Risk Factors Associated with Unplanned ICU Admissions Following Hip or Knee Arthroplasty: A Systematic Review and Meta-analysis

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Declaration

I, Muhammed Makda, herewith declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signed

On this the 24th day of October 2022

Dedication

This project is dedicated to my wife, Nazmeera, and my sons, Ahmed and Nuh. Thank you for your unwavering support. Your patience and understanding has allowed me to prosper through all trials and tribulations. Your smiles and laughter is what fuels me daily. This project is also dedicated to my parents, Ebrahim and Safiya. Your love and support have made me the man I am today.

Presentations and publications from this research project

1. Nil

Abstract

Background: Lower limb arthroplasty is not without risk with a significant proportion of patients requiring unplanned ICU admission. A collated summary of the various risk factors would contribute towards developing risk stratification methods aimed at reducing this perioperative outcome.

Objective: To perform a systematic review of published data on risk factors for unplanned ICU admissions following hip/knee arthroplasty.

Method: We conducted a systematic review with pre-defined eligibility criteria used to identify relevant manuscripts. Quality assessment was achieved using the Newcastle-Ottawa score. Study characteristics and identified risk factor data were extracted from eligible manuscripts. A meta-analysis was performed on the available data.

Results: Twelve published studies were included in our review. The pooled rate of ICU admission was 4.55% (95% CI 3.04–6.05%). Smoking history (OR 19.92, 95% CI 2.78 - 142.68, I^2 = 47.9%), Charlson comorbidity index (OR 1.97, 95% CI 1.79 – 2.17, I^2 = 0%), COPD (OR 3.25, 95% CI 1.12 – 9.4, I^2 = 88.2%), coronary artery disease **(**OR 3.04, 95% CI 1.10 – 8.45, I^2 = 81.9%), revision surgery (OR 2.17, 95% CI 1.35 – 3.50, I^2 = 0%), excessive blood loss (OR 3.76, 95% CI 1.09 – 12. 93, I^2 = 93.3%) and use of vasopressors **(**OR 5.00, 95% CI 2.22 – 11.27, I^2 = 52.6%) were associated with an increased risk of ICU admission. Most estimates showed significant heterogeneity with I^2 of >50%.

Conclusion: Multiple patient and operative characteristics confer increased risk for unplanned ICU admission following hip or knee arthroplasty and can be used as markers of elevated perioperative risk facilitating optimal clinical decision making and guiding informed consent.

Keywords: intensive care unit, critical care, risk factors, hip arthroplasty, knee arthroplasty

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- CAD-coronary artery disease
- CCF-congestive cardiac failure
- CCI-Charlson comorbidity index
- COPD-chronic obstructive pulmonary disease
- CRP-C - reactive protein
- GA- general anaesthesia
- ICED-Index of Coexistent Disease
- ICU-Intensive care unit
- OA-osteo arthritis
- PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- USA-United States of America

Draft Article

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Introduction

Global population growth is expected to see a steady increase over the next decade with the elderly population group expected to account for the most significant proportional increase in numbers leading up to the year 2030.[1] The burden of chronic non-communicable diseases, including musculoskeletal conditions, is expected to increase with the change in global population demographics leading to a greater demand for hip and knee arthroplasty surgery.[2]

As such, there are certain groups of patients that are at increased risk of developing perioperative complications which might necessitate postoperative admission to an intensive care unit (ICU).[3] ICU's have a limited number of beds and unplanned admissions, which are potentially preventable, can lead to bed shortages. They are highly specialised and thus translates into higher costs and greater financial strain on any healthcare system. Due to the life-threatening nature of the underlying acute and chronic conditions, unplanned postoperative admissions to ICU are often associated with poorer outcomes.[4] Given the implications of unplanned ICU admission on patient outcomes and healthcare resource utilisation, there is growing interest in the importance of preoperative screening to identify patients at higher risk of requiring unplanned ICU care postoperatively.

This can be achieved through risk stratification and prediction of the probability of a particular outcome of interest by quantifying the combined effects of risk factors and protective factors within a specific patient.[5] We sought to assess risk factors associated with unplanned ICU admission following hip and knee arthroplasty by conducting a systematic review of the published literature.

Methods

Registration and reporting:

This systematic review was registered with PROSPERO (registration CRD42020181580). This systematic review adheres to the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[6]

Literature search:

We searched three electronic databases: PubMed, Cochrane Library and Scopus. The process of database searching was performed independently by two authors and included all papers published from the inception of these databases until the 3rd of December 2021. Search strategies for the respective databases are outlined in Supplementary Table 1. The search strategy used was based on the following PECO structure: Population – Hip or knee arthroplasty patients, Exposure – Various risk factors, Control – (not applicable for epidemiological systematic reviews such as this one), Outcome – ICU admission. The results of the electronic database search were independently screened by two authors. Where there was a disagreement during the screening process, a third author was consulted to resolve the disagreement. We used the following inclusion criteria for manuscripts to be included in the final systematic review: Cohort or case control study of postoperative outcomes in hip/knee arthroplasty patients, ICU admission listed as primary study outcome. Our exclusion criteria were duplicate studies, studies not reported in English, studies lacking relevant multivariate/adjusted statistical comparisons performed which identified factors associated with admission to ICU. We also performed a search of the reference lists of eligible manuscripts to identify additional, relevant manuscripts which might have been missed during the electronic search.

Data Collection:

All eligible manuscripts were reviewed, and extracted information such as study author, year, country where study was done, surgery type, patient characteristics, unplanned ICU admission rate, and reported risk factors for ICU admission were collected. The data collection was done using a Microsoft Excel spreadsheet.

Quality Assessment:

The Newcastle-Ottawa scale was applied to our identified eligible papers in order to assess the quality of each individual study.[7] A score of 7 or more points was used to identify good quality studies.[7] The Newcastle-Ottawa scale was applied independently by 2 reviewers with disputes resolved with the input of the other reviewers. All eligible studies were included in our final systematic review, irrespective of their quality assessment finding.

Data Analysis:

Due to the heterogeneity clinically, by study design and statistically, random effects estimates were reported. Extracted data were used to calculate a pooled rate of unplanned ICU admission (95% CI). The presence of statistical heterogeneity of outcomes across trials was assessed using the I^2 measure and I^2>40% indicated substantial heterogeneity.

A meta-analysis was performed using Stata/SE 15 statistical software (Copyright 1985–2013 Stata Corp LP Statistics/Data Analysis Stata Corp 4905 Lakeway Drive Special Edition College Station, Texas 77845 USA 800–STATA–PC http://www.stata.com, stata@stata.com).

Ethical Considerations:

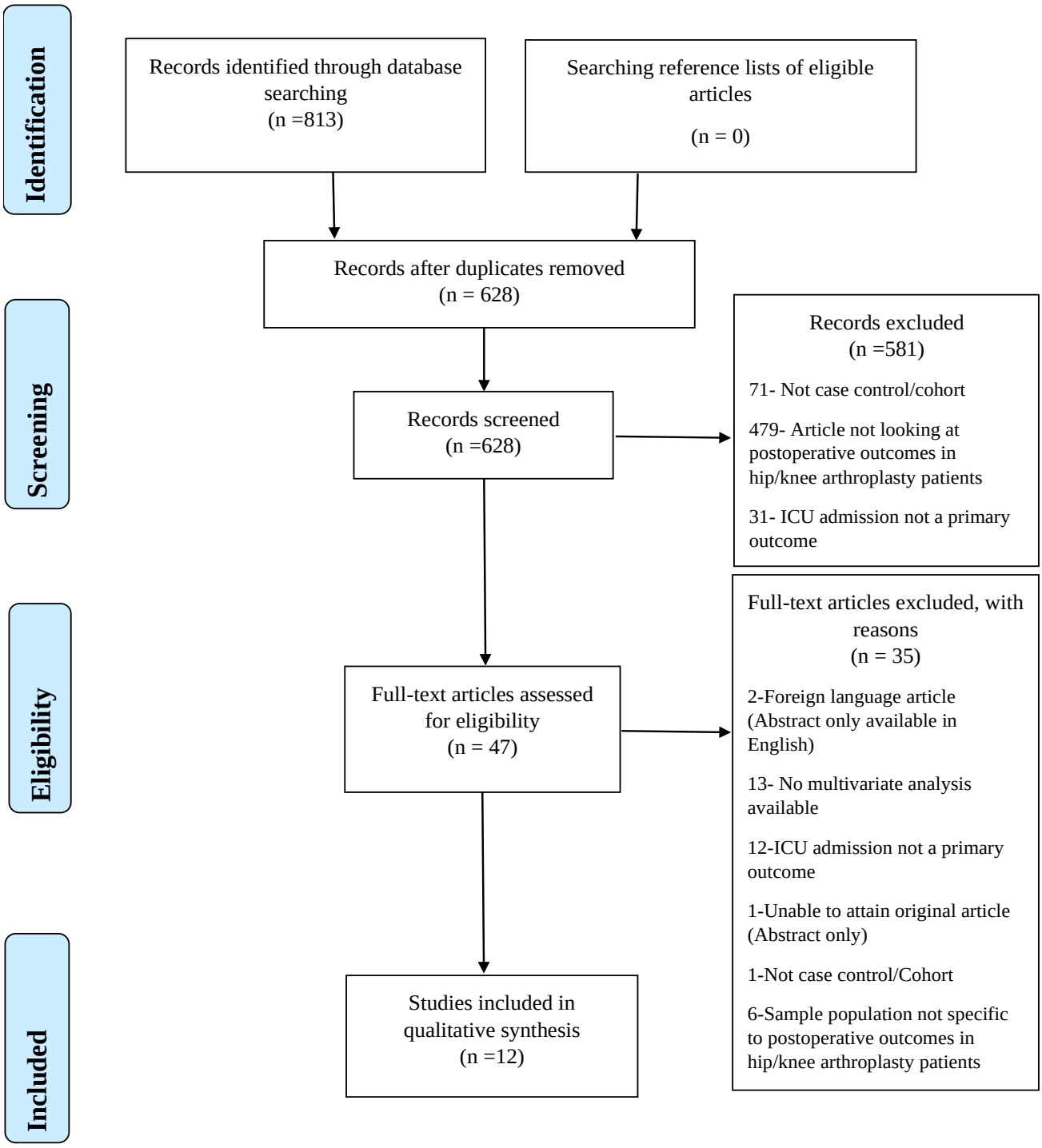
A human research ethics waiver for this research was obtained from the University of the Witwatersrand, South Africa (Protocol W-CBP-210202-01).

Results

The electronic database search from the PubMed, Cochrane and Scopus databases yielded a total of 813 articles. The search strategy is outlined in Supplementary Table 1. The PRISMA flow diagram showing each stage of the systematic review search and screening process is shown in Figure 1. A total of 185 of these articles were duplicates and were subsequently removed leaving a total of 628 articles.

Abstract screening of the remaining 628 articles was done and after application of the predetermined inclusion/exclusion criteria, a total of 47 articles were selected to undergo a full-text review. Reasons for the exclusion of articles from the 628 that were reviewed are depicted in the flow diagram (Figure 1).

Figure 1. PRISMA flow diagram



A total of 12 articles remained at the end of the full article screening process (Table 1). The reference lists of the remaining articles were screened, with the intention of identifying any articles that may warrant inclusion into our systematic review. This screening process failed

to add any further articles for inclusion in the review. The total number of articles included in our systematic review thus amounted to a total of 12 articles.[8-19]

The characteristics of all included studies is shown in Table 1. From the 12 articles included: 3 studies (25%) investigated knee arthroplasty only;[9, 16, 18] 1 study (8.3%) investigated hip arthroplasty only;[17] 8 studies (66.7%) investigated both knee and hip arthroplasty.[8, 10-15, 19] The bulk of these studies, 8 out of the 12, were conducted in the United States of America.[8-14, 19] Most of the studies (11 out of the 12) included in this review were retrospective by design.[8-10, 12-19] Only one study was conducted prospectively.[11] There were 2 case-control studies,[8, 13] and 10 cohort studies.[9-12, 14-19]

The Newcastle-Ottawa scale was used to assess the quality of our studies (Table 1). Nine of the twelve papers were considered "good" quality studies by this assessment.[8, 10-12, 14-16, 18, 19]

Table 1: Characteristics of the 12 studies included in the systematic review

Author (Year)	Country	Study Design	Type of Surgery (Hip, Knee, Both)	Proportion of patients admitted to ICU	Sample size	Newcastle-Ottawa Scale (Good quality study = Yes/No)
Abdel Salam et al. (2012)	USA	Retrospective Case-control	Both	0.6 %	22343	8 (Yes)
Brown et al. (2012)	USA	Retrospective Cohort	Knee	1.18 %	2758	6 (No)
Courtney et al. (2014)	USA	Retrospective Cohort	Both	4.2 %	1594	7 (Yes)
Courtney et al. (2015)	USA	Prospective Cohort	Both	6.7%	738	8 (Yes)
Memtsoudis et al. (2012)	USA	Retrospective Cohort	Both	3 %	528495	7 (Yes)
Memtsoudis et al. (2014)	USA	Retrospective Cohort	Both	7.61 %	795135	8 (Yes)
Memtsoudis et al. (2014)	USA	Retrospective Case-control	Both	3.27 %	530089	5 (No)
Møller et al. (2003)	Denmark	Retrospective Cohort	Both	1.6 %	811	9 (Yes)
Peskun et al. (2011)	Canada	Retrospective Cohort	Knee	8.65 %	312	8 (Yes)
Zhang et al. (2017)	China	Retrospective Cohort	Hip	13.82 %	304	6 (No)
Klausing et al. (2019)	Germany	Retrospective Cohort	Knee	8.6%	649	8(Yes)
Sukhonthamarn et al. (2020)	USA	Retrospective Cohort	Both	1.05%	23318	7(Yes)

ICU, intensive care unit; USA, United States of America

The ICU admission rate amongst included studies ranged from 0.6% to 13.8%. The pooled rate of admission was 4.55%, 95% CI 3.04 – 6.05 (Figure 2). The estimates were statistically heterogeneous with an I^2 =100%.

