PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty in Singapore: A single centre retrospective study
AUTHORS	Abdullah, Hairil; Sim, Eileen; Ying, Hao; Lin, Gengyu; Liew, Geoffrey; Lamoureux, Ecosse; Tan, Mann Hong

VERSION 1 - REVIEW

REVIEWER	Dr Michael Gillies Royal Infirmary of Edinburgh Edinburgh UK
REVIEW RETURNED	22-Dec-2016

| GENERAL COMMENTS | This is an epidemiological study exploring the relationship between preoperative anaemia and hospital length of stay. This is an important and topic issues with several recent reviews and studies suggesting that anaemia may increase risk of cardiac complications and testing interventions aimed at reducing perioperative anaemia.

Major comments:

1. I would like more detail on the data, how it is collected, curated and archived and how the data extraction was performed. There is also limited data on how the followup data was collected.This is a requirement of STROBE.
2. There is no study flow diagram, demonstrating the derivation of the final study cohort which would be useful.
3. There is only one year data which is a limitation.
4. I have issues with the reporting of the demographic data. The ASA Scale is 1-5 and the RCRI 1-6. Were there no ASA 4 or 5 patients in the cohort? Were there no patients with LRCI greater than 4 in the cohort either? If so should be stated as zero. Also it would be useful to know the individual components of the RCRI e.g. diabetes, IHD etc.
5. It would be typical for the univariate analysis (Table 2) to contain point estimates and 95% CI. It is also unclear for many categorical variables which is the "reference category". This raises concerns that the analysis was not performed correctly. A table of this type could be in a supplemental file.
5. It is unclear in Table 3 (Day of the Week analysis)which day is being used as a reference day. I am assuming it's Sunday as no LOS is given for that day but it is possible no surgery was performed on a Sunday. For this type of analysis it is usual to chose a "reference" day and compare other days to it as categorical variables. The reference day chosen is often Monday or Wednesday as it is considered the "lowest risk" day as care is supposedly worse |

	at weekends. Possible reasons why Tuesday and Thursday are associated with increased LOS should be discussed.
	6. The Multivariable model should contain day of week, components of RCRI and ASA as categorical variables (with appropriate reference variable). In my view the current approach to analysis is flawed.
	7. A readmission rate of 0.6% is much lower than other published work, e.g. recent data from the USA suggests 4% readmission rate at 30 days and 8% at 90 days (Schairer et al 2015). Could the authors comment on this large disparity?
	In summary, due to concerns about the methodology of this study I do not have confidence in its findings and thus cannot recommend it for publication.

REVIEWER	Toby Richards UCL, UK
REVIEW RETURNED	01-Jan-2017

GENERAL COMMENTS	Many thanks for asking me to review this manuscript on preoperative anaemia.
	Much data in this area is on european and US data. There is a need for validation in the Asian cohorts. Particularly as there is a baseline higher incidence of IDA in these patients,
	This is a large single center cohort.
	In the introduction, this is well structured but focused on the hospital outcome of LOS, cost and readmission. the paper only addresses LOS. There are no data on readmission, so this does not appear to be a problem. A patient outcome would be preferable - does the unit have data on complications, return to theater, DVT or perhaps reoperation / further procedure in one year?
	RESULTS Bilateral TKA or revision should be in a subgroup. These are bigger cases and the results anticipated to mirror primary TKA and would provide internal validation. You say age is associated with anaemia but no stats given> table 1 could this show % anaemia rather that % of that group it reads as though 80% anaemic. Confusing. We women more likely to have anaemia and what was the average [hb] between sexes. Table 2 please change % as reads as though78.9% had LOS > 6 days but in fact 610/1977
	Table 3 is interesting but opens a can of worms and may distract from the main purpose of the paper as not an outcome measure.
	The big thing missing here is 1.. Blood Transfusion need and impact of BT on outcomes
	BT needs to be in this analysis it is not adequate to say this was not done in the discussion and a huge confounder.
	Please also document other PBM measures such as use of Tranexemic Acid, ie what was the normal protocol in the hospital.

	Asprin used, BT trigger, TXA, cell salvage - use of drains etc. Was this standardized or not as big confounders.

VERSION 1 – AUTHOR RESPONSE

Supplementary Information File

<u>Response to Reviewers</u>

We would like to thank both Dr Michael Gillies and Professor Toby Richards for their time in reviewing our manuscript and providing invaluable comments. Please allow us to submit a point-by-point reply to these comments. We will provide the full revised manuscript if the journal is willing to consider our resubmission.

