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Association between preoperative anaemia and blood transfusion with long-term functional and quality of life outcomes amongst patients undergoing primary total knee arthroplasty in Singapore: a single-centre retrospective study

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Abstract

Purpose Preoperative anaemia affects up to one-third of patients undergoing total knee arthroplasty (TKA) and is associated with increased blood transfusion and prolonged hospitalisation. Prior studies have associated preoperative anaemia with poorer functional recovery after total hip arthroplasty. However, the association between preoperative anaemia and functional outcomes following TKA is unknown. We aim to determine whether preoperative anaemia and perioperative blood transfusion affect health-related quality of life (HRQoL) and functional outcomes following TKA.

Methods Retrospective analysis of 1994 patients who underwent primary unilateral TKA from 2013 to 2014 was performed. Anaemia was defined according to the World Health Organisation definition. Baseline and 6-month postoperative HRQoL was assessed with the 36-Item Short Form Survey (SF-36), while function was assessed with Oxford Knee Score (OKS) and Knee Society Function Score (KSFS). Physical function (PF), role physical (RP), bodily pain (BP), social function (SF) and role emotional (RE) domains of SF-36, OKS and KSFS demonstrated significant change greater than the minimal clinically important difference between baseline and 6 months. Analysis of covariance (ANCOVA) was performed to identify predictors of 6-month scores.

Results The incidence of preoperative anaemia was 22.3%. 4.3% of patients received blood transfusions. Preoperative anaemia and perioperative blood transfusion did not significantly affect SF-36, KSFS and OKS scores at 6 months postoperatively. Poor baseline SF-36, KSS and OKS scores and high BMI $\geq$ 37.5 kg/m^2 are consistently associated with lower scores at 6 months.

Conclusion Preoperative anaemia and perioperative blood transfusion did not significantly affect HRQoL and functional outcomes following primary TKA. Poor baseline and obesity were associated with poorer outcomes.

Keywords Anaemia · Arthroplasty · Knee replacement · Quality of life · Functional outcome · Perioperative blood transfusion · Obesity

Introduction

Severe osteoarthritis of the knee is associated with pain and functional limitations in activities of daily living and a poorer quality of life. Total knee arthroplasty (TKA) for severe osteoarthritis of the knee is one of the most common orthopaedic procedures performed worldwide [1] and is the treatment of choice as the majority of patients will show important improvements in pain, disabilities and health-related quality of life [2]. Given the increasing number of TKAs performed in ageing societies around the world, there

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is a lot of interest in optimising the longer term outcomes of this surgery so as to reduce the economic burden on society. Prior studies have identified several factors associated with reduced improvement in functional outcomes and quality of life following TKA, such as poorer psychosocial status [3], preoperative pain and function [4, 5], female gender [6], advanced age [7, 8], high number of comorbidities [9] and prolonged length of wait for surgery [10–12].

One possible predictor of functional and quality of life outcome following TKA that has not been well investigated is preoperative anaemia. Preoperative anaemia is common amongst patients undergoing TKA, with a recent study demonstrating incidence of up to 25% [13, 14]. Preoperative anaemia amongst patients undergoing TKA has been associated with poorer short-term clinical outcomes such as prolonged length of stay [13], increased perioperative blood transfusion requirement [15, 16] and periprosthetic joint infection [17]. Multiple population-based cohort studies have established association between anaemia and lower quality of life, as well as disability and decreased physical performance, amongst patients beyond 65 years old, which is also the main age group for TKA surgeries [18–21].

However, little is known about the association between preoperative anaemia and longer term outcomes following TKA. This is important as preoperative anaemia is a potentially modifiable risk factor [22]. Furthermore, preoperative anaemia is a major independent predictive factor for the need of blood transfusion, which is by itself an independent predictor of poor perioperative outcome [13, 23]. To address this knowledge gap, this study aims to assess the association between preoperative anaemia and blood transfusion, with the longer term postoperative HRQoL and functional outcomes, amongst patients undergoing TKA. We hypothesise that absence of preoperative anaemia and perioperative blood transfusion would be independently associated with greater reported improvements in HRQoL and functional outcomes following TKA.

Methods

Institutional Review Board approval was obtained (SingHealth CRB 2014/651/D) prior to starting the study. This retrospective, observational cohort study was performed in Singapore General Hospital—a tertiary public hospital. A previous study conducted on this study population investigated the association between preoperative anaemia and length of hospital stay amongst patients undergoing primary TKA. The findings of the study have been published separately [13].This is a follow-up study on the impact of preoperative anaemia on HRQoL and functional outcomes after TKA.

We obtained 2774 patient records of TKA for primary osteoarthritis between January 2013 and June 2014. Their electronic medical 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). Information retrieved included patient demographics; smoking; American Society of Anaesthesiologist (ASA) score; details of the operation such as surgical site, type of anaesthesia; components of the RCRI score; and perioperative blood transfusion during the hospital stay. We defined the window for preoperative haemoglobin levels to be taken at a maximum of 14 days and a minimum of 1 day prior to surgery. We defined perioperative blood transfusion to be within 2 weeks prior and up to 2 weeks after the date of surgery. Our institution does not practise universal leucodepletion and cell salvage for TKAs. Additionally, as part of the workflow for elective TKA, all patients had undergone assessment with the SF-36 score [24], Oxford Knee Score (OKS) [25] and Knee Society Score (KSS) [26].

