.61
	≥ 35	1.18 (0.78, 1.78)	0.43	1.56 (0.96, 2.53)	0.07
Gender	Male	REF		REF	
	Female	1.15 (0.90, 1.47)	0.25	1.20 (0.89, 1.63)	0.23
Details of Operation					
Type of Anaesthesia	GA	REF		REF	
	RA	0.76 (0.62, 0.94)	0.01	0.75 (0.59, 0.95)	0.02
Duration of operation (minutes)	≤ 100	REF		REF	
	> 100	1.41 (1.09, 1.84)	0.01	1.37 (1.03, 1.84)	0.03
Perioperative Blood Transfusion (units)	None	REF		REF	
	1	4.10 (2.61, 6.45)	<0.001	2.12 (1.24, 3.60)	0.006
	>= 2	13.01 (6.46, 26.17)	<0.001	6.71 (3.14, 14.33)	<0.001
Repeat Operation within Hospital Stay		25.48 (3.06, 212.14)	0.003	15.22 (1.38, 167.59)	0.03
Day of Week of Operation	Monday	2.20 (1.54, 3.13)	<0.001	2.38 (1.62, 3.49)	<0.001
	Tuesday	2.10 (1.51, 2.93)	<0.001	2.42 (1.68, 3.49)	<0.001
	Wednesday	1.93 (1.35, 2.76)	<0.001	2.21 (1.50, 3.24)	<0.001
	Thursday	REF		REF	
	Friday	2.14 (1.50, 3.06)	<0.001	1.99 (1.35, 2.94)	0.001
	Saturday	1.38 (0.79, 2.41)	0.25	1.46 (0.80, 2.67)	0.22
Patient comorbidities					

Anaemia	None	REF		REF	
	Mild	1.97 (1.53, 2.53)	<0.001	1.71 (1.29, 2.27)	<0.001
	Moderate/Severe	3.22 (2.29, 4.53)	<0.001	2.29 (1.54, 3.39)	<0.001
DM on insulin		1.55 (0.77, 3.12)	0.22	1.20 (0.53, 2.76)	0.66
Creatinine > 2mg/dL		4.26 (1.68, 10.78)	0.002	2.35 (0.78, 7.11)	0.13
Previous CVA		3.33 (1.84, 6.01)	<0.001	2.89 (1.50, 5.55)	0.001
IHD		1.92 (1.30, 2.83)	0.001	1.50 (0.95, 2.36)	0.08
CCF		2.11 (0.79, 5.66)	0.14	1.19 (0.38, 3.75)	0.77
Smoking		0.98 (0.69, 1.39)	0.90	1.15 (0.76, 1.75)	0.50
ASA Score	1	REF		REF	
	2	1.19 (0.77, 1.83)	0.44	0.96 (0.61, 1.52)	0.86
	3	2.88 (1.68, 4.92)	<0.001	1.40 (0.77, 2.56)	0.27

Legend: REF = reference

Table 3. Factors associated with Perioperative Blood Transfusion after Primary Unilateral TKR

Variable		aOR (95% CI)*	P-value
Type of Anaesthesia	GA	REF	
	RA	0.57 (0.37, 0.87)	0.009
Duration of operation (minutes)	≤ 100	REF	
	> 100	1.89 (1.14, 3.14)	0.014
Repeat Operation within Hospital Stay		16.51 (2.22, 123.04)	0.006
Anaemia	None	REF	
	Mild	4.13 (2.54, 6.71)	<0.001
	Moderate/Severe	9.13 (5.34, 15.61)	<0.001
ASA Score	1	REF	
	2	2.08 (0.63, 6.90)	0.23
	3	4.00 (1.05,15.21)	0.042
CCF		7.71 (2.24, 26.53)	0.001

* adjusted for all the variables listed in Table 1

Legend: REF = reference

Demographics

Of the 2394 patients who underwent primary TKA during the study period, 23.7% were anaemic. 403 patients (16.8%) had mild preoperative anaemia, 159 patients (6.6%) had moderate anaemia and 5 patients had severe anaemia (0.2%). In table 1, patients with prolonged LOS had higher mean age (69.2 years) compared to patients with normal LOS (65.9 years), p<0.001. There was no significant difference in BMI or gender distribution between the two groups. However, those with prolonged LOS tended to have a higher ASA score (p<0.001), higher incidence of anaemia (p<0.001), previous CVA (p<0.001), undergo repeat operation within their hospital stay (p<0.001) and received general anaesthesia compared to regional anaesthesia (p<0.01).