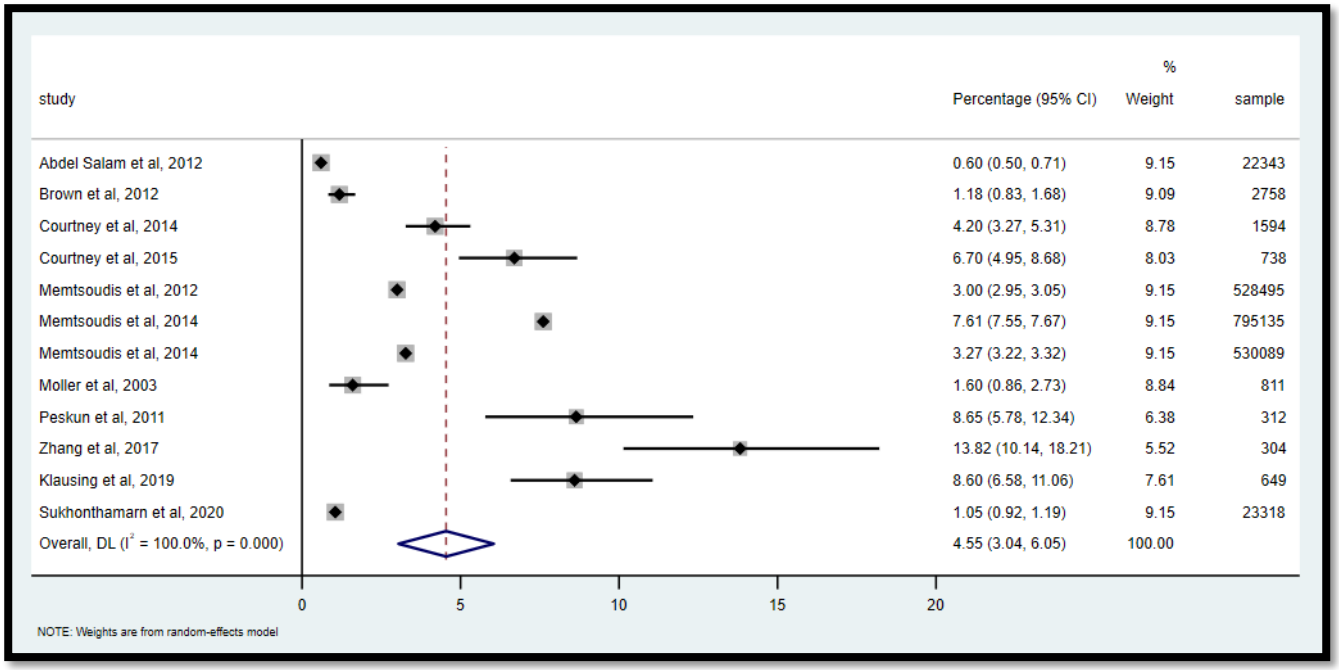
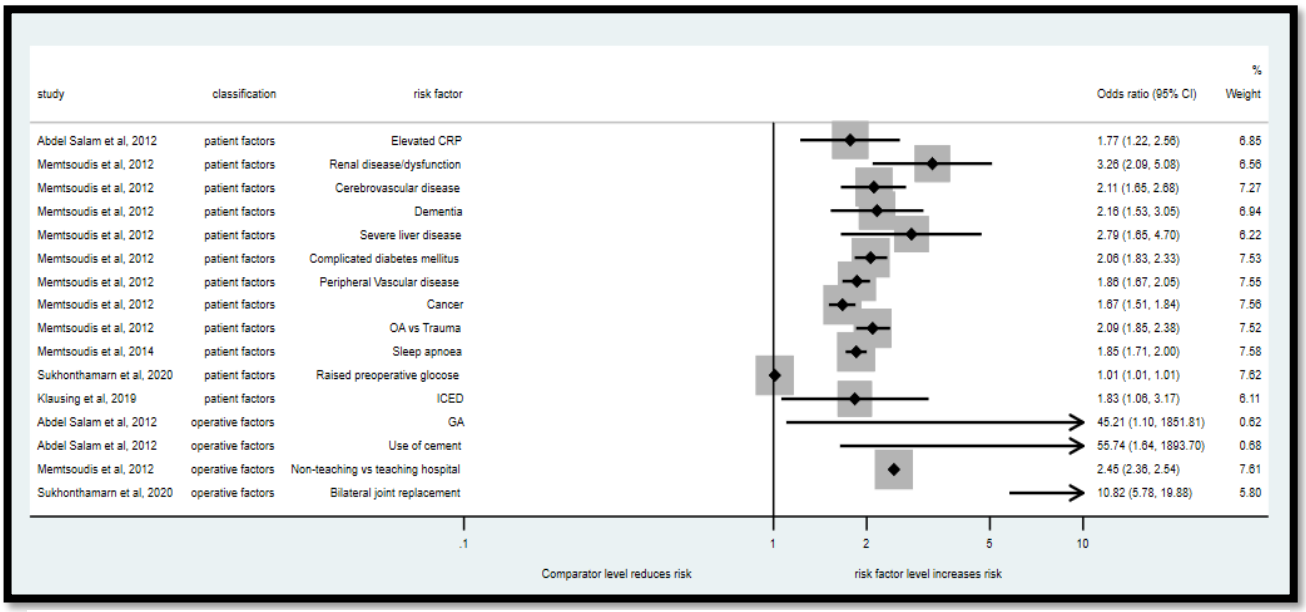


Figure 2: Proportion of patients admitted to ICU

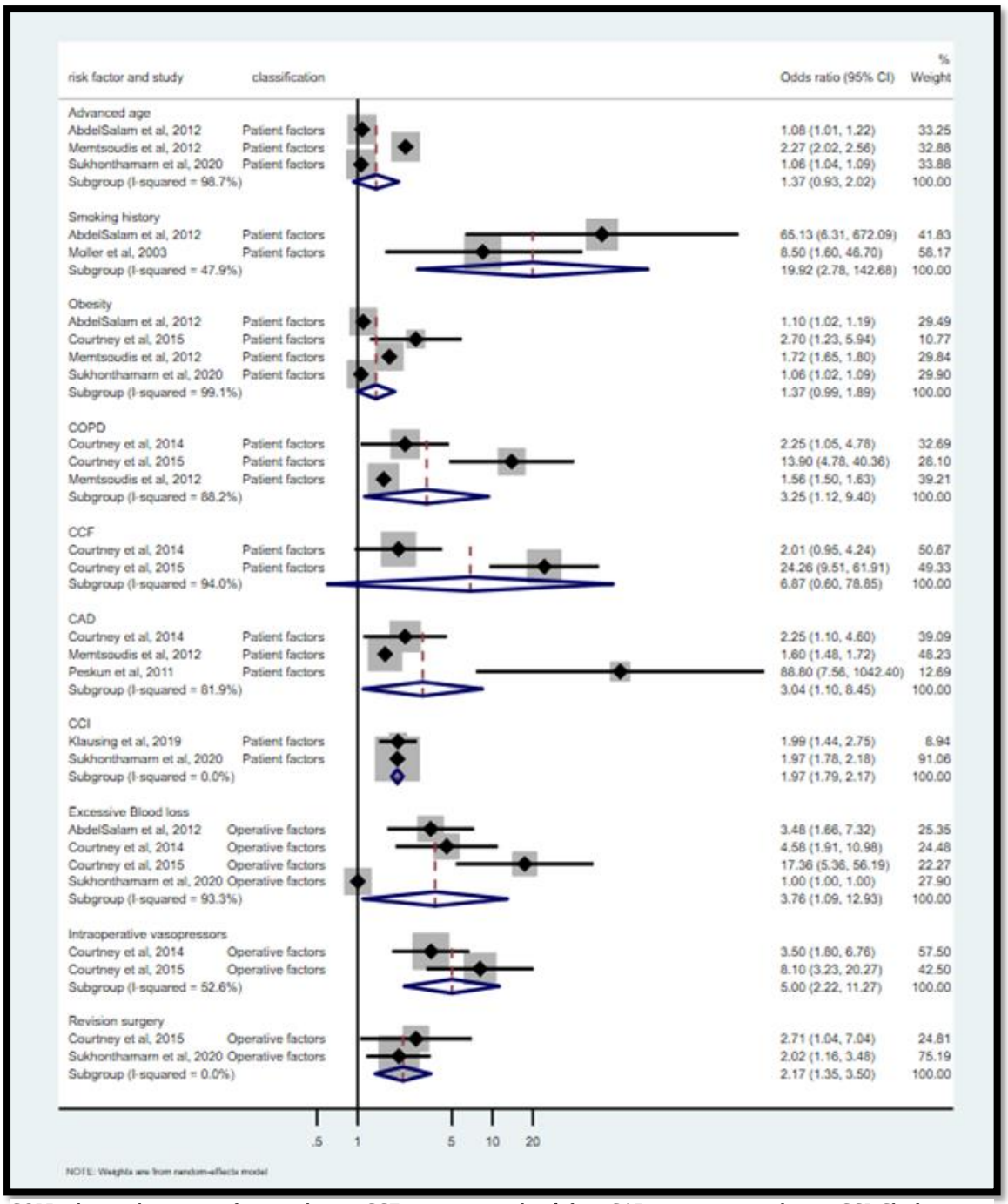
Several risk factors were reported singly and predominantly by one author. They are represented in Figure 3. These risk factors were classified into patient and operative factors. They included factors of organ dysfunction such as cerebrovascular disease, peripheral vascular disease, severe liver disease, renal disease, sleep apnoea, cancer, and diabetes mellitus. An elevated preoperative glucose level and index of coexistent disease score were also identified. The operative factors included surgical risks such as bilateral joint replacement, use of cement and type of anaesthesia. A study by Brown et al. was excluded from the forest plot in Figure 3 due to absence of CI [reported OR 7.2].