The SF-36 is a commonly utilised instrument for assessing HRQoL [24]. It comprises of one multi-item scale assessing eight different health concepts—physical function (PF), role physical (RP), social function (SF), bodily pain (BP), mental health (MH), role emotional (RE), vitality (VT) and general health (GH). The score for the SF-36 scales range from 0 (most disability) to 100 (least disability). Previous studies have shown that in the first 6 months following TKA, patients typically demonstrate improvements in the PF, RP, BP, SF, RE and VT components [27]. The OKS is a reliable and sensitive joint-specific questionnaire comprising 12-items designed to assess for function and pain in patients who have undergone TKA [25]. Each item assesses a patient's ability to complete specific activities of daily living and is completed by the patient directly. It utilises a system where each item is scored between 1 (least symptoms) to 5 (most symptoms) to give a total score that ranges from 12 to 60. A score of 12 points for the OKS indicates that the patient is experiencing minimal functional limitation and pain, while a score of 60 points indicates maximal functional limitation and pain severity. The KSS, which was first developed in 1989, is a commonly used clinician assessed outcome measure [26]. It comprises of two components: a Knee Society Knee (KS-Knee) score and Knee Society Function (KS-Function) score. The KS-Knee score, which objectively assesses the knee joint, is judged based on parameters in pain, stability and range of motion, and can be scored a maximum of 100 points. The KS-Function score, which is also scored a maximum of 100 points, takes into consideration walking distance and stair climbing with deductions for walking aids. A score of 100 points in each domain of the KSS indicates the best functionality, while a

score of 0 points indicates the presence of severe functional limitations.

After excluding 630 patients who underwent revision surgery (defined as previous TKA, previous high tibial osteotomy, unicompartmental or bicompartmental arthroplasty), unicompartmental or bicompartmental arthroplasty, bilateral knee surgeries, as well as records of primary TKA in the contralateral knee that was performed after the index TKA, we obtained 1994 patients in the final analysis (Fig. 1).

Statistical analysis

We utilised the World Health Organisation (WHO)'s gender-based definition for anaemia severity [28]. Mild anaemia was defined as haemoglobin level between 11 and 12.9 g/dL in males and 11–11.9 g/dL in females; moderate anaemia was defined as a haemoglobin level between 8 and 10.9 g/dL and severe anaemia was defined as a haemoglobin level < 8.0 g/dL for both genders. Due to the small incidence of severe anaemia ($n = 3$) in the study population, patients with moderate and severe anaemia were analysed together.

Patient demographics and clinical characteristics were compared between patients with no anaemia, mild anaemia and moderate/severe anaemia. Body Mass Index (BMI) was categorised according to the WHO Asian definition for obesity [29]. For continuous demographic variables, the one-way analysis of variance (ANOVA) was performed to compare the mean differences between the three groups, while the Chi-square (X^2) test or Fisher test was used to compare proportions between the three groups. Non-parametric tests were used to compare the functional and HRQoL scores between the three groups after checking for normality of distribution with Q–Q plots, histogram, degree of skew and kurtosis, Kolmogorov–Smirnov and Shapiro–Wilk. The baseline preoperative functional and HRQoL scores between the three groups were compared with the Kruskal–Wallis test (Table 1). The mean baseline preoperative and postoperative scores at 6 months and 2 years for OKS, KSS and SF-36 domains were compared using Repeated Measure General Linear Model analysis (Table 2). As the PF, RP, RE, BP and SF domains of SF-36 [27], OKS [30] and KSS [31] demonstrated changes larger than the minimal clinically important difference (MCID) between the baseline and 6-month mean scores, these were selected for subsequent analysis of covariance (ANCOVA) to identify predictors of the 6-month follow-up scores. We used the MCID as a cutoff for clinical relevance as it is defined as the smallest difference between the scores in a questionnaire that the patient perceives to be beneficial. It is taken to be greater than 10 for SF-36 [27], 6.4 for KS-Function score, 5.9 for KS-Knee score [31] and 5.0 for OKS [32]. The MCID scores for OKS and KS were previously validated in our institution [31, 32]. The univariate ANCOVA model was adjusted for baseline preoperative scores together with either preoperative anaemia or perioperative blood transfusion ("Appendix", Tables 6, 7), while the multivariate model was fitted with all relevant clinical variables (Tables 3, 4). We attempted to use quantile regression analysis to perform these analysis but the resulting models were unstable and thus not presented.

Sample power calculation

From a previous study published in our hospital, the prevalence of anaemia was approximately 25% and for transfusion was 5% in patients undergoing total knee arthroplasty. Thus,

