PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Increased early mortality after total knee arthroplasty using conventional instrumentation compared to technology-assisted surgery: an analysis of linked national registry data.
AUTHORS	Harris, Ian A.; Kirwan, David; Peng, Yi; Lewis, Peter; de Steiger, Richard; Graves, Steven

VERSION 1 – REVIEW

REVIEWER	Schreurs, Willem Radboudumc Instituut voor Wetenschappelijk Onderwijs en Opleidingen, Orthopedics
REVIEW RETURNED	17-Oct-2021

GENERAL COMMENTS	Comments BMJ Open This is a paper from a well-known group with a lot of experience on using national data based on arthroplasty registries. Title: no comments Abstract: no comments Introduction: At line 86 add: to detect early post-operatively mortality. However, this early post-operative mortality has been decreased during the observation period and is currently approximately 0.1 % at 30 days. Can the authors give some clue that has driven this decrease, I do not think it is driven by better surgical techniques alone, better anesthesiologic techniques and rapid recovery may be the keystones Methods: I am not a statistician, so I can not comment on these complex statistical methods. When did AOANJRR start recording detailed surgical information on the TKA procedure? Already in 2003? This is not clear in the paper. Results: The numbers are impressive. However, given the relatively low numbers of image derived instrumentation or certainly robotic assisted surgery, how valid are the found differences for these less used technique. Is the study not mainly based on the effect of computer navigation. Of course, companies promoting robotic surgery will be happy, but is this correct to state that robotic assisted surgery will improve 90 days survival? Table ! suggests these data are based on the whole population of

	581818 TKA, however the ASA and BMI are only available for a small subset of the whole group as this started in 2012 reps 2015. Discussion: The interpretation of these findings should be done cautiously, the risk is already very low. It sounds dramatic that conventional instrumentation has a 72% increased risk for 30 days mortality, but still the absolute number are low. There are also other issues like costs of these newer techniques (correctly cited by the authors) and proper training of surgeons with these newer techniques. And again, I think certainly robotic surgery can not claim this lower mortality rate as the numbers of this technique is this group of technology assisted surgery is low.

REVIEWER	Agrawal, Yuvraj Royal Orthopaedic Hospital NHS Foundation Trust, Lower Limb Arthroplasty Unit
REVIEW RETURNED	23-Jan-2022

GENERAL COMMENTS	A well written paper. There is a clearly defined research question - difference in mortality at 30 and 90 days comparing TKA using conventional techniques versus technology assisted techniques. However, my concerns are with the explanation for the difference and hence the conclusion. 1. 30-day mortality is a data recorded and accessible. Would the death due to fat embolism not be in the early stages...2-5 days? A timeline to demonstrate when the death actually occurred may be helpful before we attribute the deaths to a well established technique of intramedullary cannulation for alignment. 2. The study compares a historic group of patient with a modern group of patients with some overlap. Would it not be better to restrict the comparative analysis over the identical period? - the rehab protocols has evolved during the study period. Patients currently are mobilised and discharged much sooner than the historic cohorts. Could the longer recumbency explain the higher early complications in the conventional technique cohort? - VTE prevetive measures have also evolved. Patients in the recent years have benefitted from early mobilisation, foot and calf pumps, early discharge. Fatal PE is one of the leading causes of early death. 3. Is it possible to attempt to investigate the cause of death for these patients (1159 patients)? Is there another database that could be used to investigate these outcomes? 4. Can you please explain the impact of ASA on mortality rates? p value <0.001 with ASA 2 patients? I appreciate there is no difference between the 2 groups, but does it mean the mortality rates were higher in these patients cf. ASA 1 and not the case when ASA 3 or 4?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

At line 86 add: to detect early post-operatively mortality. However, this early post-operative mortality has been decreased during the observation period and is currently approximately 0.1 % at 30 days. Can the authors give some clue that has driven this decrease, I do not think it is driven by better surgical techniques alone, better anesthesiologic techniques and rapid recovery may be the keystones.

