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Title

Increased early mortality after total knee arthroplasty using conventional instrumentation compared to technology-assisted surgery: an analysis of linked national registry data.

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ABSTRACT

Objectives

This study aims to compare early mortality after total knee arthroplasty (TKA) using conventional intramedullary instrumentation to TKA performed using technology-assisted (non-intramedullary) instrumentation.

Design

Comparative observational study. Using data from a large national registry from 2003 to 2019 inclusive, the 30-day mortality after unilateral TKA performed for osteoarthritis was compared between procedures using conventional instrumentation and those using technology-assisted instrumentation. Firth logistic regression was used to calculate odds ratios, adjusting for age, sex, use of cement and procedure year for the whole period, and additionally adjusting for American Society of Anesthesiologists (ASA) physical status classification system class and body mass index (BMI) for the period 2015 to 2019. The analyses were repeated for 90-day mortality.

Setting

National arthroplasty registry.

Participants

People undergoing unilateral, elective TKR for osteoarthritis from 2003 to 2019 inclusive.

Interventions

TKA performed using conventional intramedullary instrumentation and TKR performed using technology-assisted instrumentation.

Main outcome measures

30- and 90-day mortality.

Results

A total of 581,818 unilateral TKA procedures performed for osteoarthritis were included, of which 602 (0.10%) and 1,159 (0.20%) died within 30 and 90 days of surgery, respectively. The odds ratio of death within 30 days following TKA performed with conventional instrumentation compared to technology-assisted instrumentation, adjusted for age, sex, cement use, procedure year, ASA and BMI was 1.72 (95% CI, 1.23 to 2.41, p=0.001). The corresponding odds ratios for 90-day mortality was 1.35 (95% CI, 1.07 to 1.69, p=0.010).

Conclusions

The use of conventional instrumentation during TKA is associated with higher odds of early post-operative death than when technology-assisted instrumentation is used. This difference may be explained by complications related to fat embolism secondary to the use of intramedullary rods used in conventional instrumentation. Given the high number of TKA performed annually worldwide, increasing the use of technology-assisted instrumentation may reduce early post-operative mortality.

Strengths and limitations of this study

- Use of national linked data
- Large sample size
- Adjustment for known likely confounders
- Observational study design (possible unmeasured confounders)

INTRODUCTION

Total knee arthroplasty (TKA) is a common procedure for severe osteoarthritis of the knee, with an average annual rate of 135 per 100,000 population in contributing OECD countries and 226 per 100,000 in Australia.[1,2] Conventional instrumentation for TKA surgery requires the insertion of a long intramedullary rod into the femur (and sometimes the tibia) which is then used as a reference for alignment of the cutting blocks applied to the bone for prosthesis preparation. This insertion creates fat and bone marrow embolization, as shown by transesophageal echocardiography and analysed by biopsy.[3] The embolic material may produce fat embolism syndrome, which includes respiratory, cardiac, haematological, and neurological complications and sudden death.[4-6] Over the last two decades, three new techniques have been introduced that allow alignment to be referenced without intramedullary instrumentation. These technology-assisted instrumentation techniques are computer navigation, image-derived instrumentation and robotic assistance. Although these techniques were developed to improve post-operative alignment, evidence for this is variable. Computer navigation has demonstrated improved alignment compared to standard instruments, however, there is mixed evidence that revision rates or patient reported outcomes are superior using this technique.[7-13]. However, trials comparing any of these newer techniques to conventional instrumentation were underpowered to detect early mortality post-operatively, which has been decreasing over time and is currently approximately 0.1% at 30 days.[14,15]

This study aims to compare the 30-day all-cause mortality after TKA between procedures performed using conventional intramedullary instrumentation to those performed using technology-assisted instrumentation using data from a large national registry.

METHODS

The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) is a national registry with near complete (over 98%) coverage of TKA procedures performed in Australia since 2003.[2] AOANJRR data from January 2003 to December 2019 for patients undergoing unilateral TKA for osteoarthritis were used. Patients undergoing bilateral same-day primary TKA or any primary TKA within 90 days of a contralateral primary TKA were excluded. AOANJRR data include patient-identified data and surgical variables, which includes the use of assistive technology, and these data are linked to the National Death Index twice yearly to record fact and date of death. The AOANJRR has collected data on American Society of Anesthesiologists (ASA) class[16] (a measure of comorbidity and mortality risk) since 2012 and body mass index (BMI) since 2015.

The increased mortality associated with TKA is maximal within 30 days but may extend to 90 days post surgery.[17,18] Therefore, 30-day mortality was chosen as the primary outcome and 90-day mortality was chosen as a secondary outcome. Age, sex, use of bone cement, ASA class and BMI were chosen as potential confounders due to their known association with mortality. Procedure year was added as a covariate due to the increase in the proportion of cases using technology-assisted instrumentation over time and, because 30-day mortality has been decreasing over time.[14]

Technology-assisted surgery was defined as any procedure using computer navigation, image derived instrumentation (IDI) or robotic assistance. Computer navigation involves the use of a tracking device, most commonly an infrared camera, and a computer. Rigid reference arrays are attached to the patient and a registration process enables the software to determine the patient's anatomy and accurately track instruments to assist surgery. The surgeon then makes the appropriate bone cuts and monitors the alignment of the knee. Robotic assistance uses similar principles, but a robotic arm guides the cutting tools to facilitate the surgery. Both these techniques allow intra operative verification of the component position. IDI is the use of

individualised custom-made 3D printed guides or cutting blocks derived from pre-operative CT or MRI scans of the patient's knee. These guides or blocks are used to perform the required bone cuts and are specific to each patient's anatomy. Conventional instrumentation was defined as any procedure not using any of the technology-assisted methods. 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.