Length of stay (LOS)

The mean LOS for all TKA patients, was 5.4 days (± 4.8 days), with a median of 4 days and 75th centile of 6 days. This result is similar to previous published LOS rates of primary unilateral TKA in our institution[24].

461 patients (19.3%) had LOS more than six days (i.e prolonged LOS). Based on the multivariate analysis presented in table 2, the variables associated with independent elevated risk of prolonged LOS include older age > 70years (aOR 1.94, p<0.001), repeat surgery within LOS (aOR 15.22, p=0.03), having mild anaemia (aOR 1.71, p<0.001) or moderate/severe anaemia (aOR 2.29, p<0.001), and previous cerebrovascular accidents (CVA) (aOR 2.89, p=0.001). Perioperative blood transfusion of 1 unit independently increased risk of prolonged LOS by 2.12 (p=0.006), while transfusion of 2 or more units independently increased risk by 6.71 (p<0.001). Variables that reduced LOS include having regional anaesthesia (aOR 0.74, p=0.02), having surgery on Thursday and being of Malay race. BMI, gender, presence of DM on insulin, previous diagnosis of ischemic heart disease, previous history of congestive heart failure or smoking, and elevated ASA scores were not associated with higher odds of prolonged LOS.

We repeated multivariate logistic regression for LOS with the non-gender based hemoglobin cutoffs as described earlier. Compared to no anemia, mild anemia (Hb 11.0-12.9g/dL) had an aOR 1.39 (1.09, 1.76, p=0.007) while moderate/severe anemia (Hb < 11.0 g/dL) had an aOR of 2.35 (1.56, 3.54, p<0.001) of prolonged LOS (> 6 days). These results were comparable to the findings generated with WHO definition of anemia.

Perioperative blood transfusion

Our overall transfusion rate was 5.0%. Factors that increased risk of perioperative blood transfusion (Table 3) included repeat operation during hospital stay (aOR 16.51, p=0.006), presence of mild anaemia (aOR 4.13, p<0.001) and moderate/severe anaemia (aOR 9.13, p<0.001), ASA score of 3 (aOR 4.00, p=0.04, and history of CCF (aOR 7.71, p=0.001). Regional anaesthesia was found to reduce risk of perioperative blood transfusion (aOR 0.57, p=0.009).

Effect size of Hemoglobin on LOS

As shown in Table 4, when perioperative transfusion was excluded, every 1g increase in preoperative hemoglobin reduced LOS by 0.2 days (95% CI 0.08,0.34, p=0.002). However, after including perioperative transfusion, every 1g increase in preoperative hemoglobin reduced LOS minimally by 0.07 days (95% CI -0.20, 0.06, p=0.28).

Table 4. Effect size of every 1g increase in Hb, with and without factoring effect of perioperative blood transfusion based on General Linear Model

Without adjusting for Perioperative Transfusion *		
Hb Increase	Incr in LOS in days (95% CI)	P-value
1g	-0.21 (-0.34, -0.08)	0.002
2g	-0.42 (-0.68, -0.16)	0.002
3g	-0.63 (-1.01, -0.24)	0.002
After adjusting for Perioperative Transfusion +		
Perioperative Transfusion 0 units	REF	

1 unit	4.02 (3.01, 5.03)	<0.001
≥ 2 units	8.35 (6.97, 9.73)	<0.001
Per unit increase in Hb by 1g	-0.07 (-0.20, 0.06)	0.28

* R^2 =0.114, adjusted R^2=0.103

+ R^2 = 0.182, adjusted R^2=0.171

Legend: REF=reference

Hospital readmission within 30 days

Table 5. Causes of related admission within 30-days of discharge after primary unilateral TKR

Causes of readmission	N
Surgical site infection	13
Pain/Swelling/Stiffness	11
Non-infective Wound Discharge	5
Deep Vein Thrombosis	4
Periprosthetic Fracture	3
Hematoma/bleeding	2
Erythema	2
Contact Dermatitis	1
Wound Dehiscence	1
Grand Total	**42**

We had 42 cases of related readmission within 30 days of discharge out of 2394 cases (1.7%) (Table 5). Due to the low rates of readmission, no further statistical analysis was done.