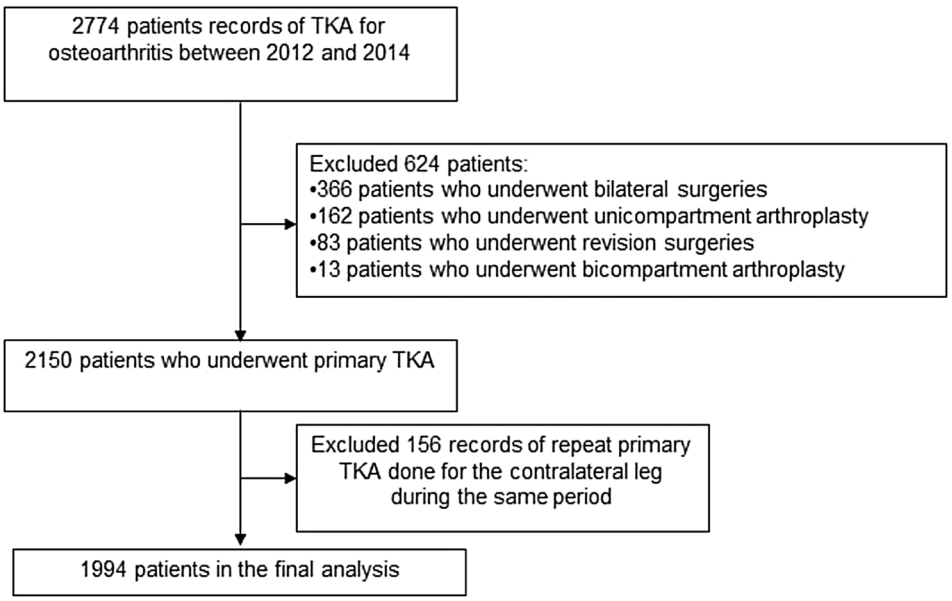

Fig. 1 Patient derivation flowchart

Table 1 Preoperative functional and HRQoL scores according to anaemia severity

	Total ($N=1994$)			No anaemia ($N=1549$)			Mild anaemia ($N=318$)			Moderate/severe anaemia ($N=127$)			p value
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	
Knee Society Score													
Function	52.59	50.00	17.90	53.64	50.00	17.57	49.75	50.00	17.82	46.85	45.00	20.28	< 0.001
Knee	37.78	36.00	17.70	38.73	38.00	17.68	34.60	30.00	17.60	34.19	31.00	17.01	< 0.001
Oxford Knee Score													
Total	35.46	35.00	8.15	35.07	35.00	8.08	36.62	37.00	8.35	37.35	36.00	8.12	< 0.001
SF-36—PCS													
PF	37.90	35.00	22.93	39.16	35.00	22.85	34.62	30.00	23.50	30.71	30.00	20.37	< 0.001
RP	21.78	0.00	34.73	22.93	0.00	35.20	16.67	0.00	31.67	20.47	0.00	35.27	0.006
BP	35.46	32.00	17.88	36.20	32.00	18.11	33.12	32.00	16.65	32.21	31.00	17.34	0.005
GH	68.97	72.00	20.84	69.47	72.00	20.76	67.61	72.00	21.71	66.37	67.00	19.32	0.055
SF-36—MCS													
VT	70.75	70.00	21.31	70.95	70.00	21.34	69.98	70.00	21.46	70.31	70.00	20.70	0.737
SF	55.42	50.00	35.60	56.66	50.00	35.54	51.22	50.00	35.49	50.79	50.00	35.59	0.014
RE	84.19	100.00	35.01	83.61	100.00	35.60	86.06	100.00	33.04	86.61	100.00	32.33	0.437
MH	80.11	84.00	17.19	79.97	84.00	17.58	80.75	84.00	16.07	80.09	84.00	15.05	0.774

Oxford Knee Score ranges from 12 to 60. Smaller scores indicate better function. Knee Society Score ranges from 0 to 100. Larger scores indicate better function

PCS physical component summary, *PF* physical function, *RP* role physical, *BP* bodily pain, *GH* general health, *MCS* mental component summary, *VT* vitality, *SF* social function, *RE* role emotional, *MH* mental health

Table 2 Changes in functional and health-related quality of life scores at 6 months and 2 years after total knee arthroplasty

SF 36	N	Baseline		6 Months		2 Years		Difference between baseline and 6 months		Difference between 6 months and 2 years	
	1670	Mean	(SD)	Mean	(SD)	Mean	(SD)				
PF		38.3	(22.8)	65.3	(22.0)	70.00	(22.9)	27.0^{+}	< 0.001	4.7	< 0.001
RP		21.8	(34.6)	63.9	(41.4)	69.30	(39.2)	42.1^{+}	< 0.001	5.4	< 0.001
BP		35.6	(17.8)	63.8	(24.0)	67.40	(26.1)	28.2^{+}	< 0.001	3.6	< 0.001
GH		68.7	(20.9)	71.7	(20.6)	70.40	(21.1)	3.0	< 0.001	− 1.3	0.04
VT		70.6	(21.1)	75.7	(19.6)	75.30	(19.6)	5.1	< 0.001	− 0.4	1
SF		55.4	(35.4)	85.1	(27.2)	88.10	(25.9)	29.7^{+}	< 0.001	3.0	< 0.001
RE		84.0	(35.1)	94.6	(21.8)	95.50	(19.6)	10.6^{+}	< 0.001	0.9	0.48
MH		79.9	(17.1)	85.9	(14.1)	84.70	(15.9)	6.0	< 0.001	− 1.2	0.017
Oxford scores	1674										
		35.5	(8.0)	20.3	(5.7)	18.8	(5.3)	− 15.2^{+}	< 0.001	− 1.5	< 0.001
KS	1623										
Knee		38.2	(17.8)	82.5	(14.0)	84.3	(13.5)	44.3	< 0.001	1.8	< 0.001
Function		53.0	(17.6)	68.8	(18.5)	72.3	(18.8)	15.8^{+}	< 0.001	3.5	< 0.001

Oxford Knee Score ranges from 12 to 60. Smaller scores indicate better function. Knee Society Score ranges from 0 to 100. Larger scores indicate better function

KS Knee Society, *OKS* Oxford Knee Score, *PF* physical function, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social function, *RE* role emotional, *MH* mental health

$^{+}$Selected for subsequent multivariate analysis as it demonstrates greater than Minimal Clinically Important Difference (MCID)

Table 3 Factors affecting health-related quality of life SF-36 domains at 6 months after total knee arthroplasty based on multivariate analysis