CRP, C - reactive protein; OA, Osteo Arthritis; GA, General Anaesthesia; ICED, Index of Coexistent Disease

Figure 3: Individual risk factor profiles

A meta-analysis of risk factors is represented in Figure 4. Estimates of smoking history (OR 19.92, 95% CI 2.78 - 142.68, I^2 = 47.9%), COPD (OR 3.25 95% CI 1.12 – 9.40, I^2 = 88.2%), CAD **(**OR 3.04, 95% CI 1.10 – 8.45, I^2 = 81.9%), Charlson comorbidity index (OR 1.97 95% CI 1.79 – 2.17, I^2 = 0%), excessive blood loss (OR 3.76, 95% CI 1.09 – 12. 93, I^2 = 93.3%), revision surgery (OR 2.17, 95% CI 1.35 – 3.50, I^2 = 0%) and use of vasopressors **(**OR 5.00, 95% CI 2.22 – 11.27, I^2 = 52.6%) were associated with the risk of admission to ICU. Most estimates showed significant heterogeneity with I^2 of >40%. The study by Peskun et al. was excluded from the forest plot because their reported OR (7.1) was outside of their 95% CI of 0.02 – 0.96. The study by Sukhonthamarn et al. presented data separately for both knee and hip risk factors. Given the similarity and closeness of the adjusted odds ratio estimates for both fields, I have decided to use one of the estimates instead to represent the risk factors for knee and hip associated risk factors.



COPD, chronic obstructive pulmonary disease; CCF, congestive cardiac failure; CAD, coronary artery disease; CCI, Charlson comorbidity index

Figure 4: A meta-analysis of risk factor profiles

Discussion

The studies included in this review differed greatly with regards to their study designs. Variations were noted with regards to the study design, methods of data collection, retrospective vs. prospective nature of the studies and population under review (hip and knee arthroplasty vs. knee or hip arthroplasty alone). The 3 largest studies included in our review, with regards to weight, were retrospective cohort studies utilising data derived from the Premier database.[12-14]

The ICU utilisation rate differed greatly amongst the studies included in this review. The pooled ICU admission rate from all included studies was 4.55%. This equates to more than 1 ICU admission for every 21 procedures completed and highlights the importance of considering critical care services in the perioperative period as a finite resource which needs to be managed in a systematic and objective manner. In healthcare settings, that are resource constraint, this becomes more pertinent as access to critical care becomes more difficult due to limited capacity and the diversion of ICU resources to more urgent needs and away from elective based procedures such as arthroplasty surgery.

We have identified 27 different factors in total, a combination of patient and operative risk factors, each occurring with varying frequency amongst the 12 studies in this review. Patient related risk factors are those which may be identified in the preoperative period and relate to the patient's general physiological status.[20] They encompass comorbid conditions and as such, allow for preoperative planning, optimisation and potential risk reduction. Patient related factors can be obtained in the preoperative period using history taking and special investigations as required.[21]

Among these patient estimates, we found that COPD, CAD, history of smoking, and a raised Charlson comorbidity index score were associated with the risk of admission to ICU. COPD and CAD have been shown to be associated with increased perioperative morbidity in other noncardiac surgery populations,[22, 23] and it is unsurprising that this also holds true for unplanned ICU admission in patients undergoing hip or knee arthroplasty.

The primary mechanism through which COPD increases the risk of ICU admission is respiratory failure and the need for mechanical ventilation.[24, 25] An existing history of CAD

may predispose a patient to an acute cardiovascular event during the period.[23] Indeed, a prior history of CAD is cited as one of the risk factors for noncardiac surgery patients.[23] There might indeed be an overlap between smoking and COPD in the pathophysiological mechanism for most of the acute perioperative illness, as both are closely linked.[26]

It is possible that those with extremes of age, obesity and congestive cardiac failure are admitted to ICU electively and hence are not found to be risk factors for unplanned ICU admission. Older age and obesity are both associated with an increase in comorbid conditions. These comorbidities may display varying degrees of severity and end organ damage.[27, 28] The finding for obesity is interesting, given the increasing levels of obesity worldwide and the high obesity rates in patients who have limited mobility such as those with osteoarthritis or osteonecrosis.[29]

The remaining patient specific risk factors identified in our review were identified just once amongst the 12 included studies. These were an elevated preoperative CRP and glucose level, renal disease, cerebrovascular disease, dementia, severe liver disease, complicated diabetes mellitus, peripheral vascular disease, cancer, osteoarthritis related to trauma and a raised index of coexistent disease score. Although these risk factors might appear less important (due to the number of studies which have cited them), they nevertheless may still have a role in a weighted risk stratification model for unplanned ICU admission following hip or knee arthroplasty.

Intraoperative events are often difficult to predict however early recognition and timeous intervention may allow for more favourable outcomes. Estimates of significant intraoperative haemorrhage were a significant risk factor for unplanned ICU admission. Bleeding results in hypovolemia and organ hypoperfusion with an accompanied decrease in oxygen delivery at a microcirculatory level.[30] Significant haemorrhage may necessitate the transfusion of blood products however this process is not innocuous and may result in further complications.[31]

Revision surgery is characterised by increased levels of technical difficulty, duration of surgery and bleeding.[32] Revision arthroplasty has been shown to demonstrate raised levels of noteworthy perioperative complications such as venous thromboembolic disease, sepsis and mortality.[33, 34]

The use of intraoperative vasopressors is indicated during hemodynamic instability. It was found to be significantly associated with unplanned ICU admission. Vasopressor use and hypotension are well established components of many critical care scoring systems.[35]

There were 4 other operative related risk factors identified, each only cited once amongst the articles in this review. These included the use of bone cement, total knee arthroplasty compared to uni-compartmental knee arthroplasty, bilateral joint replacement in a single sitting and if the procedure was done at a non-academic institute as opposed to being done at an academic one. These may reflect differences in surgical skill and increased surgical cutting times which may have resulted in increased blood loss or greater levels of physiological derangement perioperatively.

The 27 risk factors highlighted in our review show that both patient and operative risk factors are important when assessing the need for ICU. This also highlights the importance of considering the multifactorial nature of unplanned ICU admissions following lower limb arthroplasty. Thus, it indicates that the development of a multifactorial risk stratification model for unplanned ICU admission would be feasible. Most of the patient related factors identified in this review are comorbidities and are thus potentially modifiable through timely preoperative diagnosis and optimization of the patient. Similarly, most of the operative factors are also potentially modifiable through improved surgical technique or the use of minimally invasive approaches where possible. Some factors are not modifiable (for example older age) and cannot be optimized. Rather, these non-modifiable risk factors serve as markers for elevated risk and improve perioperative risk communication during the preoperative informed consent process.

There were limitations to this systematic review. Only three databases were utilised for this review as these were accessible to us through our institution. These were PubMed, Cochrane and Scopus. We do feel that these were adequate for the purpose of our review. The limited number of included studies and the heterogeneity amongst these included studies highlights the paucity of available data with regards to our topic. The studies included in our review originate from highly industrialised and developed countries which may limit the application of the findings of this review in resource constrained settings and their respective populations

Conclusion

Our review has identified several patient and operative characteristics as key potential risk factors for unplanned ICU admission following hip or knee arthroplasty. We confirm the multifactorial nature of unplanned ICU admission. Modifiable risk factors can be optimized to reduce the risk of ICU admission. Non-modifiable risk factors can be used as markers of elevated risk, and to communicate perioperative risk to patients during the preoperative informed consent process. Our research supports the development of a weighted multifactorial risk prediction tool to reduce unplanned ICU admission rates. We recommend that further prospective research be conducted to strengthen the knowledge base around risk factors for ICU admission following hip or knee arthroplasty