Between-group differences in mortality were expressed as odds ratios, calculated by logistic regression adjusting for age, sex and procedure year. Due to low numbers of deaths, Firth logistic regression (which uses penalized likelihood) was used to avoid the small sample bias inherent in regression using conventional maximum likelihood estimation.[20] Adjusted mortality was obtained after direct standardisation of the crude cumulative mortality data, by 5-year age intervals and sex, to the Estimated Resident Population Status, based on the 2001 census. Interaction terms were tested for each covariate against instrumentation type.

A secondary analysis of mortality adjusted for age, sex, procedure year, bone cement use, ASA and BMI was performed in the subset of procedures performed since 2015 (when ASA and BMI data were available). Both analyses were repeated using 90-day mortality as the outcome measure.

A sensitivity analysis was performed by restricting the population to patients who had only one primary TKA recorded in the AOANJRR, which excluded all patients with contralateral TKA.

As it was unlikely that patients died in another country within 30 or 90 days of surgery without registration of their death, an assumption of no missing data was made.

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 581,818 unilateral TKA procedures were included from 1 January 2003 to 31 December 2019. The increasing use of technology-assisted instrumentation over time is shown in Figure 1, and descriptive data of patient demographics and the use of technology-assisted surgery is provided in Table 1. Procedures using technology-assisted surgery comprised 129,179 computer navigation, 34,898 image-derived instrumentation, 7,288 robotic assisted and 869 using a combination of technologies.

Table 1. Demographic data and use of technology-assisted surgery in patients undergoing unilateral TKA.

	Technology-assisted surgery	**Not technology-assisted surgery**	**Total**
Mean age (SD) in years	68.5 (9.0)	69.1 (9.2)	69.0 (9.1)
Sex (proportion male)	43.3%	42.0%	42.4%
ASA Class (proportion)			
1	5.6%	5.2%	5.4%
2	53.8%	54.5%	54.2%
3	39.4%	39.1%	39.3%
4	1.2%	1.2%	1.2%
5	0.0%	0.0%	0.0%
Mean BMI (SD)	32.0 (14.2)	32.3 (17.1)	32.2 (15.8)
Procedures	170,496	411,322	581,818

The distribution of deaths between groups for 30-day and 90-day post-surgical periods are provided in Tables 2 and 3, respectively. The odds ratio of death within 30 days for TKA performed with conventional instrumentation compared to technology-assisted

instrumentation, adjusted for age, sex, cement use and procedure year was 1.48 (95% CI, 1.19 to 1.85, p<0.001). For the subset of 212,937 procedures where ASA and BMI data were available, the odds ratio adjusted for age, sex, procedure year, cement use, ASA and BMI was 1.72 (95% CI, 1.23 to 2.41, p=0.001). The corresponding odds ratios for 90-day mortality were 1.27 (95% CI, 1.09 to 1.47, p=0.002) and 1.35 (95% CI, 1.07 to 1.69, p=0.010). The models for the fully adjusted analyses are shown in Table 4. Two-way interaction terms between age, sex, BMI, ASA class, cement use and procedure year, and use of technology-assisted instrumentation were tested and found to be not significant for both 30- and 90-day mortality.

The sensitivity analysis restricted to patients who had only one unilateral TKA recorded showed similar significant differences between technology assisted and conventional instrumentation, although the overall (and standardised) mortality was higher in this group (analyses not shown).

Table 2. 30-day mortality following unilateral TKA for osteoarthritis.

	Patients (n)	**Deaths (n)**	**Deaths (%)**	**Standardised mortality**
Conventional instrumentation	411,322	495	0.120	0.036
Technology-assisted instrumentation	170,496	107	0.063	0.018
Total	581,818	602	0.103	0.031

Table 3. 90-day mortality following unilateral TKA for osteoarthritis.

	Patients (n)	**Deaths (n)**	**Deaths (%)**	**Standardised mortality**

Conventional instrumentation	411,322	919	0.233	0.074
Technology-assisted instrumentation	170,496	240	0.141	0.043
Total	581,818	1,159	0.199	0.065

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Table 4. Full regression model for 30-day mortality using data from 2015 to 2019, inclusive.