Discussion

In this retrospective cohort study of 2394 consecutive patients who underwent elective unilateral primary TKA in our center, the prevalence of WHO-defined preoperative anaemia was 23.7%. Patients with mild preoperative anaemia had an adjusted Odd Ratio (aOR) of prolonged LOS (> 6 days) of 1.71, while patients with moderate/severe anemia had an aOR of 2.29. Our findings are consistent with previous studies which show that preoperative anaemia independently increased LOS in “fast-track” knee arthroplasty [11] and in the “traditional

pathway" elective primary knee arthroplasty [25]. As these studies were done in the western world health systems and variations in practice and rehabilitation protocols between countries may lead to a wide disparity in postoperative hospital stays after TKA [26–29], our study provided a perspective from a South East Asian healthcare system. In countries with advanced healthcare systems and an ageing population, the exponentially increasing number of TKAs performed yearly [3] importunes that more effort is needed to identify modifiable risk factors for delayed hospital discharges.

Our study showed that every 1g increase in preoperative Hb reduced the patient's LOS in hospital by 0.2 days. While this number is small, the presence of preoperative anemia is one of the strongest independent predictor of perioperative blood transfusion (mild anemia is associated with aOR of blood transfusion of 4.13, $p<0.001$; moderate severe anemia with aOR of transfusion of 9.13, $p<0.001$), which has a strong independent influence on prolonging LOS in our study. The transfusion of 1 unit of blood is associated with aOR of prolonged LOS of 2.12, $p=0.006$, while transfusion of 2 or more units has an aOR of 6.71, $p<0.001$. Other studies have also found preoperative anaemia to be a strong predictor for perioperative allogeneic blood transfusion in knee surgeries[30,31], which is associated with poorer outcomes and prolonged LOS [11,32]. Thus, optimizing preoperative anemia becomes an important health care cost containment strategy, since TKAs are elective procedures that can be postponed to allow optimization of risk factors for suboptimal outcomes.

Our study adds to the growing body of publications from Asian countries on the negative impact of preoperative anemia on postoperative outcomes in orthopaedic and non-orthopaedic surgeries[33,34]. International guidelines now recommend patient blood management programs with early detection of preoperative anaemia to identify the cause and treat any underlying reversible causes, such as iron-deficiency anaemia[35]. Such intervention can reduce postoperative blood transfusion, LOS and readmission. In particular, iron deficiency anemia is amenable to administration of IV iron treatment. Froessler et al demonstrated that preoperative intravenous iron treatment of iron deficiency anaemia among patients who underwent major abdominal surgery resulted in reduction of median LOS by three days [36]. In the UK, preoperative iron supplementation prior to elective hip/knee arthroplasty has reduced

transfusion rates, 90-day readmission rates and halved median hospital LOS[37]. In Australia, transfusion rates have also been reduced since similar interventions for the same surgeries[38]. Unfortunately in our institution, further evaluation and management of anaemia is often left to the ordering physician's discretion, and a more systematic approach to the detection and management of preoperative anaemia is timely.

We found comparable aOR of prolonged LOS using the WHO gender based definition of anaemia, which defines mild anemia in men to be between 11.0-12.9g/dL and that in women to be 11.0-11.9g/dL, and a non-gender based definition which defines mild anemia as Hb 11.0-12.9 g/dL for both genders. Therefore, this lends weight to the recent proposition for a non-gender based cutoff of < 13.0g/dL in defining preoperative anaemia for the purpose of Patient Blood Management initiatives.[39,40]

One of the aims of our study was to identify the risk factors for 30-day hospital readmission in our study population. However, we were unable to do so due to the small incidence of 42 readmissions out of 2349 cases, which precludes any meaningful analysis. Our 30-day related readmission rates are similar to previous published rate in our institution, which is between 1.7-2.9% for primary unilateral TKR.[24]. This is lower than the 30-day all-cause readmission rates in literature of 4.0 -5.5% [41–43], because it only looks at readmission that is related to complications attributable to the surgery. Nevertheless, our readmission rates are similar to Schairer et al's 30-day surgical readmission rate of 2.4%, of which cellulitis and surgical site infection are the most common causes. In our study, surgical site infection was also the most common cause of readmission (31.1%).