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APPENDICES

Appendix 1: Supplementary Table 1: Database search strategy

Database	Query	MeSH term/Phrases
PubMed	Population	Arthroplasty, Replacement, Hip [MeSH]; Hip Prosthesis [MeSH]; Hip Arthroplast* [Title/Abstract]; Hip Hemiarthroplast* [Title/Abstract]; Hip replacement* [Title/Abstract]; Hip repair* [Title/Abstract]; Hip prosthes*[Title/Abstract]; Hip implant*[Title/Abstract]; Hip hemi-arthroplast* [Title/Abstract]; Hip hemi arthroplast*[Title/Abstract]; Hip surger* [Title/Abstract]; Arthroplasty, Replacement, Knee [MeSH]; Knee Prosthesis [MeSH]; Knee Arthroplast* [Title/Abstract]; Knee Hemiarthroplast* [Title/Abstract]; Knee replacement* [Title/Abstract]; Knee repair* [Title/Abstract]; Knee prosthes* [Title/Abstract]; Knee implant* [Title/Abstract]; Knee hemi-arthroplast* [Title/Abstract]; Knee hemi arthroplast* [Title/Abstract]; Knee surger* [Title/Abstract].
	Exposure	Risk [MeSH]; Risk factors [MeSH]; Odds Ratio [MeSH]; Risk* [Title/Abstract]; Odd* [Title/Abstract]; Hazard* [Title/Abstract]; Predict* [Title/Abstract]; Likel* [Title/Abstract]; Factor* [Title/Abstract]; Associat* [Title/Abstract]; Increas* [Title/Abstract]; High* [Title/Abstract]; Event* [Title/Abstract].
	Outcome	Critical Care [MeSH]; Intensive care units [MeSH]; Critical illness [MeSH]; Catastrophic illness [MeSH]; Critical care* [Title/Abstract]; ICU [Title/Abstract]; Critical Care unit [Title/Abstract]; CCU [Title/Abstract]; High care* [Title/Abstract]; High Dependency Unit [Title/Abstract]; Acute illness [Title/Abstract]; Critical illness* [Title/Abstract]; Intensive care* [Title/Abstract]; Catastrophic illness* [Title/Abstract].
Scopus	All	Searched using phrases as outlined in PubMed search (No MeSH search function in Scopus database)
Cochrane	All	Searched using phrases as outlined in PubMed search (No MeSH search function in Cochrane database)

Appendix 2: Ethics waiver certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

02/02/2021

Ref: W-CBP-210202-01

TO WHOM IT MAY CONCERN

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)

Investigator: Drs M, P & Y Makda, Motshabi & Moodley
Student No. (if appropriate): 352182
Staff No. (if appropriate):

Supervisor: Dr N Biyase

School: Clinical Medicine
Department: Anaesthesiology
Medical School
University

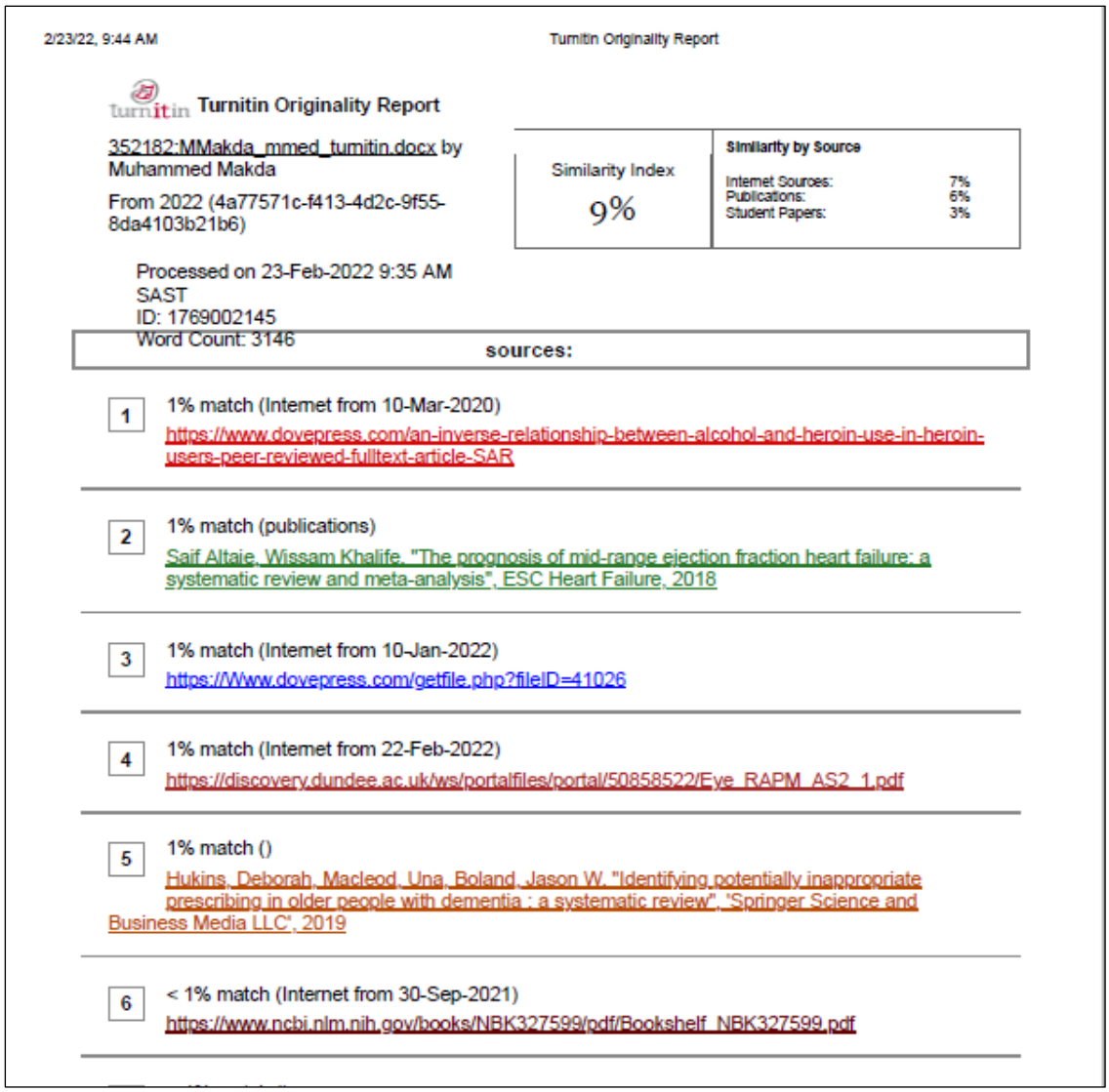
Project title: *Risk factors associated with unplanned ICU admission following hip or knee arthoplasty: a systematic review*

Reason: Review of information in the public domain
No human participants will be involved in the study

Dr CB Penny
Chairperson: Human Research Ethics Committee (Medical)

Research Office Secretariat:
Third Floor, Phillip Tobias Building, corner of St Andrews and York Roads, Parktown, Johannesburg 2193
Postal address: Private Bag 3, Wits 2050
Tel Nos: +27 (0)11 717 1234/1252/2656/2700
Office E-mail: HREC-Medical.ResearchOffice@wits.ac.za
Website:
https://www.wits.ac.za/research/researcher-support/research-ethics/ethics-committees/

Appendix 3: Plagiarism/ turnitin report cover page



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Hukins, Deborah, Macleod, Una, Boland, Jason W, "Identifying potentially inappropriate prescribing in older people with dementia : a systematic review", 'Springer Science and Business Media LLC', 2019

6 < 1% match (Internet from 30-Sep-2021)
https://www.ncbi.nlm.nih.gov/books/NBK327599/pdf/Bookshelf_NBK327599.pdf

Appendix 4: PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page: 1,5
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page: 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page:14
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page:14
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page:15
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page:15
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page:15,29
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page:15
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page:15
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page:15
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page:15,16, 19,20
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page:15
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page:18,19, 20
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page:15,16, 17
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page:16,18, 19,20
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page:16,18, 19,20
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of	Page:16,20, 21

Section and Topic	Item #	Checklist item	Location where item is reported
		statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page:16,20, 21
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page:16,20, 21
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page:16,20, 21
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page:16,20, 21
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page:17
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page:17
Study characteristics	17	Cite each included study and present its characteristics.	Page:17,18
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page:18
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page:18,19, 20
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page:17,18, 19,20
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page:20,21
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page:18,19, 20,21
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page:20,21
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page:19,20, 21
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page:19,20, 21
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page:21,22, 23,24
	23b	Discuss any limitations of the evidence included in the review.	Page:24
	23c	Discuss any limitations of the review processes used.	Page:24
	23d	Discuss implications of the results for practice, policy, and future research.	Page:23,24, 25
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page:14
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page:38
	24c	Describe and explain any amendments to information provided at	Page: N/A

Section and Topic	Item #	Checklist item	Location where item is reported
		registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page:13
Competing interests	26	Declare any competing interests of review authors.	Page:13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	On request from author

Appendix 5: Newcastle – Ottawa Quality assessment scale

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Appendix 6: Protocol

Risk factors associated with unplanned ICU admission following hip or knee arthroplasty: a systematic review

MMed Protocol

Student name: Muhammed Makda

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Co-supervisor:	Dr Palesa Motshabi Palesa.Motshabi@wits.ac.za Department of Anaesthesiology (WITS)
Co-investigator:	Dr Yoshan Moodley Yoshan.Moodley@wits.ac.za Department of Anaesthesiology (WITS)

Background:

In 2015 the number of people in the world aged 60 years or older approximated over 900 million people(1). By 2030 it is estimated that this number will rise to approximately 1.4 billion people. The eldelrly segment of our population is expected to show the greatest proportional increase in numbers leading up to year 2030 (1). As the population ages, we are likely to see an increase in the burden of chronic non-communicable diseases such as hypertension, diabetes and osteoarthritis. Population growth coupled with the relative increase in the elderly component of the population is likely to place a strain on existing healthcare systems, including an expected increase in the burden of musculoskeletal conditions.