The decreasing post-operative mortality over the observation period may be due to factors such as early mobilisation and better anaesthetic management (as suggested). These explanations have been offered in the references provided. We have added a general explanation to the sentence as follows:

> "… to detect early mortality post-operatively, which has been decreasing over time (possibly due to improvements in operative and peri-operative management) and is currently approximately 0.1% at 30 days."

When did AOANJRR start recording detailed surgical information on the TKA procedure? Already in 2003? This is not clear in the paper.

All data were available since inception except ASA grade and BMI. This has been clarified by editing this section in the Methods as follows:

> "All data used in the analysis were available in the AOANJRR ~~has collected data on~~ from inception except the American Society of Anesthesiologists (ASA) class[16] (a measure of comorbidity and mortality risk, available since 2012) and body mass index (BMI, available since 2015)."

The numbers are impressive. However, given the relatively low numbers of image derived instrumentation or certainly robotic assisted surgery, how valid are the found differences for these less used technique. Is the study not mainly based on the effect of computer navigation. Of course, companies promoting robotic surgery will be happy, but is this correct to state that robotic assisted surgery will improve 90 days survival?

We have been careful not to state that robotic surgery (compared to other technology-assisted techniques) will improve mortality. We disagree that the effect is mainly due to computer navigation, *per se*. Instead, we have suggested that the effect may be due to avoiding intramedullary instrumentation (whether by using computer navigation, robotic assistance, patient-specific guides or any other method).

Table 1 suggests these data are based on the whole population of 581818 TKA, however the ASA and BMI are only available for a small subset of the whole group as this started in 2012 reps 2015.

This is correct. The data for ASA and BMI only refer to a subset of the population. This has been clarified with footnotes in the Table as follows:

> "* ASA Class was available for 293,624 procedures
> ** BMI was available for 213,259 procedures"

The interpretation of these findings should be done cautiously, the risk is already very low. It sounds dramatic that conventional instrumentation has a 72% increased risk for 30 days mortality, but still the absolute number are low. There are also other issues like costs of these newer techniques (correctly cited by the authors) and proper training of surgeons with these newer techniques. And again, I think certainly robotic surgery can not claim this lower mortality rate as the numbers of this technique is this group of technology assisted surgery is low.

We agree and feel that we have been cautious in the discussion. We have translated the odds ratios into an approximate number needed to treat in the discussion, for perspective. We have also been careful not to single out robotic surgery, but given that it avoids intra-medullary instrumentation,

it is likely to be associated with reduced mortality. We have also pointed out the need for replication of the findings and the associated increased costs of technology-assisted surgery. No changes have been made in response to this comment.

Reviewer 2

30-day mortality is a data recorded and accessible. Would the death due to fat embolism not be in the early stages...2-5 days? A timeline to demonstrate when the death actually occurred may be helpful before we attribute the deaths to a well established technique of intramedullary cannulation for alignment.

We had asked the same question and had already performed a separate analysis using 7-day mortality as the outcome. This was not reported in the original manuscript as 30-day mortality is more commonly used and was thought to better include all possible deaths associated with embolisation (as patients may be in intensive care for several weeks with this condition). The findings of the analysis using 7-day mortality showed a stronger association, and we have added this to the manuscript as a secondary outcome alongside 90-day mortality, as we agree that this lends weight to the hypothesis. The following changes have been made and the 7-day statistics have been added to Tables 3 and 4.

Abstract:

> "**Main outcome measures**
> 30-day mortality (primary), and 7-day and 90-day mortality."
>
> "**Results**
> The corresponding odds ratios for 7-day and 90-day mortality were 2.21 (96% CI, 1.34 to 3.66, p = 0.002) and 1.35 (95% CI, 1.07 to 1.69, p = 0.010), respectively."

Methods:

> "Therefore, 30-day mortality was chosen as the primary outcome; 7-day and 90-day mortality ~~was~~were chosen as secondary outcomes."
>
> "Fully adjusted analyses were repeated using 7-day and 90-day mortality as the outcome measures."