Variable	Physical function		Role physical		Bodily pain		Social function		Role emotional	
	B-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value
Preoperative anaemia										
Mild	−1.970 (−4.445, 0.506)	0.119	−0.129 (−5.223, 4.965)	0.960	−1.168 (−4.081, 1.744)	0.431	−0.633 (−3.985, 2.719)	0.711	−0.132 (−2.933, 2.669)	0.926
Moderate/severe	−2.552 (−6.348, 1.243)	0.187	−0.586 (−8.392, 7.221)	0.883	−0.819 (−5.285, 3.646)	0.719	−1.135 (−6.274, 4.005)	0.665	0.230 (−4.069, 4.530)	0.916
No anaemia	REF		REF		REF		REF		REF	
Perioperative blood transfusion										
1 unit	−4.802 (−10.254, 0.650)	0.084	−9.786 (−21.024, 1.453)	0.088	−2.106 (−8.522, 4.311)	0.520	−4.884 (−12.279, 2.511)	0.195	0.553 (−5.628, 6.733)	0.861
≥2 units	−6.603 (−14.507, 1.302)	0.102	−2.675 (−18.967,13.616)	0.747	3.049 (−6.259, 12.357)	0.521	−7.840 (−18.576, 2.896)	0.152	5.445 (−3.522, 14.413)	0.234
None	REF		REF		REF		REF		REF	
BMI (kg/m^2)										
<17.5	−1.852 (−21.141, 17.437)	0.851	−23.720 (−63.457, 16.017)	0.242	−10.274 (−33.006, 12.458)	0.375	4.823 (−21.352, 30.998)	0.718	4.982 (−16.889, 26.863)	0.655
23.0–27.4	−0.934 (−3.813, 1.945)	0.525	−0.942 (−6.873, 4.990)	0.756	−0.479 (−3.870, 2.912)	0.782	0.283 (−3.622, 4.188)	0.887	0.399 (−2.868, 3.665)	0.811
27.5–32.4	**−4.045 (−6.993, −1.098)**	**0.007**	−3.656 (−9.720, 2.408)	0.237	−3.260 (−6.727, 0.206)	0.065	−0.835 (−4.828, 3.158)	0.682	−0.326 (−3.665, 3.014)	0.848
32.5–37.4	**−6.717 (−10.468, −2.966)**	**<0.001**	−3.137 (−10.845, 4.572)	0.425	−2.617 (−7.023, 1.789)	0.244	1.067 (−4.004, 6.138)	0.680	0.912 (−3.330, 5.153)	0.673
≥37.5	**−15.442 (−20.927, −9.958)**	**<0.001**	**−20.674 (−31.937, −9.411)**	**<0.001**	**−8.194 (−14.638, −1.750)**	**0.013**	**−8.728 (−16.142, −1.313)**	**0.021**	**−6.799 (−12.994, −0.604)**	**0.031**
17.5–22.9	REF		REF		REF		REF		REF	
Baseline scores	**0.343 (0.302, 0.383)**	**<0.001**	**0.200 (0.147, 0.253)**	**<0.001**	**0.376 (0.316, 0.436)**	**<0.001**	**0.162 (0.127, 0.196)**	**<0.001**	**0.079 (0.050, 0.108)**	**<0.001**
Age in years										
>61 and ≤67	0.788 (−1.743, 3.319)	0.542	**9.119 (3.898, 14.339)**	*0.001*	**5.753 (2.773, 8.733)**	**<0.001**	**4.756 (1.320, 8.193)**	**0.007**	**2.912 (0.032, 5.792)**	**0.047**
>67 and ≤73	−0.296 (−2.952, 2.359)	0.827	**8.774 (3.298, 14.250)**	*0.002*	**5.573 (2.441, 8.704)**	**<0.001**	**3.645 (0.040, 7.249)**	**0.048**	1.589 (−1.435, 4.612)	
>73	**−7.881 (−10.596, −5.165)**	**<0.001**	−1.049 (−6.596, 4.498)	0.711	**3.295 (0.124, 6.465)**	**0.042**	−1.691 (−5.343, 1.960)	0.364	1.021 (−2.048, 4.090)	0.303
<61	REF		REF		REF		REF		REF	0.514
Gender										
Female	**−3.773 (−6.124, −1.423)**	**0.002**	−2.546 (−7.355, 2.263)	0.299	**−4.735 (−7.486, −1.984)**	**0.001**	−2.897 (−6.065, 0.271)	0.073	−0.735 (−3.381, 1.911)	0.586
Male	REF		REF		REF		REF		REF	
ASA status										
III	−3.324 (−8.555, 1.908)	0.213	**−11.937 (−22.712, −1.162)**	**0.030**	−5.977 (−12.135, 0.180)	0.057	**−10.916 (−18.007, −3.825)**	**0.003**	2.037 (−3.902, 7.975)	0.501
II	−1.440 (−5.040, 2.159)	0.433	−2.680 (−10.095, 4.736)	0.479	−2.796 (−7.034, 1.442)	0.196	**−5.278 (−10.160, −0.396)**	**0.034**	1.947 (−2.139, 6.033)	0.350
I	REF		REF		REF		REF		REF	
Diabetes mellitus on insulin										
Present	0.083 (−6.858, 7.025)	0.981	−8.930 (−23.228, 5.368)	0.221	**−8.626 (−16.804, −0.448)**	**0.039**	−4.813 (−14.219, 4.593)	0.316	−2.658 (−10.526, 5.210)	0.508
Absent	REF		REF		REF		REF		REF	
Ischemic heart disease										
Present	**−4.807 (−8.932, −0.682)**	**0.022**	−5.769 (−14.266, 2.727)	0.183	−0.083 (−4.940, 4.774)	0.973	−2.238 (−7.832, 3.356)	0.433	−1.738 (−6.417, 2.941)	0.466
Absent	REF		REF		REF		REF		REF	
Chronic kidney disease										
Present	−7.663 (−18.486, 3.160)	0.165	−15.139 (−37.434, 7.156)	0.183	1.004 (−11.741, 13.749)	0.877	−11.016 (−25.699, 3.668)	0.141	−11.650 (−23.930, 0.630)	0.063