	30-day mortality		90-day mortality	
Variable	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Technology assisted (vs conventional)	1.72 (1.23, 2.43)	0.001	1.35 (1.07, 1.69)	0.01
ASA class (ref = 1)				
2	2.14 (0.43, 10.66),	<0.001	1.52 (0.59, 3.91)	0.001
3	4.68 (0.94, 23.25)	0.07	3.33 (1.30, 8.53)	0.08
4	16.62 (3.04, 90.78)	0.19	12.07 (4.37, 33.38)	0.07
5	419.4 (11.78, 14934)	0.003	141.8 (5.11, 3935)	0.02
Age (per year)	1.08 (1.06, 1.10)	<0.001	1.08 (1.07, 1.10)	0.01
BMI (ref = normal)				
Underweight	0.96 (0.56, 1.64)	0.80	5.87 (2.38, 14.51)	<0.001
Overweight	0.95 (0.51, 1.77)	0.79	0.99 (0.69, 1.42)	0.02
Obese class 1	1.25 (0.63, 2.48)	0.55	0.88 (0.61, 1.29)	0.002
Obese class 2	0.93 (0.55, 1.56)	0.70	0.89 (0.57, 1.38)	0.01
Obese class 3	1.12 (0.07, 18.12)	0.94	1.06 (0.65, 1.75)	0.26
Procedure year (per year)	1.06 (0.94, 1.18)	0.35	1.02 (0.95, 1.11)	0.57
Female (vs male)	0.63 (0.46, 0.87)	0.004	0.62 (0.50, 0.78)	<0.001
No cement (vs cement)	1.89 (1.15, 3.09)	<0.001	1.35 (0.91, 2.00)	0.14

DISCUSSION

Statement of principal findings

The use of conventional instrumentation during unilateral TKA was associated with a significantly higher 30-day mortality when compared to technology-assisted instrumentation, allowing for differences in age, sex, cement use, ASA class, BMI and year of procedure.

Strengths and weaknesses of the study

A strength of this study is the use of national data and the large sample size. Furthermore, adjusting for patient-level factors and procedure year, has accounted for differences in patient selection, improvements in perioperative management and the increasing use of technology-assisted instrumentation over time.

This study is limited by the possibility that the associations may be subject to residual confounding from unknown variables. Randomised trials to answer this question may not be feasible due to the very large sample size required due to the small event rate. Surgical times are reported to be slightly longer when technology-assisted methods are used,[35] but this would not be expected to be associated with a reduction in mortality.

Strengths and weaknesses in relation to other studies

The relative mortality of conventional and technology assisted instrumentation in TKA has not been previously reported.

Meaning of the study: possible explanations and implications for clinicians and policymakers

This difference in mortality has not been previously reported and may be related to the insertion of an intramedullary rod into the femur (and in some cases, the tibia) during conventional instrumentation and the resulting fat embolism. Initial studies using non-invasive intra-operative ultrasound have demonstrated that there are less emboli with computer navigation

compared to conventional instrumentation, although these studies were small.[21,22] However, later studies with larger study populations have shown that while avoiding intramedullary instrumentation does not significantly reduce the incidence of fat embolization during TKA,[23,24] it may reduce the embolic load.[25] Cerebral fat embolism has also been reported after standard TKA[4,26] but there is a lack of studies comparing technology assisted and standard instrumented TKA. Alternatively, fat emboli may arise from other parts of the surgery such as impaction of the femoral and tibial implants, but this is unlikely to differ between technology assisted and conventionally instrumented TKA.[23-25]

The higher 30-day mortality associated with cementless fixation may also be related to fat emboli due to potential higher impaction forces used in cementless fixation. This association has not previously been reported, however a recent study from the Dutch arthroplasty register showed that the odds ratio for 30-day mortality in cementless fixation compared to cemented fixation was 1.46 (95% CI 0.74 to 2.90). This difference was not statistically significant but used a smaller sample than that used in the current study.[27]

Stein et al examined over 900 million patients using data from the US National Hospital Discharge Survey from 1979 to 2005 and reported 41,000 patients (0.004%) with fat embolism syndrome.[28] They stated that the incidence of fat embolism with lower limb joint replacement was too low to calculate accurately. However, it is possible that cases of sudden death associated with surgery were not diagnosed as fat embolism syndrome.[4,29]

Another possible cause for the observed difference in mortality is perioperative blood loss. Although blood loss was not measured in this study, previous research has shown surgical blood loss is lower with technology-assisted knee surgery.[30,31] This factor may also affect mortality directly or by reducing the need for blood transfusion.

Although the odds ratios for the associations were lower for 90-day mortality, the 90-day mortality is higher, such that the difference likely relates to a similar risk difference. The higher odds ratio for 30-day mortality compared to 90-day mortality suggests that the largest difference in mortality occurs in the early post-operative period. Mortality after TKA has fallen over the last few decades and the current 30-day mortality after TKA is approximately 0.1%.[14,15] Given the low event rate for death post-TKA, the odds ratios found in this analysis can be approximated as risk ratios. This suggests that the use of conventional instrumentation is associated with a 72% increase in 30-day mortality after TKA when compared to assistive technology use. It is estimated that approximately one million TKA are performed in the US annually with that rate expected to rise significantly up to 2050.[32,33] Globally, assuming over two million cases are performed annually,[34] if the difference in mortality is due to the use of conventional instrumentation, the use of technology assisted instrumentation would result in approximately one thousand fewer deaths per year, depending on the current rate of technology assisted instrumentation.

Unanswered questions and future research

This study should be replicated using large datasets and joint registries from other regions that collect data on technology assisted TKA. If verified, this finding has a major implication for the conduct of TKA surgery worldwide. While there is little clinical disadvantage to using technology-assisted surgery, there is an increased cost. Future research may determine the cost effectiveness of using technology assisted instrumentation.