Reviewer: 1

Reviewer Name: Dr Michael Gillies

Institution and Country: Royal Infirmary of Edinburgh, Edinburgh, UK

Competing Interests: None declared

1. I would like more detail on the data, how it is collected, curated and archived and how the data extraction was performed. There is also limited data on how the follow up data was collected. This is a requirement of STROBE.

- We have updated the methodology in the revised manuscript to incorporate the requested information:
  "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."

2. There is no study flow diagram, demonstrating the derivation of the final study cohort which would be useful.

- We have added a flow diagram in our methodology:
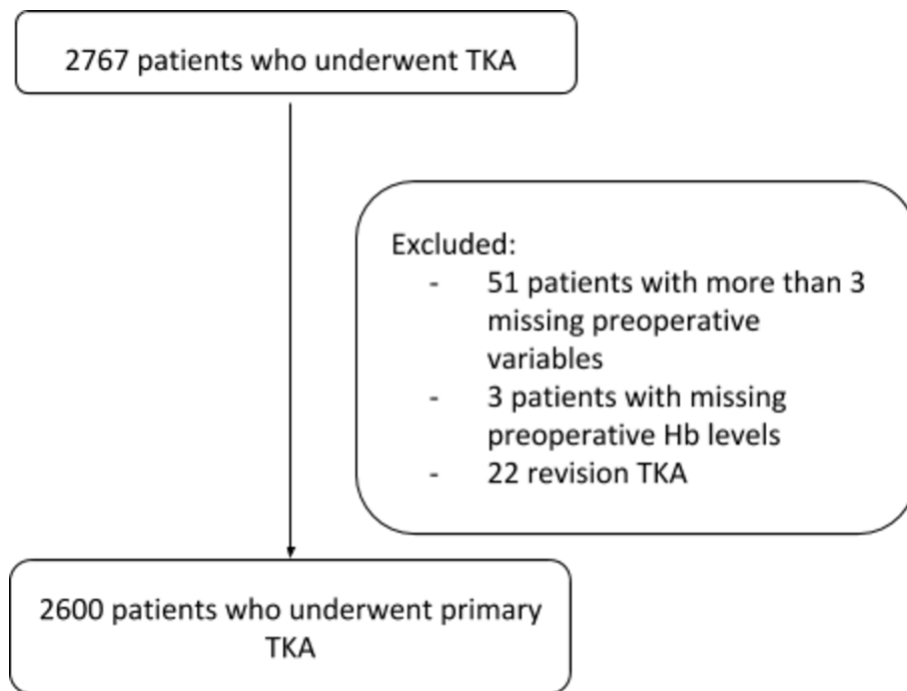
3. There is only one year data which is a limitation.

- We acknowledge that our data collection only spans over 1.5 years. However, we report a modest sample size (2600) of patients who underwent the same procedure (primary TKR). This is similar in scale and size to other recently published studies [1]

4. I have issues with the reporting of the demographic data. The ASA Scale is 1-5 and the RCRI 1-6. Were there no ASA 4 or 5 patients in the cohort? Were there no patients with LRCI greater than 4 in the cohort either? If so should be stated as zero. Also it would be useful to know the individual components of the RCRI e.g. diabetes, IHD etc.

- We only have patients of ASA 1-3 in our study cohort. Patients of higher ASA scores were not intentionally excluded, but they were probably not considered to be eligible for this elective procedure by the surgeons. We have updated the demographics table (Table 1) to reflect this informations as well as to display the distribution of the individual components of the RCRI score.

5. It would be typical for the univariate analysis (Table 2) to contain point estimates and 95% CI. It is also unclear for many categorical variables which is the "reference category". This raises concerns that the analysis was not performed correctly. A table of this type could be in a supplemental file.

- We have edited our tables to reflect the point estimates and 95% CI of the univariate and multivariate analysis. (Table 2).

5. It is unclear in Table 3 (Day of the Week analysis) which day is being used as a reference day. I am assuming it's Sunday as no LOS is given for that day but it is possible no surgery was performed on a Sunday. For this type of analysis it is usual to chose a "reference" day and compare other days to it as categorical variables. The reference day chosen is often Monday or Wednesday as it is considered the "lowest risk" day as care is supposedly worse at weekends. Possible reasons why Tuesday and Thursday are associated with increased LOS should be discussed.

- We have revised our analysis, after adding in new variables such as the amount of perioperative blood transfusion, incidence of reoperation within length of stay, and found

Thursday to be the lowest risk day for prolonged LOS. Thus, it is the reference point for the other days of the week in Table 2. There was no TKR done on Sunday.