Strengths of study

One of the strengths of our study was that it is amongst the first few to control for the day of the week the surgery was done, which has recently been shown to affect LOS in TKA and total hip arthroplasty [21]. We found that having surgery on Thursday is significantly associated with the lowest odds of prolonged LOS. We postulate that this is because patients would have received standard physiotherapy for at least two days, on Friday and Saturday, and may be inclined to go home on Sunday where there is more familial support at home.

Another strength of our study is that we included both subjective measures of clinical risk estimates such as the ASA score [27,43], as well as the components of the RCRI which comprise of diagnosis of specific conditions. This allowed us to find that out of the 5 clinical conditions within the RCRI score, only a history of previous CVA was significantly associated with increased LOS (aOR 2.89, p=0.001). Furthermore, a history of CCF was found to be associated with increased risk of perioperative blood transfusion (aOR 7.71, p=0.001).

Finally, we focused our study on patients who underwent primary total knee arthroplasty rather than combining hip and knee arthroplasty together, which is more commonly done in literature, as we wanted a more homogenous study population. We excluded revision and bilateral TKA as they are known in literature to be associated with increased need for blood transfusion and LOS.[44,45].

Our study recruitment occurred over 1.5 years. Our recruitment period is similar to another study published on this topic, which recruited over a 2 year period[11]. We feel that this is an advantage as no major changes in health care and discharge policy occurred during this short time frame that would influence our primary outcome of LOS.

Limitations of study

We also had a modest study cohort of 2349 patients which is comparable to other studies [11,41]. While our study was performed retrospectively, it had minimal missing data (2.0%). This may be due to the fact that our clinical data, such as the preoperative variables, were collected electronically in a mandatory, prospective manner during routine preoperative anaesthesia assessment. Due to the observational nature of the study, a causal relationship between preoperative anaemia and adverse outcomes is difficult to establish. In addition, while our selection of the 75th centile for defining prolonged LOS can be viewed as an arbitrary cut-off in the absence of a universal definition of prolonged LOS, the use of 75th centile has been done in literature before for a similar study [22]. We do not have data on whether drains were placed by the surgeons during the surgery, however, a recent study done in the same institution showed that while drains were associated with a larger drop in Hb level and greater total blood loss, it did not significantly impact blood transfusion rate, LOS or 30-day readmission rates[24].

We also did not have data on the prevalence of the use of intraoperative tranexamic acid infiltration into the joint, administration of IV tranexamic acid by the anesthesiologists, or use of leucodepleted blood products for transfusion. Non-leucodepleted blood has been postulated to reduce transfusion related immunomodulatory (TRIM) effects including mortality[46], although clinical studies in cardiac surgery have not proven to be conclusive so far[47,48].

Conclusion

In conclusion, we found the prevalence of preoperative anaemia to be 23.7% among patients who underwent primary total knee arthroplasty in Singapore. It was an independent risk factor for prolonged length of hospital stay and perioperative blood transfusion. We suggest measures to correct anaemia prior to surgery, including the use of non-gender based haemoglobin cut-off for establishing diagnosis.

Acknowledgements

We would like to thank Ms Serene Ong, Academic Medicine Research Institute, Duke-NUS Medical School, for her help in manuscript preparation. We also like to thank Ms Sudha Harikrishnan, from the Department of Anaesthesiology, for her invaluable help in data extraction. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Lastly, we would also like to thank Dr Chan Yiong Huak, Head, Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore for his invaluable help in data analysis and interpretation.

Contributorship statement

Abdullah HR - Contributed to the study conception and design, data acquisition, analysis and interpretation, drafting and final approval of the manuscript.

Sim YE – Contributed to data analysis and interpretation, drafting, revision and final approval of the manuscript

Y Hao – Contributed to data analysis and interpretation, drafting of the manuscript and final

approval

Lin GY – Contributed to data acquisition, analysis and interpretation, drafting of the manuscript and final approval

Liew GHC - Contributed to the study conception and design, data analysis, revision of the manuscript and final approval

EL Lamoureux – Contributed to data analysis and critical appraisal, revision and final approval of the manuscript.

MH Tan – Contributed to the study conception and design, drafting of manuscript and final approval.

Competing interests

No conflicts of interest to declare.

Funding

This research was funded by the hospital department funds.