Table 3 (continued)

Variable	Physical function		Role physical		Bodily pain		Social function		Role emotional	
	B-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value
Absent	REF		REF		REF		REF		REF	

Variables which attained statistical significance (as defined by $p < 0.05$) are highlighted in bold. The results are adjusted for other variables such as cerebrovascular accident (CVA), congestive cardiac failure (CCF) and type of anaesthesia which were not statistically significant

REF reference, *BMI* body mass index, *ASA* American Society of Anaesthesiology Physical Status Score

we will need a sample of 1880 patients (470 anaemic and 1410 non-anaemic) to achieve 80% power and two-sided *p* value of 5% to show a statistically significant difference of a small Cohen's *D* value of 0.15 for HRQoL outcomes. With this sample of 1880 patients, based on a transfusion ratio of 1:20, it has a 90% power and two-sided *p* value of 5% to achieve the same Cohen's *D* value of 0.15.

Results

Patient characteristics

The average age of the 1994 patients who underwent TKA was 67.3 years old and 76.3% ($n = 1521$) were female. All patients had preoperative baseline SF-36, OKS and KS scores. The average 6-month follow-up rate is 96.0% and 2-year follow-up rate is 85.1% for all scores.

445 patients (22.3%) patients had preoperative anaemia of whom 318 (15.9%) had mild anaemia and 127 (6.4%) had moderate/severe anaemia. Anaemic patients were older (mean age 68.4 years and 69.9 years for mild and moderate/severe anaemia, respectively) compared to patients without anaemia (66.9 years old), $p < 0.001$ (Table 5). Anaemic patients also had a poorer mean preoperative KS-Function ($p < 0.001$), KS-Knee ($p < 0.001$), OKS ($p < 0.001$), physical function ($p < 0.001$), bodily pain ($p = 0.005$) and social function ($p = 0.014$) score compared to those without anaemia at baseline preoperatively (Table 1).

Health-related quality of life (HRQoL)

Of the eight SF-36 domains assessed for our study, only five exhibited improvements greater than the MCID of 10 at 6 months post-TKA (Table 2) [27]. The five domains are physical function (27.0 points, $p = 0.001$), role physical (42.1 points, $p < 0.001$), bodily pain (28.2, $p < 0.001$), social function (29.7 points, $p < 0.001$) and role emotional (10.6 points, $p < 0.001$). Between 6 months and 2 years post-TKA, however, none of the eight domains showed improvements greater than the MCID.

Preoperative moderate/severe anaemia is associated with lower 6-month physical function (PF) scores on univariate analysis ($B = -4.123$, $p = 0.033$) (Table 6, "Appendix"). However, this influence is not significant after adjusting for age, gender, BMI and other comorbidities. Perioperative transfusion is significantly associated with lower social function (SF) and physical function (PF) on univariate analysis (Table 6, "Appendix") but not on multivariate analysis (Table 3). Neither preoperative anaemia nor perioperative blood transfusion had any significant impact on other 6-month HRQoL domains on univariate and multivariate analysis. Factors associated with poorer improvements across all five domains on

Table 4 Factors affecting functional outcomes 6 months after total knee arthroplasty based on multivariate analysis

Variable	KS-Function		OKS	
	B-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value
Preoperative anaemia				
Mild	−0.716 (−2.768, 1.337)	0.494	−0.047 (−0.758, 0.663)	0.896
Moderate/severe	−2.387 (−5.535, 0.761)	0.137	0.761 (−0.328, 1.850)	0.171
No anaemia	REF		REF	
Perioperative blood transfusion				
1 unit	−3.668 (−8.196, 0.860)	0.112	1.067 (−0.497, 2.630)	0.181
≥2 units	−5.029 (−11.587, 1.529)	0.133	0.294 (−1.975, 2.563)	0.799
None	REF		REF	
BMI (kg/m^2)				
<17.5	8.112 (−7.890, 24.114)	0.320	0.844 (−4.691, 6.380)	0.765
23.0–27.4	−2.258 (−4.647, 0.131)	0.064	0.478 (−0.348, 1.304)	0.257
27.5–32.4	*−4.921 (−7.365, −2.477)*	*<0.001*	0.749 (−0.097, 1.594)	0.083
32.5–37.4	*−7.158 (−10.269, −4.046)*		*1.398 (0.323, 2.474)*	*0.011*
≥37.5	*−14.827 (−19.380, −10.274)*	*<0.001*	*2.835 (1.261, 4.410)*	*<0.001*
17.5–22.9	REF	*<0.001*	REF	
Baseline scores	*0.367 (0.323, 0.411)*	*<0.001*	*0.164 (0.131, 0.197)*	*<0.001*
Age				
>61 and ≤67	−0.777 (−2.876, 1.322)	0.468	*−1.103 (−1.828, −0.377)*	*0.003*
>67 and ≤73	*−3.474 (−5.677, −1.272)*	*0.002*	*−0.816 (−1.577, −0.055)*	*0.036*
>73	*−8.452 (−10.723, −6.182)*	*<0.001*	*0.922 (0.150, 1.694)*	*0.019*
<61	REF		REF	
Gender				
Female	*−4.678 (−6.609, −2.746)*	*<0.001*	0.314 (−0.359, 0.987)	0.361
Male	REF		REF	
ASA status				
III	*−4.893 (−9.217, −0.568)*	*0.027*	0.190 (−1.307, 1.687)	0.804
II	−1.706 (−4.692, 1.281)	0.263	0.273 (−0.760, 1.306)	0.604
I	REF		REF	
Chronic kidney disease				
Present	*−11.855 (−20.841, −2.869)*	*0.010*	2.266 (−0.839, 5.371)	0.152
Absent	REF		REF	