6. The Multivariable model should contain day of week, components of RCRI and ASA as categorical variables (with appropriate reference variable). In my view the current approach to analysis is flawed.

- We have updated the multivariate model with your suggestion (Table 2).

7. A readmission rate of 0.6% is much lower than other published work, e.g. recent data from the USA suggests 4% readmission rate at 30 days and 8% at 90 days (Schairer et al 2015). Could the authors comment on this large disparity?

- Our previous data was obtained from an administrative database maintained by the orthopaedics department. To ensure veracity, we re-extracted the 30-day readmission data from our clinical system database, and reviewed the individual medical records to confirm the cause of readmission. Thus, our new 30-day readmission rate for causes related to the primary TKR is now 1.7%, which is consistent with another paper published by our department.[2]

- In the study on readmission rates after TKR by Schairer et al [3], their 30-day readmission rate for primary TKA was (3.4%), revision TKA (5.7%), and revision for infected TKA (6.2%). These readmission rates included all causes of readmission, ranging from medical to surgical conditions. However, our readmission rates were only reflective of readmissions that were related to complications from the surgery itself, hence it is lower. They also had a figure of 60% for surgical causes contributing to 30-day readmission rates, although not specifically for primary TKR. Thus, their 30-day surgical related readmission rate could be 60% of 3.4%, which is approximately 2.0%.

Reviewer: 2

Reviewer Name: Toby Richards

Institution and Country: UCL, UK

Competing Interests: None

Does the unit have data on complications, return to theater, DVT or perhaps reoperation / further procedure in one year?

- Unfortunately we only have 30-day return to theater and readmission rates.

Bilateral TKA or revision should be in a subgroup. These are bigger cases and the results anticipated to mirror primary TKA and would provide internal validation.

- When we did separate multivariate logistic regression 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), mild anaemia had an aOR of 048 (p=0.15) and moderate/severe anaemia had an aOR of 2.74 (p=0.24).

- We postulate that the lack of significance is due to the small number of cases of patients who had anaemia (43) and underwent bilateral TKR, of which 31 had mild anaemia and only 12 had moderate/severe anaemia, hence we did not report the findings in our manuscript.

You say age is associated with anaemia but no stats given.

- The statistics are now available in Table 1 and 2.

Table 2 please change % as reads as though 78.9% had LOS > 6 days but in fact 610/1977

- We have edited the table to address this.

Table 3 is interesting but opens a can of worms and may distract from the main purpose of the paper as not an outcome measure.

- Thank you for pointing this out. We have removed this table from our manuscript.

The big thing missing here is

1.. Blood Transfusion need and impact of BT on outcomes - BT needs to be in this analysis it is not adequate to say this was not done in the discussion and a huge confounder.

- We have added perioperative blood transfusion as one of the variables in our analysis. Please see the revised Table 1 and 2.

- 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. (Table 2)

Please also document other PBM measures such as use of Tranexemic Acid, ie what was the normal protocol in the hospital. Asprin used, BT trigger, TXA, cell salvage - use of drains etc. Was this standardized or not as big confounders.

We have now added mention of these PBM measures in our methodology: "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.""

Hairil Rizal, Abdullah

References for Supplementary Information File

1. Jans Ø, Jørgensen C, Kehlet H, Johansson PI, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. Transfusion . 2014;54: 717–726.
2. Chen JY, Lee WC, Chan HY, Chang PCC, Lo NN, Yeo SJ. Drain use in total knee arthroplasty is neither associated with a greater transfusion rate nor a longer hospital stay. Int Orthop. 2016;40: 2505–2509.
3. Schairer WW, Vail TP, Bozic KJ. What are the rates and causes of hospital readmission after total knee arthroplasty? Clin Orthop Relat Res. 2014;472: 181–187.