Data Sharing

Full dataset can be downloaded from http://dx.doi.org/10.5061/dryad.73250/1

Figure Legends

Figure 1. TKA – total knee arthroplasty

1

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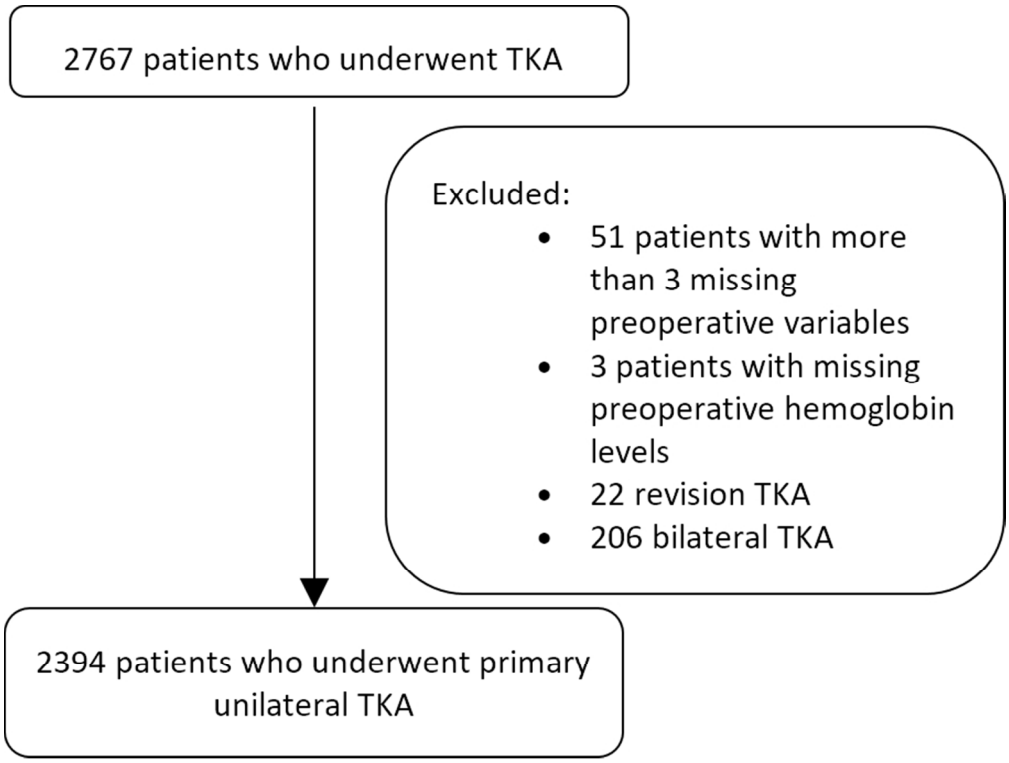

Figure 1. Flowchart of study cohort derivation

76x57mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Page where Item can be found	Recommendation
Title	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
Abstract	5	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		Introduction
Background/rationale	7-8	Explain the scientific background and rationale for the investigation being reported
Objectives	8	State specific objectives, including any prespecified hypotheses
		Methods
Study design	8-9	Present key elements of study design early in the paper
Setting	8-9	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	8-9	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
	NA	(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	8-10	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	*8-9*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	NA	Describe any efforts to address potential sources of bias
Study size	NA	Explain how the study size was arrived at
Quantitative variables	10-11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	10-11	(*a*) Describe all statistical methods, including those used to control for confounding
	10-11	(*b*) Describe any methods used to examine subgroups and interactions
	9	(*c*) Explain how missing data were addressed
	NA	(*d*) If applicable, explain how loss to follow-up was addressed
	11	(*e*) Describe any sensitivity analyses
		Results
Participants	9	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	9	(b) Give reasons for non-participation at each stage
	10	(c) Consider use of a flow diagram
Descriptive data	9	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	9	(b) Indicate number of participants with missing data for each variable of interest
	NA	(c) Summarise follow-up time (eg, average and total amount)
Outcome data	11-12	Report numbers of outcome events or summary measures over time
Main results	12-14	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
	NA	(*b*) Report category boundaries when continuous variables were categorized
	NA	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	15	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	14-17	Summarise key results with reference to study objectives
Limitations	20	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	17-18	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	NA	Discuss the generalisability (external validity) of the study results
Other information		
Funding	21	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.