Ethics approval statement

The project was approved by the following ethics committees: University of South Australia HREC (200890), Sydney Local Health District Ethics Review Committee (RPAH Zone, HREC/18/RPAH/90), Calvary Health Care Adelaide HREC (18-CHREC-F004), Mater Misericordiae Ltd HREC (HREC/18/MHS/45), St Vincent's Health and Aged Care HREC (HREC 18/14), University of Tasmania HREC (H0017292), Calvary Health Care Tasmania HREC (010418), St John of God HREC (1408), Calvary Health Care (ACT)(25-2018).

Figure legend

Figure 1: The use of technology assisted instrumentation over time for primary unilateral TKA.

Contributorship statement

IAH and DK conceived the study. All authors contributed to the methods. YP performed the statistical analysis. IAH drafted the manuscript. All authors contributed to the literature review and manuscript preparation. IAH is guarantor for the study.

Competing interests

There are no competing interests for any author.

Funding statement

No funding was received for the conduct of this study.

Data sharing statement

Data are held by the Australian Orthopaedic Association National Joint Replacement Registry and are available on request subject to conditions. External access to and use of de-identified AOANJRR data must be in accordance with AOANJRR policies (Ref No POL.S3.3, S3.4,

S3.5) available on the registry website: https://aoanjrr.sahmri.com/policies. Requests for data use can be made by contacting the AOANJRR Manager:

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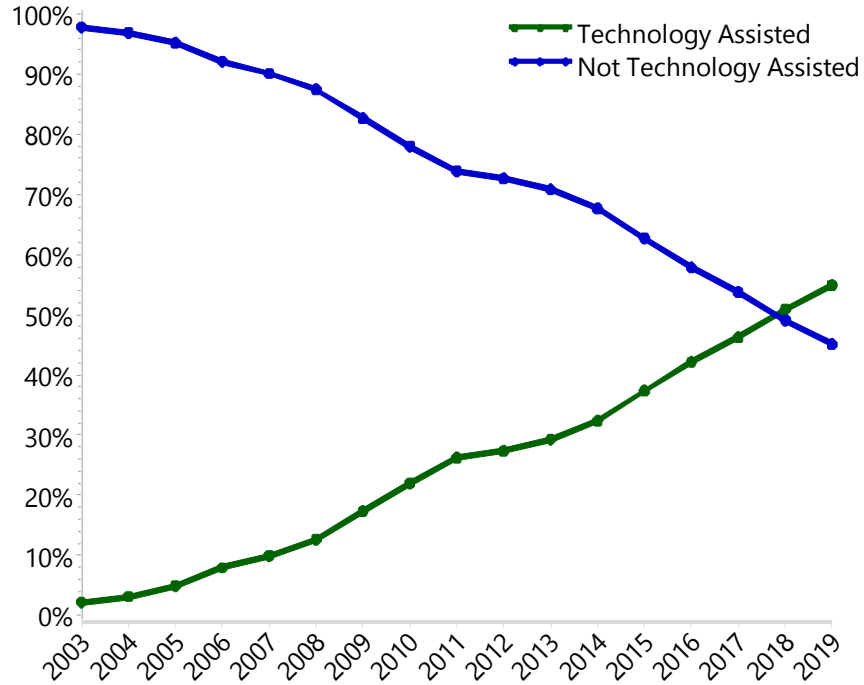

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Line 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Line 26
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Line 70
Objectives	3	State specific objectives, including any prespecified hypotheses	Line 88
Methods			
Study design	4	Present key elements of study design early in the paper	Lines 92-137
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Lines 92-101
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Lines 92-101
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Lines 102-122
Data sources/ measurement	8*	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	Lines 102-129
Bias	9	Describe any efforts to address potential sources of bias	Lines 123-137
Study size	10	Explain how the study size was arrived at	Convenience sample. Lines 95-95
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Lines 123-129
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Lines 123-137
		(*b*) Describe any methods used to examine subgroups and interactions	Lines 130-137
		(*c*) Explain how missing data were addressed	Lines 136-137
		(*d*) If applicable, explain how loss to follow-up was addressed	Lines 136-137
		(*e*) Describe any sensitivity analyses	Lines 134-135
Results			
Participants	13*	(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	Lines 141-146

		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Not necessary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Line 148
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	Lines 151-152
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2, 3. Lines 167, 169
Main results	16	(*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	Table 4, Line 171
		(*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	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Lines 160-163
Discussion			
Key results	18	Summarise key results with reference to study objectives	Lines 174-177
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Lines 178-187
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Lines 191-232
Generalisability	21	Discuss the generalisability (external validity) of the study results	Lines 234-235
Other information			
Funding	22	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	Line 22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Increased early mortality after total knee arthroplasty using conventional instrumentation compared to technology-assisted surgery: an analysis of linked national registry data.

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Title

Increased early mortality after total knee arthroplasty using conventional instrumentation compared to technology-assisted surgery: an analysis of linked national registry data.

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ABSTRACT

Objectives

This study aims to compare early mortality after total knee arthroplasty (TKA) using conventional intramedullary instrumentation to TKA performed using technology-assisted (non-intramedullary) instrumentation.

Design

Comparative observational study. Using data from a large national registry, the 30-day mortality after unilateral TKA performed for osteoarthritis was compared between procedures using conventional instrumentation and those using technology-assisted instrumentation. Firth logistic regression was used to calculate odds ratios, adjusting for age, sex, use of cement and procedure year for the whole period, and additionally adjusting for American Society of Anesthesiologists (ASA) physical status classification system class and body mass index (BMI) for the period 2015 to 2019. This analysis was repeated for 7-day and 90-day mortality.

Setting

National arthroplasty registry.

Participants

People undergoing unilateral, elective TKR for osteoarthritis from 2003 to 2019 inclusive.

Interventions

TKA performed using conventional intramedullary instrumentation or technology-assisted instrumentation.

Main outcome measures

30-day mortality (primary), and 7-day and 90-day mortality.

Results

A total of 581,818 unilateral TKA procedures performed for osteoarthritis were included, of which 602 (0.10%) died within 30 days of surgery. The odds ratio of death within 30 days following TKA performed with conventional instrumentation compared to technology-assisted instrumentation, adjusted for age, sex, cement use, procedure year, ASA and BMI was 1.72 (95% CI, 1.23 to 2.41, p=0.001). 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.

Conclusions

The use of conventional instrumentation during TKA is associated with higher odds of early post-operative death than when technology-assisted instrumentation is used. This difference may be explained by complications related to fat embolism secondary to intramedullary rods used in conventional instrumentation. Given the high number of TKA performed annually worldwide, increasing the use of technology-assisted instrumentation may reduce early post-operative mortality.

Strengths and limitations of this study

- Use of national linked data

- Large sample size
- Adjustment for known likely confounders
- Observational study design (possible unmeasured confounders)

INTRODUCTION

Total knee arthroplasty (TKA) is a common procedure for severe osteoarthritis of the knee, with an average annual rate of 135 per 100,000 population in contributing OECD countries and 226 per 100,000 in Australia.[1,2] Conventional instrumentation for TKA surgery requires the insertion of a long intramedullary rod into the femur (and sometimes the tibia) which is then used as a reference for alignment of the cutting blocks applied to the bone for prosthesis preparation. This insertion creates fat and bone marrow embolization, as shown by transesophageal echocardiography and analysed by biopsy.[3] The embolic material may produce fat embolism syndrome, which includes respiratory, cardiac, haematological, and neurological complications and sudden death.[4-6] Over the last two decades, three new techniques have been introduced that allow alignment to be referenced without intramedullary instrumentation. These technology-assisted instrumentation techniques are computer navigation, image-derived instrumentation and robotic assistance. Although these techniques were developed to improve post-operative alignment, evidence for this is variable. Computer navigation has demonstrated improved alignment compared to standard instruments, however, there is mixed evidence that revision rates or patient reported outcomes are superior using this technique.[7-13]. However, trials comparing any of these newer techniques to conventional instrumentation were underpowered 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.[14,15]

This study aims to compare the 30-day all-cause mortality after TKA between procedures performed using conventional intramedullary instrumentation to those performed using technology-assisted instrumentation using data from a large national registry.

METHODS

The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) is a national registry with near complete (over 98%) coverage of TKA procedures performed in Australia since 2003.[2] AOANJRR data from January 2003 to December 2019 for patients undergoing unilateral TKA for osteoarthritis were used. Patients undergoing bilateral same-day primary TKA or any primary TKA within 90 days of a contralateral primary TKA were excluded. AOANJRR data include patient-identified data and surgical variables, which includes the use of assistive technology, and these data are linked to the National Death Index twice yearly to record fact and date of death. All data used in the analysis were available in the AOANJRR 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 increased mortality associated with TKA is maximal within 30 days but may extend to 90 days post surgery.[17,18] Therefore, 30-day mortality was chosen as the primary outcome; 7-day and 90-day mortality were chosen as secondary outcomes. Age, sex, use of bone cement, ASA class and BMI were chosen as potential confounders due to their known association with mortality. Procedure year was added as a covariate due to the increase in the proportion of cases using technology-assisted instrumentation over time and, because 30-day mortality has been decreasing over time.[14]

Technology-assisted surgery was defined as any procedure using computer navigation, image derived instrumentation (IDI) or robotic assistance. Computer navigation involves the use of a tracking device, most commonly an infrared camera, and a computer. Rigid reference arrays are attached to the patient and a registration process enables the software to determine the patient's anatomy and accurately track instruments to assist surgery. The surgeon then makes the appropriate bone cuts and monitors the alignment of the knee. Robotic assistance uses similar principles, but a robotic arm guides the cutting tools to facilitate the surgery. Both these

techniques allow intra operative verification of the component position. IDI is the use of individualised custom-made 3D printed guides or cutting blocks derived from pre-operative CT or MRI scans of the patient's knee. These guides or blocks are used to perform the required bone cuts and are specific to each patient's anatomy. Conventional instrumentation was defined as any procedure not using any of the technology-assisted methods. 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.

Between-group differences in mortality were expressed as odds ratios, calculated by logistic regression adjusting for age, sex and procedure year. Due to low numbers of deaths, Firth logistic regression (which uses penalized likelihood) was used to avoid the small sample bias inherent in regression using conventional maximum likelihood estimation.[20] Adjusted mortality was obtained after direct standardisation of the crude cumulative mortality data, by 5-year age intervals and sex, to the Estimated Resident Population Status, based on the 2001 census. Interaction terms were tested for each covariate against instrumentation type.

A secondary analysis of mortality adjusted for age, sex, procedure year, bone cement use, ASA and BMI was performed in the subset of procedures performed since 2015 (when ASA and BMI data were available). Fully adjusted analyses were repeated using 7-day and 90-day mortality as the outcome measures.

A sensitivity analysis was performed by restricting the population to patients who had only one primary TKA recorded in the AOANJRR, which excluded all patients with contralateral TKA.

As it was unlikely that patients died in another country within 30 or 90 days of surgery without registration of their death, an assumption of no missing data was made.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 581,818 unilateral TKA procedures were included from 1 January 2003 to 31 December 2019. The increasing use of technology-assisted instrumentation over time is shown in Figure 1, and descriptive data of patient demographics and the use of technology-assisted surgery is provided in Table 1. Procedures using technology-assisted surgery comprised 129,179 computer navigation, 34,898 image-derived instrumentation, 7,288 robotic assisted and 869 using a combination of technologies.

Table 1. Demographic data and use of technology-assisted surgery in patients undergoing unilateral TKA.

	Technology-assisted surgery	**Conventional surgery**	**Total**
Mean age (SD) in years	68.5 (9.0)	69.1 (9.2)	69.0 (9.1)
Sex (proportion male)	43.3%	42.0%	42.4%
ASA Class* (proportion)			
1	5.6%	5.2%	5.4%
2	53.8%	54.5%	54.2%
3	39.4%	39.1%	39.3%
4	1.2%	1.2%	1.2%
5	0.0%	0.0%	0.0%
Mean BMI** (SD)	32.0 (14.2)	32.3 (17.1)	32.2 (15.8)
Procedures	170,496	411,322	581,818

* ASA Class was available for 293,624 procedures

** BMI was available for 213,259 procedures

The distribution of deaths between groups for 30-day, and 7- and 90-day post-surgical periods are provided in Tables 2 and 3, respectively. The odds ratio of death within 30 days for TKA performed with conventional instrumentation compared to technology-assisted instrumentation, adjusted for age, sex, cement use and procedure year was 1.48 (95% CI, 1.19 to 1.85, p<0.001). For the subset of 212,937 procedures where ASA and BMI data were available, the odds ratio adjusted for age, sex, procedure year, cement use, ASA and BMI was 1.72 (95% CI, 1.23 to 2.41, p=0.001). 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. The models for the fully adjusted analyses are shown in Table 4. Two-way interaction terms between age, sex, BMI, ASA class, cement use and procedure year, and use of technology-assisted instrumentation were tested and found to be not significant.

The sensitivity analysis restricted to patients who had only one unilateral TKA recorded showed similar significant differences between technology assisted and conventional instrumentation, although the overall (and standardised) mortality was higher in this group (analyses not shown).

Table 2. 30-day mortality following unilateral TKA for osteoarthritis.

Group	Patients (n)	Deaths (n)	Deaths (%)	Standardised mortality
Conventional instrumentation	411,322	495	0.120	0.036
Technology-assisted instrumentation	170,496	107	0.063	0.018
Total	581,818	602	0.103	0.031

Table 3. 7-day and 90-day mortality following unilateral TKA for osteoarthritis.

Group	Patients (n)	7-day mortality			90-day mortality		
		Deaths (n)	Deaths (%)	Standardised mortality	Deaths (n)	Deaths (%)	Standardised mortality
Conventional instrumentation	411,322	214	0.052	0.005	919	0.233	0.074
Technology-assisted instrumentation	170,496	38	0.022	0.015	240	0.141	0.043
Total	581,818	252	0.043	0.012	1,159	0.199	0.065