VERSION 2 – REVIEW

REVIEWER	Bernd Froessler Department of Anaesthesia Lyell McEwin Hospital, Elizabeth Vale SA 5112 Australia
REVIEW RETURNED	03-Mar-2017

| GENERAL COMMENTS | Dear Authors,

General comment:
This is a thorough analysis of patients undergoing TKR in Singapore. The findings confirm that pre-operative anaemia predisposes to adverse outcomes and increased LOS. This appears to be a universal finding and is independent of region and ethnicity. The authors claim that their study is unique due to the regional setting. I am uncertain if similar studies in the elective orthopaedic setting exist, but there are previous publications discussing anaemia that have been conducted in Asia.
Could the authors please mention this in the text. The reviewer included 2 references below.
Zhang, L., et al. (2016). "Anemia on Admission Is an Independent Predictor of Long-Term Mortality in Hip Fracture Population: A Prospective Study With 2-Year Follow-Up." Medicine (Baltimore) 95(5): e2469.
Jung, D. H., et al. (2013). "Impact of perioperative hemoglobin levels on postoperative outcomes in gastric cancer surgery." Gastric Cancer 16(3): 377-382

Page 4:
Line 47 to 54
Could the authors please also refer to improved outcomes from the patient perspective. Economics are important but should not be the only driver.
P7
L34-43
The authors retrieved a lot of information from the SCM. While investigating the impact of anaemia on LOS, can they please explain why assessment for iron status is not included?

P8
L8: all anti-platelets apart from Aspirin, please fill in missing word "drugs/medication"
L11: infiltration, also is IV TXA utilised? |

	P11
	Table 1, please specify columns (LOS) in the table
	REF needs to be spelled out once somewhere
	P16
	L7-16
	The authors should discuss a structured assessment and approach to PBM. The data indeed is a very strong driver for the implementation of PBM measures to improve patient outcome and economics.
	L13; Froessler et al.
	P17
	L20: The authors excluded revision TKR due to the increased need for blood transfusion.
	Can the authors explain why they did not exclude bilateral TKR for the same reason?

REVIEWER	Manuel Muñoz
	Perioprrative Transfusion Medicine, School of Medicine, University of Málaga, Málaga (Spain)
	I have received honoraria for lectures/consultancies from Vifor Pharma Ltd, Pharmacosmos, Wellspect HealthCare, Sandoz Pharma, and Zambon.
REVIEW RETURNED	03-Mar-2017

GENERAL COMMENTS	The authors performed a retrospective study of data from 2600 patients who underwent TKA between January 2013 to June 2014, including demographics, comorbidities, preoperative haemoglobin level, LOS and 30-day readmission . Anaemia severity was graded according to WHO classification. Multivariate logistic regression were performed to identify factors that predispose to prolonged LOS (as defined as more than 6 days).
	The prevalence of anaemia was 23.5%, and based on multivariate logistic regression, preoperative anaemia, red blood cell transfusion, bilateral TKA, re-operation during hospital stay, previous CVA, age >65 years, and general anaesthesia were associated with prolonged LOS. The low number hospital readmissions precluded a statistical analysis.
	From these data, the authors concluded that anaemia is common among patients undergoing elective total TKA in Singapore and is independently associated with prolonged length of stay and increased perioperative blood transfusion.
	Overall, this study adds to the growing body of evidences supporting a negative impact of preoperative anaemia on postoperative outcome of patients undergoing major elective orthopaedic surgery. However, there are some issues that should be addressed:
	1. Bilateral TKA and re-operation during hospital stay should be excluded, as they are low number and known to increase LOS and transfusion rates.
	2. Why prolonged LOS and not absolute difference in LOS was analysed? Every single day of LOS increase resulted in increased health care costs. There was a well-defined discharge protocol?
	3. Though not standardized, the use of tranexamic acid is very important for the analysis, as it reduces blood loss and transfusion rates and, therefore, might have influenced LOS.
	4. Authors should provide the effect size of significance, to distinguish between just statistically significance and clinical

relevance.
5. They should clarify whether leuko-depleted RBC units were used.
6. Most importantly, the same Hb cut-off for anaemia definition should be used in both genders, and data re-analysed accordingly (for discussion, see ref 30 and Muñoz et al Anaesthesia 2017).
7. Please, pay attention to co-variability between preoperative anaemia and transfusion rate; if high, one of the two should be eliminated from the multivariate analysis of increased LOS.
8. As Chinese patients are 85% of the total patient population, they should be the reference population.
9. No analysis of data regarding the effect of preoperative anaemia on transfusion is presented (only a sentence in the conclusion section of the abstract).
10. Reasons for re-admission should be better presented.
11. A recruitment period of 1.5 years should not be regarded as a limitation. It could even be considered as study strength, as no major changes in health care and discharge policy are expected to occur in such a short period.

VERSION 2 – AUTHOR RESPONSE

Response to 2nd Reviewers Dr Bernd Froessler and Manuel Muñoz
We would like to thank both Dr Bernd Froessler and Manuel Muñoz for their time in reviewing our manuscript and providing invaluable comments. Please allow us to submit a point-by-point reply to these comments.
Comments from Dr Bernd Froessler
The authors claim that their study is unique due to the regional setting. I am uncertain if similar studies in the elective orthopaedic setting exist, but there are previous publications discussing anaemia that have been conducted in Asia.
Could the authors please mention this in the text. The reviewer included 2 references below.
Zhang, L., et al. (2016). "Anemia on Admission Is an Independent Predictor of Long-Term Mortality in Hip Fracture Population: A Prospective Study With 2-Year Follow-Up." Medicine (Baltimore) 95(5): e2469.
Jung, D. H., et al. (2013). "Impact of perioperative hemoglobin levels on postoperative outcomes in gastric cancer surgery." Gastric Cancer 16(3): 377-382
Thank you for the suggestion. These are reflected in this revised version on Page 18, Line 15

Page 4:
Line 47 to 54
Could the authors please also refer to improved outcomes from the patient perspective. Economics are important but should not be the only driver.
P7
This is reflected on page 8, Line 3-4 in this revised manuscript.

L34-43
The authors retrieved a lot of information from the SCM. While investigating the impact of anaemia on LOS, can they please explain why assessment for iron status is not included?
Iron studies were not routinely performed in our institution during the study period. Perioperative patient blood management program has only been recently introduced, and is an ongoing quality improvement effort here in SGH. The findings of our study would certainly strengthen our effort and promote awareness and acceptance among other clinicians and hospital administrators.

P8
L8: all anti-platelets apart from Aspirin, please fill in missing word "drugs/medication"

Changes done as suggested (page 9, line 9)

L11: infiltration, also is IV TXA utilised?
P11
Changes done as suggested (page 9, line 11)

Table 1, please specify columns (LOS) in the table
REF needs to be spelled out once somewhere
Changes done as suggested.

P16
L7-16
The authors should discuss a structured assessment and approach to PBM. The data indeed is a very strong driver for the implementation of PBM measures to improve patient outcome and economics.
Thank you for the encouraging comment. We have expanded the discussion on the importance of a systemic approach to PBM (Page 18 line 13 to 27)

L13; Froessler et al.
Apologies for the mistake. Correction done. (page 18 line 19)

P17
L20: The authors excluded revision TKR due to the increased need for blood transfusion.
Can the authors explain why they did not exclude bilateral TKR for the same reason?
We have excluded bilateral TKR in this revised version.

Comments from Dr Manuel Muñoz

The authors performed a retrospective study of data from 2600 patients who underwent TKA between January 2013 to June 2014, including demographics, comorbidities, preoperative haemoglobin level, LOS and 30-day readmission . Anaemia severity was graded according to WHO classification. Multivariate logistic regression were performed to identify factors that predispose to prolonged LOS (as defined as more than 6 days).
The prevalence of anaemia was 23.5%, and based on multivariate logistic regression, preoperative anaemia, red blood cell transfusion, bilateral TKA, re-operation during hospital stay, previous CVA, age >65 years, and general anaesthesia were associated with prolonged LOS. The low number hospital readmissions precluded a statistical analysis.
From these data, the authors concluded that anaemia is common among patients undergoing elective total TKA in Singapore and is independently associated with prolonged length of stay and increased perioperative blood transfusion.
Overall, this study adds to the growing body of evidences supporting a negative impact of preoperative anaemia on postoperative outcome of patients undergoing major elective orthopaedic surgery. However, there are some issues that should be addressed:

1. Bilateral TKA and re-operation during hospital stay should be excluded, as they are low number and known to increase LOS and transfusion rates.
Thank you for the comment. Indeed the same concern was raised by the first reviewer. We have now excluded these from our analyses.

2. Why prolonged LOS and not absolute difference in LOS was analysed? Every single day of LOS increase resulted in increased health care costs. There was a well-defined discharge protocol?
In this revised version, we have included both the estimate of risk for prolonged LOS as well as the effect size in days prolonged per unit of hemoglobin. There is a standard postoperative management

and discharge protocol for TKA in our institution. We have now reflected this on page 9, Line 13-14

3. Though not standardized, the use of tranexamic acid is very important for the analysis, as it reduces blood loss and transfusion rates and, therefore, might have influenced LOS.
We agree with your comment. Unfortunately we do not have data on the administration of IV tranexamic acid by our anaesthesiologists intraoperatively, and neither is this a standard practice in our institution. (Page 20, line 14-15)

4. Authors should provide the effect size of significance, to distinguish between just statistically significance and clinical relevance.
Thank you for the suggestion. We have made the changes and obtained an effect size of preoperative hemoglobin by using a General Linear Model in our statistical analysis in table 4.