Variables which attained statistical significance (as defined by $p<0.05$) are highlighted in italics. The results are adjusted for other variables such as cerebrovascular accident (CVA), congestive cardiac failure (CCF), diabetes mellitus on insulin, ischemic heart disease and type of anaesthesia which were not statistically significant

Oxford Knee Score ranges from 12 to 60. Smaller scores indicate better function. Knee Society Score ranges from 0 to 100. Larger scores indicate better function

OKS Oxford Knee Score, *KS* Knee Society, *REF* reference, *BMI* body mass index, *ASA* American Society of Anaesthesiology Physical Status Score

multivariate analysis are BMI ≥ 37.5 kg/m^2 and lower baseline scores. After adjustment, female gender was associated with poorer improvements in the physical function ($B=-3.773$, $p=0.002$) and bodily pain ($B=-4.735$, $p=0.001$) domains. Comorbidities such as ischemic heart disease ($B=-4.807$, $p=0.022$) and diabetes mellitus on insulin ($B=-8.626$, $p=0.039$) were associated with poorer improvements in the physical function and bodily pain domains, respectively, "after multivariate adjustment".

Functional outcomes

The mean improvement in KS-Function score from baseline to 6 months post-TKA and from 6 months to 2 years post-TKA was 15.8 ($p<0.001$) and 3.5 ($p<0.001$), respectively (Table 2). Similarly, from baseline to 6 months and from 6 months to 2 years post-TKA, the OKS score decreased by 15.2 ($p<0.001$) and 1.5 ($p<0.001$), respectively.

Table 5 Characteristics of TKA patients by anaemia severity

	Total ($N=1994$)	No anaemia ($N=1549$)	Mild anaemia ($N=318$)	Moderate/severe anaemia ($N=127$)	p value
Age—mean (SD)		66.9 (7.9)	68.4 (8.0)	69.9 (8.3)	< 0.001
Gender					
Male	473	339 (71.7%)	113 (23.9%)	21 (4.4%)	< 0.001
Female	1521	1210 (79.6%)	205 (13.5%)	106 (7.0%)	
ASA status					
1	125	102 (81.6%)	17 (13.6%)	6 (4.8%)	0.059
2	1753	1367 (78.0%)	279 (15.9%)	107 (6.1%)	
3	116	80 (69.0%)	22 (19.0%)	14 (12.1%)	
Race					
Chinese	1695	1327 (78.3%)	265 (15.6%)	103 (6.1%)	0.094
Indian	101	79 (78.2%)	19 (18.8%)	3 (3.0%)	
Malay	165	121 (73.3%)	26 (15.8%)	18 (10.9%)	
Others	33	22 (66.7%)	8 (24.2%)	3 (9.1%)	
BMI (kg/m^2)					
< 17.5	4	3 (75.0%)	0 (0.0%)	1 (25.0%)	0.045
17.5–22.9	252	175 (69.4%)	53 (21.0%)	24 (9.5%)	
23.0–27.4	756	585 (77.4%)	125 (16.5%)	46 (6.1%)	
27.5–32.4	660	534 (80.9%)	91 (13.8%)	35 (5.3%)	
32.5–37.4	209	164 (78.5%)	30 (14.4%)	15 (7.2%)	
≥ 37.5	71	55 (77.5%)	13 (18.3%)	3 (4.2%)	
IHD	106	69 (65.1%)	31 (29.2%)	6 (5.7%)	0.001
CCF	16	9 (56.3%)	6 (37.5%)	1 (6.3%)	0.059
CVA	39	27 (69.2%)	8 (20.5%)	4 (10.3%)	0.401
CKD	14	6 (42.9%)	5 (35.7%)	3 (21.4%)	0.005
DM on insulin	35	24 (68.6%)	7 (20.0%)	4 (11.4%)	0.336
Perioperative blood transfusion					
None	1908	1513 (79.3%)	292 (15.3%)	103 (5.4%)	< 0.001
1 unit	59	29 (49.2%)	15 (25.4%)	15 (25.4%)	
≥ 2 units	27	7 (25.9%)	11 (40.7%)	9 (33.3%)	
Smoking	193	135 (69.9%)	48 (24.9%)	10 (5.2%)	0.002
Type of anaesthesia					
GA	681	531 (78.0%)	112 (16.4%)	38 (5.6%)	0.553
RA	1313	1018 (77.5%)	206 (15.7%)	89 (6.8%)	

Percentages taken as percentage across rows

BMI body mass index, *IHD* ischemic heart disease, *CCF* congestive cardiac failure, *CVA* cerebrovascular accident, *CKD* chronic kidney disease, *DM* diabetes mellitus, *GA* general anaesthesia, *RA* regional anaesthesia, *ASA* American Society of Anaesthesiology Physical Status Score

Perioperative blood transfusion is significantly associated with lower 6-month KS-Function scores on univariate analysis ("Appendix", Table 7) but not after adjusting for age, gender, BMI and comorbidities. Neither preoperative anaemia nor perioperative blood transfusion had a significant impact on the 6-month KS-Function and OKS scores on multivariate analysis (Table 4). The factors associated with poorer improvements in KS-Function scores were a higher BMI, lower baseline score, older age female gender, higher ASA status and impaired renal function. Likewise, higher BMI and lower baseline scores were associated with poorer improvements in total OKS score.

Discussion

Our study revealed preoperative anaemia to be more common in males, ASA 3 patients and patients with chronic kidney disease or congestive heart failure. Patients with preoperative anaemia had significantly lower preoperative (baseline) scores in the physical function, role physical

and social function domains of SF-36 when compared to patients without anaemia. We found no independent association between preoperative anaemia or blood transfusion with quality of life and functional outcomes at 6 months following TKA.