The World Health Organization (WHO) has come to recognise the impact that musculoskeletal conditions place on society and individuals (2). According to statistics gathered by the WHO, musculoskeletal conditions account for a large and ever increasing proportion of the global health disease burden. According to the WHO data, musculoskeletal conditions accounted for 13% of the total global burden of disease in 2016 (2).

Various disease processes contribute towards the need for hip or knee arthroplasty however osteoarthritis accounts for the bulk of the contribution (3, 4). The earliest attempts at major joint arthroplasty began in Germany in the 1890's and has progressed substantially over the past century. It is currently viewed as one of the most succesful interventions in the field of orthopaedic surgery (5). Arthroplasty involves the process of replacing the native joint and its articular surfaces, which have been worn down by various inflammatory processes. The damaged joint is replaced with an artificial prosthesis (6).

Indications for hip or knee arthroplasty include pain, functional impairment and significant deformity, however guidelines and practices differ around the world. The decision to proceed to surgery is generally made following a trial of conservative therapy. According to a systematic review conducted in 2016, there exisits a common consensus around the world with regards to the indications for hip or knee arthroplasty however the time allowed for alternative modalities varies around the world evident by varying degrees of disease severity at the time of surgery (7). The systematic review also notes the influence of the

surgeon's attitude towards arthroplasty with higher procedural rates among surgeons with more favorable views towards surgical intervention (7).

The conservative or non operative alternatives to arthroplasty include physical therapy, adequate pain control, assistive or orthotic devices and weight reduction. The conservative approach aims to reduce the mechanical forces acting on the articular surfaces of the joint and thus slow the destructive wear and tear on the joint and allow for joint regeneration and healing. A symptomatic approach to pain is taken with paracetamol, nonsteroidal anti-inflammatory drugs and opioid agents. Other pharmacological agents include hyaluronic acid and corticosterioid injections. With progression to advanced disease, medical management alone may not be sufficient to treat patients. In such cases surgical intervention is warranted. As disease severity progressively worsens, the expected surgical outcomes are less favourable (8).

There are established risks associated with arthroplasty such as bleeding, cardiac and pulmonary complications as well as thromboembolic events(9). One of the more notable complications following arthroplasty is that of an unplanned admission to an intensive care unit following surgery.

A study conducted by Memtsoudis et al showed that 1 in 30 patients undergoing hip or knee arthroplasties required postoperative critical care services. This retrospective study included a cohort of 528 495 patients over a 5 year period and translated into an ICU admission rate of 3% following surgery(10). Furthermore this study showed that patients who required critical care services postoperatively had a greater median length of stay,a higher average cost per stay and an increased rate of complications. One of the more significant findings to come out of this study was the 30 day mortality rate. Higher mortality rates were noted in patients that required critical care services following surgery with a 30 day mortality rate of 2.5%. Patients whom did not require critical care services showed a 30 day mortality rate of 0.1% (10). A retrospective study by Kamath et al, involving a cohort of 1259 patients, showed that 7.1% of patients experienced unplanned ICU admissions following hip or knee arthroplasty(11). A study looking only at hip arthroplasty procedures showed unplanned ICU admission rates of 4% for unilateral total hip arthroplasty and 12% for bilateral hip arthroplasty(12). Despite the wide variation in reported results it is reasonable to conclude that an unplanned ICU admission following any elective procedure is a complication which

carries increased morbidity,mortality and costs to patient care. It is also reasonable to conclude that this complication is one that can be mitigated against by means of an evidence based analytical approach and the use of risk stratification tools preoperatively so as to identify patients which are likely to need critical care services postoperatively.

Risk stratification can be useful in identifying patients that are at risk of unplanned ICU admission, which can sometimes be associated with increased mortality. This has various implications, such as improving the informed consent process by advising patients who are at high risk or allowing physicians and surgeons to anticipate ICU requirements (which is a scarce resource in all hospitals) and plan in advance methods to mitigate this risk or secure a bed in the intensive care unit if need be. Risk stratification within the sphere of healthcare involves designing a tool or scoring system which identifies patients which are at a high risk for potential adverse outcomes and optimising their management and care to minimise the risk of events. Within the field of perioperative care there exists various risk stratification tools that anaesthesiologists have come to rely on to guide their decision making processes during patient assesments. A widely used risk stratification tool used by anaesthesiologists is the American Society of Anesthesiologists Physical Status score (ASA-PS). Other validated risk stratification tools within the field of anaesthesiology include Lee's Revised Cardiac Risk Index (RCRI), the Charlson Index and the POSSUM (Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity) scoring systems (13). When assessing patients presenting for hip or knee arthroplasty, there is no universally accepted and validated risk stratification tool which can be used to predict unplanned ICU admissions following surgery. For joint replacement surgery, the ideal clinical risk scoring system should aim to identify patients at risk for adverse postoperative events and should be objective, accurate, easy to perform and economical (13).

A search of the literature shows various studies reporting multiple varied risk factors which may be associated with an unplanned ICU admssion following hip or knee arthroplasty. A retrospective review by Kamath et al was done over a two-year period and 1259 hip arthroplasty cases were identified. A total of 89 patients were identified as unplanned ICU admissions equating to 7.1%. The initial univariate analysis identified nine factors which were statistically significant risk factors for an unplanned ICU admission. These included intraoperative use of vasopressors, intraoperative need for blood transfusions, patients

classified according to the American Society of Anesthesiologists (ASA) class 3 or above, revision surgery, creatinine clearance below 60 mL/min, prior myocardial infarction, an increased body mass index(BMI) of greater than 35 kg/m^2, diagnosed obstructive sleep apnoea and patients aged 75 years and above(11).

A study by AbdelSalam et al involved a retrospective review of cases over an 8 year period looking at independent risk factors associated with ICU admissions in hip and knee athroplasty surgeries. Over 22 000 cases were reviewed and the cases admitted to ICU were studied and compared to a control group not admitted to ICU at a 1:2 ratio. Findings from this study showed that cemented arthroplasty, general anesthesia, intraoperative blood transfusion, elavated preoperative CRP levels, decreased preoperative heamoglobin levels, an increased BMI, cigarette smoking and older age were risk factors for ICU admission following hip or knee arthroplasty(14).

A more recent study conducted by Sukhonthamarn et al identified different independent risk factors for hip and knee arthroplasty. This study divided hip and knee arthroplasties into individual catergories and looked at risk factors associated with each type of surgery. For both hip and knee arthroplasty, identified risk factors for an unplanned postoperative ICU admission included advanced age, revision procedures, bilateral procedures, general anaesthesia, an increased Charlson comorbidity index, increased estimated blood loss and an elevated preoperative blood glucose level. A unique risk factor identified with regards to hip arthroplasty was that of a lower preoperative heamoglobin level while a unique risk factor identified with regards to knee arthroplasty was that of an elavated BMI(9).

Although there are clinical prediction rules and observational studies from around the world which have investigated risk factors for unplanned ICU admission following hip or knee arthroplasty, it should be noted that there are differences between the studies in terms of identifed risk factors. A systematic review seeks to consolidate the data available in the literature and identify common risk factors across various studies. This information would be useful reference material in instances where prospective studies of new risk stratification models for unplanned ICU admission in hip and knee arthroplasty patients are proposed. The information collected from a systematic review may also be used to create a risk stratification tool which can be used to decrease future occurances of unplanned ICU admissions.