5. They should clarify whether leuko-depleted RBC units were used.
Leucodepletion of RBC is not a standard practice in our hospital. Unfortunately we do not have details on whether leucodepleted blood were given, and we have now reflected this in our discussion and limitation on page 20, line 16)

6. Most importantly, the same Hb cut-off for anaemia definition should be used in both genders, and data re-analysed accordingly (for discussion, see ref 30 and Muñoz et al Anaesthesia 2017).
Thank you for the suggestion. Indeed, we take Professor Munoz's point on equal cutoff for both genders as discussed in his publications. However, the two most recent interventional RCTs on preoperative optimisation of anemia (IVICA and Froessler et al) used the WHO-gender based classification as their cut-off.[36,47] We have also performed sensitivity analysis with the same hemoglobin cutoff for both genders, and found no significant difference in the adjusted odds ratios. We presented both findings in our results, on page 15, line 20-24. Because of these, we are not fully comfortable yet in applying equal cutoffs in our publication. This will of course be in our consideration for future studies and clinical practice.

7. Please, pay attention to co-variability between preoperative anaemia and transfusion rate; if high, one of the two should be eliminated from the multivariate analysis of increased LOS.
We performed univariate linear regression and found significant collinearity between preoperative anemia and transfusion rates. However we did find that inclusion of transfusion in our GLM reduced the significance and effect size of preoperative hemoglobin. In our logistic regression, both preoperative hemoglobin and transfusion were independently significant predictors of prolonged LOS.

8. As Chinese patients are 85% of the total patient population, they should be the reference population.
We have adopted your suggestion and made the changes.

9. No analysis of data regarding the effect of preoperative anaemia on transfusion is presented (only a sentence in the conclusion section of the abstract).
We have revised Table 3 to show the effect of preoperative anemia on transfusion.

10. Reasons for re-admission should be better presented.
We have presented the reasons for readmission in table 5.

11. A recruitment period of 1.5 years should not be regarded as a limitation. It could even be considered as study strength, as no major changes in health care and discharge policy are expected to occur in such a short period.

Thank you for your comment and we have reflected this in the section on 'strengths of our study' on page 19 line 26-29.

<div align="center">VERSION 3 – REVIEW</div>

REVIEWER	Bernd Froessler Lyell McEwin Hospital, Adelaide, South Australia Discipline of Acute Care Medicine University of Adelaide Australia
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	Thank you to the authors for addressing all reviewers concerns adequately. The manuscript is improved and adds valuable information to the evidence on the impact of pre-operative anaemia on outcomes

REVIEWER	Manuel Muñoz Perioperative Transfusion Medicine School of Medicine University of Málaga 29071-Málaga (Spain) I have received honoraria for lectures/consultancies from from Vifor Pharma Ltd, Pharmacosmos AS. Iron4you, and Zambon.
REVIEW RETURNED	08-Apr-2017

GENERAL COMMENTS	The authors stated that "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" On my oppinion this clearly indicates that women with Hb between 12 and 12.9 g/dL could also benefit from preoperative Hb optimisation. In other words, for this kind of surgical procedures in which moderate-to-high blood losses are expected, preoperative anaemia should be defined by an Hb level below 13 g/dL, regardeless patients's gender, and anaemic patients classified and treated accordingly. This should be clearly stated in the abstract, discussion and conclusion of this paper.

<div align="center">VERSION 3 – AUTHOR RESPONSE</div>

Reviewer: 2
Reviewer Name: Manuel Muñoz
Comments:
The authors stated that "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"
On my oppinion this clearly indicates that women with Hb between 12 and 12.9 g/dL could also

benefit from preoperative Hb optimisation. In other words, for this kind of surgical procedures in which moderate-to-high blood losses are expected, preoperative anaemia should be defined by an Hb level below 13 g/dL, regardeless patients's gender, and anaemic patients classified and treated accordingly. This should be clearly stated in the abstract, discussion and conclusion of this paper. We agree with your interpretation of our findings, and thank you for providing us with a fresh perspective on the matter. We have included the statement in our abstract, discussion on page 19 (lines 3-8), and conclusion on page 21 (lines 7-9).

VERSION 4 – REVIEW

REVIEWER	Manuel Muñoz Perioperative Transfusion Medicine School of Medicine University of Málaga Málaga (Spain)
REVIEW RETURNED	14-Apr-2017

GENERAL COMMENTS	Authors have adequately addressed the questions by this reviewer