This lack in association between HRQoL and preoperative anaemia is in agreement with a study by Wallis et al. which followed 30 patients undergoing unilateral hip arthroplasty, up till 56 days postoperatively, to assess their recovery from postoperative anaemia and its impact on quality of life scores [33]. They postulated that the lack of association may be attributed to the benefits of surgery being greater than the adverse effects of anaemia, thereby resulting in other postoperative changes in quality of life overwhelming the small effect of haemoglobin level. Furthermore, the degree of anaemia could have improved after surgery, and this is not accounted for in our study as we did not collect pre-discharge nor post-discharge haemoglobin levels during their follow-up visit. Postoperative iron supplementation which may boost haemoglobin levels is not routinely prescribed in our institution.

Our study found no association between preoperative anaemia and functional outcomes at 6 months post-TKA. At present, there is little literature regarding the association between preoperative anaemia and long-term functional outcomes following joint replacement surgery. Where available, the majority has been obtained from patients undergoing hip surgery and this has yielded conflicting results [34–41]. Contrary to our findings, a retrospective study involving 394 patients who were treated for hip fracture (347 of whom underwent surgical repair) demonstrated that anaemia on admission was associated with a poorer ambulatory ability at discharge [34]. Another prospective study, however, found that amongst patients undergoing hip fracture repair, there was no association between haemoglobin level at admission and functional recovery at 3, 6 and 12 months postoperatively [35]. We postulate that the conflicting findings may be due to the different methods of assessing function and different postoperative periods at which functional assessments are performed (upon discharge vs 3–6 months after discharge). Studies which assessed the relationship between preoperative anaemia and functional outcomes in the early postoperative period were more likely to find an association as opposed to those who assessed functional outcomes in the later postoperative period. The association between anaemia and functional outcomes in the early postoperative period might be explained by the correlation between severity of anaemia and exercise capacity [18, 42, 43]. By 3 months, however, haemoglobin levels may have improved thereby resulting in no significant difference in functional improvements between patients with and without anaemia [33].

In our cohort, patients with a greater degree of preoperative anaemia received more blood transfusion. However, we found no independent association between perioperative blood transfusion, HRQoL and functional outcomes following TKA. This is in concordance with Halm et al's findings from a prospective study of 551 patients undergoing hip fracture surgery [44]. While Halm et al. analysed outcomes at 60 days following discharge, we analysed our outcomes at 6 months postoperatively as this period was associated with the greatest change in scores compared to baseline. Preoperative anaemia could be a reflection of the poorer general health status of these patients that results in lower quality of life and functional outcomes, and short-term measures like transfusion does not alter their underlying physical disposition. Notwithstanding the lack of association between perioperative blood transfusion and poorer outcomes, there is mounting evidence to suggest an association between transfusions and increased shorter term morbidity, mortality and healthcare costs [45–47]. Thus, it is still prudent to avoid unnecessary blood transfusions in the perioperative period, especially for an elective surgery such as TKA.

Despite the negative findings for our primary outcomes, our study carries clinical implications. We demonstrated significantly lower preoperative scores in the physical function, role physical and social function domains of SF-36 in anaemic patients awaiting TKA, as compared to patients without anaemia. The physical symptoms associated with anaemia are possibly explained by reduced exercise tolerance from poor muscle oxygenation and reduced physical strength [18, 20]. The waiting time for patients undergoing elective TKA varies between institutions. Locally, the average waiting time for patients is approximately 2 months. However, in countries such as England, Spain and Canada, this wait may span longer than 3 months, 7 months and 9 months, respectively [48, 49]. As such, there is sufficient time to investigate the cause of anaemia and to optimise haemoglobin levels. As the commonest reason include iron deficiency and anaemia of chronic disease, a protocol-based approach instituting iron or epoetin therapy may potentially improve HRQoL while awaiting surgery [50, 51].

Although our study found no association between preoperative anaemia and perioperative blood transfusion with long-term outcomes following TKA, we identified other factors which may predispose to poorer outcomes at 6 months post-TKA. A higher BMI (≥ 37.5 kg/m^2) was associated with poorer scores in the KS-Function domain, OKS and chosen SF-36 domains at 6 months post-TKA. This finding resonates another study published from our institution that reports poorer 10-year outcomes in KS-function domain, OKS and (Mental component score) MCS of the SF-36 in morbidly obese patients after primary TKA [52]. While our study accounted for baseline preoperative scores in our analysis, we did not examine the gain in scores between the obese and non-obese patients as this was not the scope of the study. Most literature suggest that while non-obese patients

obtained better postoperative functional and reported quality of life scores than obese patients, their gain in quality of life and knee functionality were similar compared to obese patients [53–56]. This may be achieved through more intensive inpatient rehabilitation for the obese patients compared to the non-obese patients [57].

We also noted that a female gender and poorer baseline scores were associated with poorer functional outcome and HRQoL 6 months following TKA. Similar to us, Katz et al. found that in addition to female patients reporting poorer improvements in functional status post-TKA, they also had significantly worse preoperative functional status as compared to male patients [58]. Studies with similar findings suggest this to be due to women with anaemia perceiving greater impairment of their HRQoL compared to males, and may report symptoms more readily [59–62]. Furthermore, this gender difference may also be attributed to delayed surgical management amongst women, resulting in more severe baseline knee symptoms and quality of life, than in men [6].

Within our study population, a diagnosis of ischemic heart disease and diabetes mellitus on insulin was also associated with poorer HRQoL scores at 6 months post-TKA. More specifically, ischemic heart disease was associated with poorer scores in the PF domain following TKA. This may be attributed to patients with ischemic heart disease having a poorer effort tolerance thereby impeding their ability to participate in postoperative rehabilitation exercise and recover following surgery. Diabetes mellitus on insulin, on the other hand, was associated with poorer scores in the BP domain following TKA. This was also demonstrated in a prospective study by Rajamaki et al. who found that a previous diagnosis of diabetes mellitus was a risk factor for persistent pain 1–2 years following total hip or knee arthroplasty [63]. Gandhi et al. theorised that this may be linked to the systemic proinflammatory state seen in patients with metabolic syndrome [64].

Strengths of study

To the best of our knowledge, this is the first study to investigate the association between preoperative anaemia, HRQoL and long-term functional outcomes in a cohort of patients who exclusively underwent TKA. We included a large cohort of 1994 patients amassed over a 2-year period, with a high follow-up rate (> 95% at 6 months) and minimal missing data. We used subjective risk stratification systems, such as the ASA classification [65], as well as objective measures such as components of the Revised Cardiac Risk Index (RCRI) [66]. Additionally, the patient reported outcome measures used to assess changes in HRQoL and functional status following TKA have been validated both globally and within the local population [67–69].

Limitations of study

One limitation of our study lies in its retrospective nature. Additionally, we did not measure our patients' haemoglobin levels at 6 months and 2 years postoperatively when they completed the follow-up assessment. Hence, we do not know the rate of recovery of haemoglobin levels after the surgery. Therefore, analyses were performed based on their preoperative haemoglobin levels and may not be an accurate reflection of their postoperative haemoglobin levels. However, the majority of patients in our cohort did not require blood transfusion (95.7%), and thus most would have experienced a similar drop in haemoglobin levels during surgery and gradual improvement afterwards. Our decision to use the SF-36, a generic quality of life measure, as opposed to a disease-specific measure such as the Functional Assessment of Cancer Therapy-Anemia (FACT-An) [70] might also have reduced sensitivity to detect small changes in HRQoL. However, the use of SF-36 to monitor long-term changes in HRQoL following TKA has been extensively validated globally [71, 72] particularly in the physical function, role physical and bodily pain domains [27, 73]. Similarly, in our study, the most responsive scales after TKA were physical function and role physical domains.

Conclusion

In conclusion, preoperative anaemia and perioperative blood transfusions are not associated with poorer HRQoL and functional outcomes at 6 months following TKA. However, we demonstrated significantly lower baseline HRQoL scores among anaemic patients awaiting TKA, as compared to patients without anaemia. A strategy for optimisation of haemoglobin during the waiting period for surgery should be considered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent As this is a retrospective study that did not involve any patient contact, waiver of formal consent is approved by our institutional review board (Singhealth Centralised Institutional Review Board).

Appendix

See Tables 6 and 7.

Table 6 Association between preoperative anaemia, perioperative blood transfusion and HRQoL at 6 months post-TKA based on univariate analysis

Variable	Physical function		Role physical		Bodily pain		Social function		Role emotional	
	B-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value
Preoperative anaemia										
Mild	−2.304 (−4.797, 0.189)	0.070	−1.096 (−6.126, 3.934)	0.669	−0.639 (−3.504, 2.226)	0.662	−1.631 (−4.957, 1.695)	0.336	−0.043 (−2.764, 2.679)	0.975
Moderate/severe	*−4.123 (−7.909, −0.337)*	*0.033*	−3.465 (−11.085, 4.154)	0.373	−1.455 (−5.800, 2.890)	0.511	−2.680 (−7.723, 2.363)	0.297	0.291 (−3.839, 4.420)	0.89
No anaemia	REF		REF		REF		REF		REF	
Perioperative blood transfusion										
1 unit	*−6.968 (−12.198, −1.738)*	*0.009*	*−10.806 (−21.356, −0.255)*	*0.045*	−3.244 (−9.254, 2.766)	0.290	*−8.471 (−15.443, −1.500)*	*0.017*	1.249 (−4.459, 6.957)	0.668
≥2 units	*−10.271 (−18.210, −2.332)*	*0.011*	−7.155 (−23.198, 8.887)	0.382	1.850 (−7.291, 10.991)	0.691	*−11.385 (−22.004, −0.767)*	*0.036*	5.738 (−2.951, 14.427)	0.195
None	REF		REF		REF		REF		REF	

Variables which attained statistical significance (as defined by $p < 0.05$) are highlighted in italics. The results have been adjusted for their respective preoperative scores

PF physical function, *RFP* role physical, *BP* bodily pain, *SF* social function, *RE* role emotional, *REF* reference

Table 7 Association between preoperative anaemia, perioperative blood transfusion and functional outcomes at 6 months post-TKA based on univariate analysis

Variable	KS-Function		OKS	
	B-coefficient (95% CI)	*p* value	*B*-coefficient (95% CI)	*p* value
Preoperative anaemia				
Mild	−1.006 (−3.110, 1.099)	0.349	0.046 (−0.665, 0.757)	0.898
Moderate/severe	*−3.666* (*−6.858*, *−0.473*)	*0.024*	*1.167* (*0.089, 2.244*)	*0.034*
No anaemia	REF		REF	
Perioperative blood transfusion				
1 unit	*−6.447* (*−10.871*, *−2.023*)	*0.004*	*1.992* (*0.503, 3.480*)	*0.009*
≥ 2 units	*−7.534* (*−14.232*, *−0.836*)	*0.028*	1.087 (−1.176, 3.350)	0.346
None	REF		REF	

Variables which attained statistical significance (as defined by $p < 0.05$) are highlighted in italics. The results have been adjusted for their respective preoperative scores

KS-Function Knee Society function, *OKS* Oxford Knee Score

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