Results:

> "The corresponding (fully adjusted) odds ratios for 7-day and 90-day mortality were 2.27 (95%CI, 1.33 to 8.74, p = 0.002) and 1.35 (95% CI, 1.07 to 1.69, p=0.010), respectively."

Discussion:

> "The higher odds ratio for 7-day compared to 30-day mortality, and 30-day compared to 90-day mortality suggests that the largest difference in mortality occurs in the early post-operative period."

The study compares a historic group of patient with a modern group of patients with some overlap. Would it not be better to restrict the comparative analysis over the identical period?
- the rehab protocols has evolved during the study period. Patients currently are mobilised and discharged much sooner than the historic cohorts. Could the longer recumbency explain the higher early complications in the conventional technique cohort?
- VTE preventive measures have also evolved. Patients in the recent years have benefitted from early mobilisation, foot and calf pumps, early discharge. Fatal PE is one of the leading causes of early death.

We feel that the problems referred to (secular changes) have been addressed in two ways. Firstly, for the overall analysis, we have included year of procedure as a variable, therefore adjusting for the improvement in mortality over time. Secondly, the analysis that includes ASA and BMI is restricted to cases performed from 2015, i.e., only using a recent, modern cohort (as suggested). We have mentioned the decrease in mortality over time in the introduction and discussion and provided references and explanations for this.
As per above explanation, no changes have been made in response to the comments

Is it possible to attempt to investigate the cause of death for these patients (1159 patients)? Is there another database that could be used to investigate these outcomes?

While this is possible, we have deliberately avoided including cause of death and have justified this in the methods (see below). Our previous experience with cause of death statistics has shown that this is difficult to interpret and reliably classify.

> "Cause of death was not used, as multiple causes are often reported, it may be inconsistently reported,[19] and it is less relevant than overall mortality."

Can you please explain the impact of ASA on mortality rates? p value <0.001 with ASA 2 patients? I appreciate there is no difference between the 2 groups, but does it mean the mortality rates were higher in these patients cf. ASA 1 and not the case when ASA 3 or 4?

Table 4 shows that the odds ratio of death increases with each increasing class of ASA (compared to ASA class I), as expected. For example, the odds ratio of 30-day mortality for ASA classes II, III, IV and V (compared to ASA class I) were 2.14, 4.68. 16.62 and 419.4, respectively. The varying p values reflect the numbers in each class (the high number of patients in ASA class II make even small differences highly statistically significant).

Other edits

1. Please note that we updated the referencing due to one reference being out of place (current reference 21 was previously listed as reference 35, out of order).

2. We have changed the ethics statement as the previous statement was incorrect – it was for a separate sub-study.

3. We have reformatted Table 4 to include the 7-day outcomes (see above) and corrected the labelling of the exposure variable to "Conventional vs technology assisted" from "Technology assisted vs conventional".

4. We have added a reference to our recently published study on this topic for bilateral TKA (line 229, reference 22):

> "This difference in mortality has been recently reported (with stronger effect) for bilateral TKA[22]"

5. The abstract has been shortened to fit within the word count.

6. Minor typos and other minor changes have been marked in the tracked version.

VERSION 2 – REVIEW

REVIEWER	Schreurs, Willem Radboudumc Instituut voor Wetenschappelijk Onderwijs en Opleidingen, Orthopedics
REVIEW RETURNED	13-Apr-2022

GENERAL COMMENTS	Have read the revised paper with great interest. My questions have been addressed in a satisfying manner. At reading I think there is wrong quote of the data in Table 3. The 7 days standardized mortality for conventional instrumentation is 0.005 and for instrumented 0.015. That is not in line with the data proposed in the paper, I suggest there is a mistake in the data cited in this table.

REVIEWER	Agrawal, Yuvraj Royal Orthopaedic Hospital NHS Foundation Trust, Lower Limb Arthroplasty Unit
REVIEW RETURNED	04-Apr-2022

GENERAL COMMENTS	The article is acceptable for print with the revisions.