Research question:

What are the risk factors associated with unplanned admission to an intensive care unit following hip or knee arthroplasty? The research question was developed using the patient-exposure-control-outcome (PECO) framework as follows:

P – Hip or knee arthroplasty patients

E – Various risk factors

C – Control (not applicable for epidemiological systematic reviews such as this one)

O – ICU admission

Aim:

- To investigate, by means of a systematic review, risk factors associated with unplanned ICU admissions post arthroplasty surgery.

Objective:

- To describe variables associated with an increased risk of an unplanned ICU admission following hip or knee arthroplasty.

Methodology

Study design:

The design of this project will be a qualitative systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and PRISMA checklist will be used to plan and conduct this systematic review. The design of this may produce a quantitative meta-analysis depending on the data collected.

Study setting:

Not applicable as this will be a systematic review of the published literature.

Study population:

The population reviewed will include patients undergoing hip or knee arthroplasty surgeries.

Search strategy and study selection:

The PubMed, Cochrane and Scopus electronic medical literature databases will be searched until the end of October 2019 using a structured search strategy (Appendix 1). Titles and abstracts will be scanned and full-text articles independently retrieved by two reviewers. Relevant citations will be selected and disputes resolved by consensus. A third reviewer will oversee the process. The search strategy was developed using the PECO (population-exposure-control-outcome) framework. Once an electronic literature search has been conducted, the inclusion and exclusion criteria, tabulated below, will be applied.

Inclusion criteria	Exclusion criteria
• Published full/original research manuscripts • Cohort and case-control studies reporting postoperative outcomes in hip or knee arthroplasty patients • Admission to intensive care unit is the primary study outcome	• Duplicate studies • No relevant multivariate/adjusted statistical comparisons performed which identify factors associated with admission to intensive care unit (i.e. Risk estimate – odds, hazard, or risk ratio and p-value) • Not English language

A finite number of studies applicable to the review will then be identified. A manual search of the reference lists of these applicable articles will then be screened for additional research studies.

Data extraction and quality assessment:

A review of the entire text of each of these studies will be conducted and the relevant information extracted will be captured onto a Microsoft Excel spreadsheet. The following information from each applicable study will be collected: authors, year of publication, country where study was conducted, patient population (hip or knee arthroplasty patients or both), patient age, patient gender, proportion of patients admitted to ICU and factors associated with ICU admission(Appendix 2). The process of data extraction will follow the steps set out by the PRISMA guidelines and will follow the PRISMA flow diagram (Appendix 3)

The Newcastle-Ottawa Scale will be applied to assess the quality of each study (Appendix 4). The information gathered will then be used to create the qualitative synthesis component and discussion section of this systematic review.

Sample size:

All eligible articles will be included in the systematic review. At least 200 articles are expected to be returned from the combined PubMed and Scopus electronic search which will need to be screened for inclusion in the final systematic review.

Data analysis:

Descriptive statistics will be used to present the most common risk factors for ICU admission. Should a meta-analysis be feasible, extracted data from included studies will be used to calculate the mean differences / standardised mean differences for continuous outcomes, odds ratios for binary outcomes, 95% confidence intervals and two-sided p-values for each outcome. A p-value < 0.05 will be considered statistically significant. The presence of statistical heterogeneity of outcomes across trials will be assessed using the I2

measure, and I2>50% when p<0.10 indicates substantial heterogeneity. Trials with significant heterogeneity will be reported as standardised mean differences and those with insignificant heterogeneity as mean differences. Overall effects in studies with significant heterogeneity will be reported as random effects and those with insignificant heterogeneity as fixed effects. A meta-analysis will be performed with the assistance of a biostatistician using the RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) statistical software. These data analysis methods are conventionally used in meta-analysis.

Limitations and bias:

- The study will only include published manuscripts and will not include unpublished or grey literature. This might be a source of bias in the study (publication bias).
- The study will only include English language manuscripts, which is also a potential source of bias.
- The study will not include other large databases such as EMBASE. It is likely that the Scopus search will pick up the articles which would also be on EMBASE as both databases are managed by Elsevier Publishers.

Ethics:

This is a systematic review of the published literature. There is no contact with human subjects. This research will be sent as a minimal risk application to the Wits University ethics committee for review. Alternatively, an application for an ethics waiver will be sought from the ethics committee.

Expected outputs:

Once the review is completed it will be submitted to an accredited peer-review medical journal. The anticipated goal of this project is to be accepted for publication as a journal manuscript.

Activity	Sep-Oct	Nov-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun
	2019		2020				2021	
Proposal preparation								
Literature review								
Proposal submission								
Ethics approval								
Postgraduate approval								
Data collection								
Data analysis								
Draft article								
Submission								

Timeline:

This project is expected to be completed by April 2021.

Financial plan:

The only likely expenses may come from the printing of documents or expenditure on internet data.

Budget estimate:

Item	Price per page	Number of pages	Copies	Total
Proposal	1	20	10	R 200
Ethics	1	2	3	R 6
Post graduate form	1	2	6	R 12
Complete report	1	100	4	R 400
Grand total				R 618

References:

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Appendix 1

Population	*Exposure*	*Control*	*Outcome*
"Hip Arthroplast*"	Risk*	Not Applicable	"Critical care*"
"Hip Hemiarthroplast*"	Risk		Critical Care
"Hip replacement*"	Odd*		ICU
"Hip repair*"	Hazard*		Intensive care units
"Hip prosthes*"	Predict*		"Critical Care unit"
"Hip implant*"	Likel*		CCU
"Hip hemi-arthroplast*"	Factor*		"High care*"
"Hip hemi arthroplast*"	Associat*		"High Dependency
"Hip surger*"	Increas*		Unit"
Arthroplasty, Replacement, Hip	High*		"Acute illness"
Hip Prosthesis	Event*		Critical illness
	Risk factors		"Critical illness*"
"Knee Arthroplast*"	Odds Ratio		"Intensive care*"
"Knee Hemiarthroplast*"			Catastrophic illness
"Knee replacement*"			"Catastrophic
"Knee repair*"			illness*"
"Knee prosthes*"			
"Knee implant*"			
"Knee hemi-arthroplast*"			
"Knee hemi arthroplast*"			
"Knee surger*"			
Arthroplasty, Replacement, Knee			
Knee Prosthesis			

Note: All terms in red denote MESH controlled vocabulary terms. Terms not in red will be used for title/abstract search

Search Strategy:

Pubmed= A combination of keywords/phrases (in Title/Abstract) and controlled vocabulary (MeSH) terms will be used to obtain the final search results for each concept.

Population **Keyword/s or Search term/s**			
Note: All terms in red denote MESH controlled vocabulary terms. Terms not in red will be used for title/abstract search			
#1	Arthroplasty, Replacement, Hip	#2	Hip Prosthesis
#3	"Hip Arthroplast*"	#4	"Hip Hemiarthroplast*"
#5	"Hip replacement*"	#6	"Hip repair*"
#7	"Hip prosthes*"	#8	"Hip implant*"
#9	"Hip hemi-arthroplast*"	#10	"Hip hemi arthroplast*"
#11	"Hip surger*"	#12	Knee Prosthesis
#13	Arthroplasty, Replacement, Knee	#14	"Knee Arthroplast*"
#15	"Knee Hemiarthroplast*"	#16	"Knee replacement*"
#17	"Knee repair*"	#18	"Knee prosthes*"
#19	"Knee implant*"	#20	"Knee hemi-arthroplast*"
#21	"Knee hemi arthroplast*"	#22	"Knee surger*"
#23	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR		

	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21OR #22		
Exposure **Keyword/s or Search term/s**			
Note: All terms in red denote MESH controlled vocabulary terms. Terms not in red will be used for title/abstract search			
#24	Odds Ratio	#25	Risk factors
#26	Risk	#27	Risk*
#28	Odds*	#29	Hazard*
#30	Predict*	#31	Likel*
#32	Associat*	#33	Increas*
#34	High*	#35	Event*
#36	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35		
Outcome **Keyword/s or Search term/s**			
Note: All terms in red denote MESH controlled vocabulary terms. Terms not in red will be used for title/abstract search			
#37	catastrophic illness	#38	Critical Care
#39	Intensive care units	#40	“Critical care*”
#41	ICU	#42	“Critical Care unit”
0#43	CCU	#44	“High care”

#45	“High Dependency Unit”	#46	“Acute illness*”
#47	“Catastrophic illness*”	#48	Critical illness
#49	“Intensive care*”	#50	“Critical illness*”
#51	#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50		
Combined search			
#52	#23 AND #36 AND #51		

Scopus = Only phrases (in Title/Abstract/Keywords) will be searched as the database does not have a controlled vocabulary.