172 Table 4. Full regression model for mortality using data from 2015 to 2019, inclusive.

	30-day mortality		7-day mortality		90-day mortality	
Variable	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Conventional vs technology assisted	1.72 (1.23, 2.43)	0.001	2.21 (1.34, 3.66)	0.002	1.35 (1.07, 1.69)	0.01
ASA class (ref = 1)						
2	2.14 (0.43, 10.66),	<0.001	1.10 (0.22, 5.47)	0.91	1.52 (0.59, 3.91)	0.001
3	4.68 (0.94, 23.25)	0.07	1.89 (0.38, 9.38)	0.44	3.33 (1.30, 8.53)	0.08
4	16.62 (3.04, 90.78)	0.19	4.23 (0.64, 27.99)	0.07	12.07 (4.37, 33.38)	0.07
5	419.4 (11.78, 14934)	0.003	451.5 (13.69, 14894)	<0.001	141.8 (5.11, 3935)	0.02
Age (per year)	1.08 (1.06, 1.10)	<0.001	1.08 (1.05, 1.17)	0.01	1.08 (1.07, 1.10)	0.01
BMI (ref = normal)						
Underweight	0.96 (0.56, 1.64)	0.80	3.25 (0.20, 53.22)	0.09	5.87 (2.38, 14.51)	<0.001
Overweight	0.95 (0.51, 1.77)	0.79	1.06 (0.47, 2.37)	0.89	0.99 (0.69, 1.42)	0.02
Obese class 1	1.25 (0.63, 2.48)	0.55	1.23 (0.54, 2.81)	0.62	0.88 (0.61, 1.29)	0.002
Obese class 2	0.93 (0.55, 1.56)	0.70	1.25 (0.49, 3.19)	0.65	0.89 (0.57, 1.38)	0.01
Obese class 3	1.12 (0.07, 18.12)	0.94	2.50 (0.95, 6.57)	0.06	1.06 (0.65, 1.75)	0.26
Procedure year (per year)	1.06 (0.94, 1.18)	0.35	0.97 (0.83, 1.14)	0.73	1.02 (0.95, 1.11)	0.57
Female (vs male)	0.63 (0.46, 0.87)	0.004	0.52 (0.33, 0.83)	0.005	0.62 (0.50, 0.78)	<0.001
No cement (vs cement)	1.89 (1.15, 3.09)	<0.001	1.84 (0.92, 3.67)	0.09	1.35 (0.91, 2.00)	0.14

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DISCUSSION

Statement of principal findings

The use of conventional instrumentation during unilateral TKA was associated with a significantly higher 30-day mortality when compared to technology-assisted instrumentation, allowing for differences in age, sex, cement use, ASA class, BMI and year of procedure.

Strengths and weaknesses of the study

A strength of this study is the use of national data and the large sample size. Furthermore, adjusting for patient-level factors and procedure year, has accounted for differences in patient selection, improvements in perioperative management and the increasing use of technology-assisted instrumentation over time.

This study is limited by the possibility that the associations may be subject to residual confounding from unknown variables. Randomised trials to answer this question may not be feasible due to the very large sample size required due to the small event rate. Surgical times are reported to be slightly longer when technology-assisted methods are used,[21] but this would not be expected to be associated with a reduction in mortality.

Strengths and weaknesses in relation to other studies

The relative mortality of conventional and technology assisted instrumentation in TKA has not been previously reported.

Meaning of the study: possible explanations and implications for clinicians and policymakers

This difference in mortality has been recently reported (with stronger effect) for bilateral TKA[22] and may be related to the insertion of an intramedullary rod into the femur (and in some cases, the tibia) during conventional instrumentation and the resulting fat embolism. Initial

studies using non-invasive intra-operative ultrasound have demonstrated that there are less emboli with computer navigation compared to conventional instrumentation, although these studies were small.[23,24] However, later studies with larger study populations have shown that while avoiding intramedullary instrumentation does not significantly reduce the incidence of fat embolization during TKA,[25,26] it may reduce the embolic load.[27] Cerebral fat embolism has also been reported after standard TKA[4,28] but there is a lack of studies comparing technology assisted and standard instrumented TKA. Alternatively, fat emboli may arise from other parts of the surgery such as impaction of the femoral and tibial implants, but this is unlikely to differ between technology assisted and conventionally instrumented TKA.[25-27]

The higher 30-day mortality associated with cementless fixation may also be related to fat emboli due to potential higher impaction forces used in cementless fixation. This association has not previously been reported, however a recent study from the Dutch arthroplasty register showed that the odds ratio for 30-day mortality in cementless fixation compared to cemented fixation was 1.46 (95% CI 0.74 to 2.90). This difference was not statistically significant but used a smaller sample than that used in the current study.[29]

Stein et al examined over 900 million patients using data from the US National Hospital Discharge Survey from 1979 to 2005 and reported 41,000 patients (0.004%) with fat embolism syndrome.[30] They stated that the incidence of fat embolism with lower limb joint replacement was too low to calculate accurately. However, it is possible that cases of sudden death associated with surgery were not diagnosed as fat embolism syndrome.[4,31]

Another possible cause for the observed difference in mortality is perioperative blood loss. Although blood loss was not measured in this study, previous research has shown surgical blood loss is lower with technology-assisted knee surgery.[32,33] This factor may also affect mortality directly or by reducing the need for blood transfusion.

Although the odds ratios for the associations were lower for 90-day mortality, the 90-day mortality is higher, such that the difference likely relates to a similar risk difference. 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. Mortality after TKA has fallen over the last few decades and the current 30-day mortality after TKA is approximately 0.1%.[14,15] Given the low event rate for death post-TKA, the odds ratios found in this analysis can be approximated as risk ratios. This suggests that the use of conventional instrumentation is associated with a 72% increase in 30-day mortality after TKA when compared to assistive technology use. It is estimated that approximately one million TKA are performed in the US annually with that rate expected to rise significantly up to 2050.[34,35] Globally, assuming over two million cases are performed annually,[36] if the difference in mortality is due to the use of conventional instrumentation, the use of technology assisted instrumentation would result in approximately one thousand fewer deaths per year, depending on the current rate of technology assisted instrumentation.

Unanswered questions and future research

This study should be replicated using large datasets and joint registries from other regions that collect data on technology assisted TKA. If verified, this finding has a major implication for the conduct of TKA surgery worldwide. While there is little clinical disadvantage to using technology-assisted surgery, there is an increased cost. Future research may determine the cost effectiveness of using technology assisted instrumentation.

Ethics approval statement

The AOANJRR is approved by the Commonwealth of Australia as a federal quality assurance activity (QAA 3/2017) under Part VC of the Health Insurance Act, 1973. All AOANJRR studies are conducted in accordance with ethical principles of research (the Helsinki Declaration II).

Figure legend

Figure 1: The use of technology assisted instrumentation over time for primary unilateral TKA.

Contributorship statement

IAH contributed to study concept, design, analysis, interpretation and drafted the manuscript. IAH has approved the final version of the manuscript and agrees to be accountable for the work. IAH has approved the final version of the manuscript and agrees to be accountable for the work. DK contributed to concept, interpretation and revising the manuscript. DK has approved the final version of the manuscript and agrees to be accountable for the work. YP conducted the statistical analysis and revised the manuscript. YP has approved the final version of the manuscript and agrees to be accountable for the work. PL contributed to study design, interpretation and manuscript revision. PL has approved the final version of the manuscript and agrees to be accountable for the work. RdS contributed to study design, interpretation and manuscript revision. RdS has approved the final version of the manuscript and agrees to be accountable for the work. SEG contributed to study design, interpretation and manuscript revision. SEG has approved the final version of the manuscript and agrees to be accountable for the work.

Competing interests

There are no competing interests for any author.

Funding statement

No funding was received for the conduct of this study.

Data sharing statement

Data are held by the Australian Orthopaedic Association National Joint Replacement Registry and are available on request subject to conditions. External access to and use of de-identified AOANJRR data must be in accordance with AOANJRR policies (Ref No POL.S3.3, S3.4, S3.5) available on the registry website: https://aoanjrr.sahmri.com/policies. Requests for data use can be made by contacting the AOANJRR Manager:

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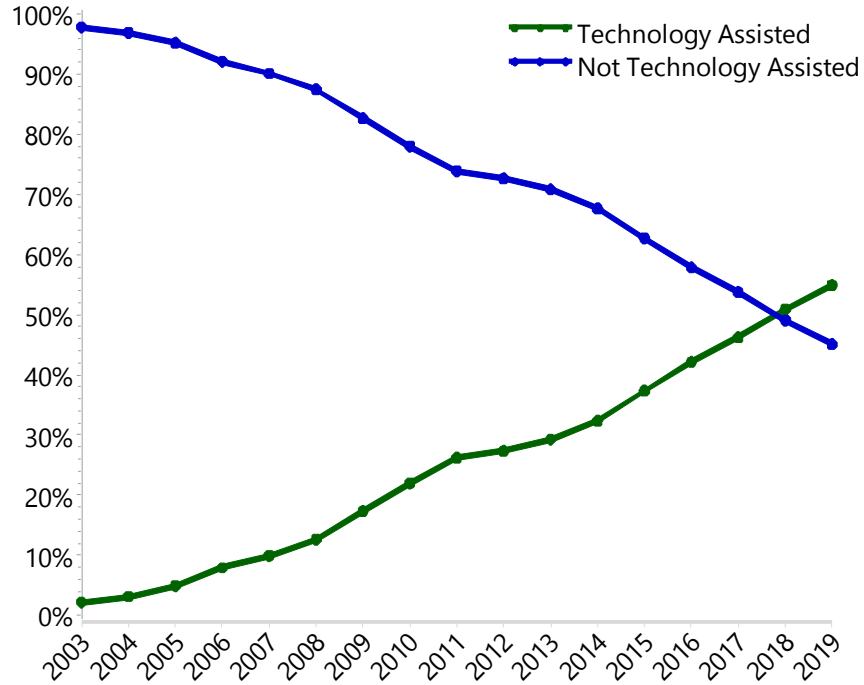

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Line 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Lines 26-64
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Lines 74-92
Objectives	3	State specific objectives, including any prespecified hypotheses	Lines 93-95
Methods			
Study design	4	Present key elements of study design early in the paper	Lines 98-150
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Lines 98-108
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Lines 100-103
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Lines 103-142
Data sources/ measurement	8*	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	Lines 103-133
Bias	9	Describe any efforts to address potential sources of bias	Lines 137-150
Study size	10	Explain how the study size was arrived at	Convenience sample. Lines 100-103
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Lines 136-142
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Lines 136-150
		(*b*) Describe any methods used to examine subgroups and interactions	Lines 142-148
		(*c*) Explain how missing data were addressed	Lines 149-150
		(*d*) If applicable, explain how loss to follow-up was addressed	Lines 149-150
		(*e*) Describe any sensitivity analyses	Lines 147-148
Results			
Participants	13*	(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	Lines 156-161

		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Not necessary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Line 162
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	Lines 168-169
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2, 3. Lines 183, 185
Main results	16	(*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	Table 4, Line 202
		(*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	Tables 2 and 3 contain absolute risks
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Lines 174-182
Discussion			
Key results	18	Summarise key results with reference to study objectives	Lines 207-209
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Lines 215-219
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Lines 224-280
Generalisability	21	Discuss the generalisability (external validity) of the study results	Line 282
Other information			
Funding	22	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	Line 306

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.