Population **Keyword/s or Search term/s**			
#1	"Hip Arthroplast*"	#2	"Hip Hemiarthroplast*"
#3	"Hip replacement*"	#4	"Hip repair*"
#5	"Hip prosthes*"	#6	"Hip implant*"
#7	"Hip hemi-arthroplast*"	#8	"Hip hemi arthroplast*"
#9	"Hip surger*"	#10	"Knee Arthroplast*"
#11	"Knee Hemiarthroplast*"	#12	"Knee replacement*"
#13	"Knee repair*"	#14	"Knee prosthes*"
#15	"Knee implant*"	#16	"Knee hemi-arthroplast*"
#17	"Knee hemi arthroplast*"	#18	"Knee surger*"
#19	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18		
Exposure **Keyword/s or Search term/s**			
#20	Odds*	#21	Risk*
#22	Predict*	#23	Hazard*

#24	Associat*	#25	Likel*
#26	High*	#27	Increas*
#28	Event*		
#29	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28		
Outcome **Keyword/s or Search term/s**			
#30	"Intensive care*"	#31	"Critical care*"
#32	ICU	#33	"Critical Care unit"
#34	CCU	#35	"High care"
#36	"High Dependency Unit"	#37	"Acute illness*"
#38	"Catastrophic illness*"	#39	"Critical illness*"
#40	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40		
Combined search			
#41	#19 AND #29 AND #40		

Cochrane = Only phrases (in Title/Abstract/Keywords) will be searched as the database does not have a controlled vocabulary.

Population **Keyword/s or Search term/s**			
#1	"Hip Arthroplast*"	#2	"Hip Hemiarthroplast*"
#3	"Hip replacement*"	#4	"Hip repair*"
#5	"Hip prosthes*"	#6	"Hip implant*"
#7	"Hip hemi-arthroplast*"	#8	"Hip hemi arthroplast*"
#9	"Hip surger*"	#10	"Knee Arthroplast*"
#11	"Knee Hemiarthroplast*"	#12	"Knee replacement*"
#13	"Knee repair*"	#14	"Knee prosthes*"
#15	"Knee implant*"	#16	"Knee hemi-arthroplast*"
#17	"Knee hemi arthroplast*"	#18	"Knee surger*"
#19	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18		
Exposure **Keyword/s or Search term/s**			
#20	Odds*	#21	Risk*
#22	Predict*	#23	Hazard*

#24	Associat*	#25	Likel*
#26	High*	#27	Increas*
#28	Event*		
#29	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28		
Outcome **Keyword/s or Search term/s**			
#30	"Intensive care*"	#31	"Critical care*"
#32	ICU	#33	"Critical Care unit"
#34	CCU	#35	"High care"
#36	"High Dependency Unit"	#37	"Acute illness*"
#38	"Catastrophic illness*"	#39	"Critical illness*"
#40	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40		
Combined search			
#41	#19 AND #29 AND #40		

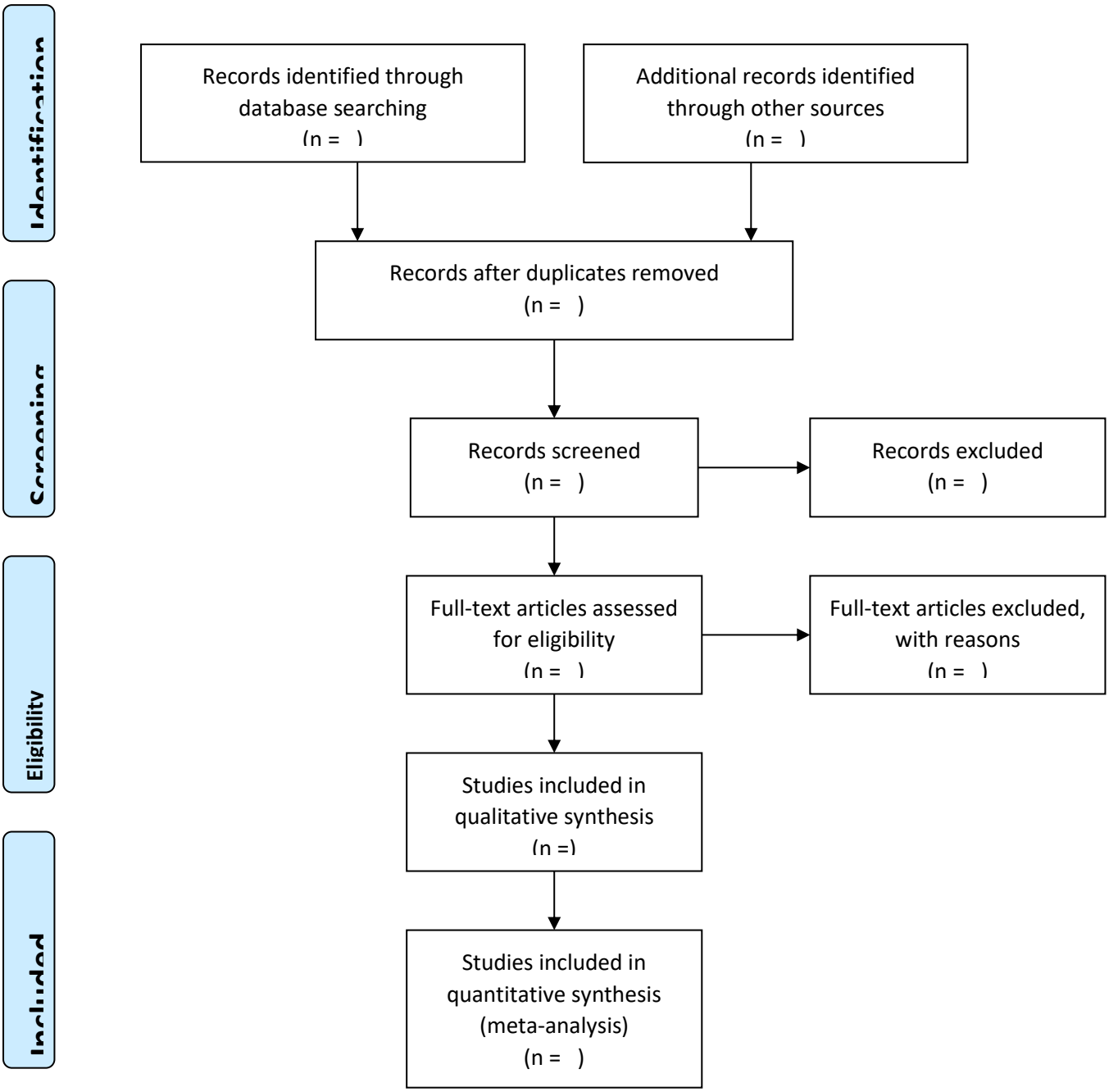
Appendix 2

Characteristic of enrolled studies

1st author	Year of publication	Country of Publication	Patient population Hip/knee/both	Proportion of patients admitted to ICU	Sample Size	Identfied risk factors

Appendix 3

PRISMA 2009 Flow Diagram



Appendix 4

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

5) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

6) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

7) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

8) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

2) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

4) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

5) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

6) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

5) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community *

b) somewhat representative of the average _____ in the community *

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

6) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort *

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

7) Ascertainment of exposure

a) secure record (eg surgical records) *

b) structured interview *

c) written self report

d) no description

8) Demonstration that outcome of interest was not present at start of study

a) yes *

b) no

Comparability

2) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) *

b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

4) Assessment of outcome

a) independent blind assessment *

b) record linkage *

c) self report

d) no description

5) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) *

b) no

6) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for *

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement