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Title	Perioperative Hypothermia Is Associated With Increased 30-Day Mortality in Hip Fracture Patients in the United Kingdom: A Systematic Review and Meta-analysis
Type	Article
URL	https://clock.uclan.ac.uk/48804/
DOI	##doi##
Date	2022
Citation	Mroczek, Thomas J., Prodromidis, Apostolos D., Pearce, Adrian, Malik, Rayaz A. and Charalambous, Charalambos P (2022) Perioperative Hypothermia Is Associated With Increased 30-Day Mortality in Hip Fracture Patients in the United Kingdom: A Systematic Review and Meta-analysis. <i>Journal of Orthopaedic Trauma</i> , 36 (7). pp. 343-348. ISSN 0890-5339
Creators	Mroczek, Thomas J., Prodromidis, Apostolos D., Pearce, Adrian, Malik, Rayaz A. and Charalambous, Charalambos P

It is advisable to refer to the publisher's version if you intend to cite from the work. ##doi##

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Journal of Orthopaedic Trauma

Perioperative hypothermia is associated with increased 30-day mortality in hip fracture patients in the UK . A systematic review and meta-analysis

--Manuscript Draft--

Manuscript Number:	JOT12994R2
Full Title:	Perioperative hypothermia is associated with increased 30-day mortality in hip fracture patients in the UK . A systematic review and meta-analysis
Article Type:	Original Article
Keywords:	body temperature; hypothermia; hip fracture; mortality
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Manuscript Region of Origin:	UNITED KINGDOM

Dear Professor Sanders,

Many thanks for the valuable comments of your reviewers that we have now addressed as follows. There are references to the relevant lines of the text with changes in the text highlighted in red. We hope that the manuscript now meets the requirements for acceptance to The Journal.

Yours sincerely,

Charalambos P Charalambous

Reviewers' Comments:

The authors need an epidemiologist to review the concept of combining 3 separate papers and provide this information. RWS

Reviewer #2:

Article is much better, clearer on purpose of article, the results from the 3 articles and differences clearer.

Still, the question remains and has been posed before, can you combine the results of the 3 studies as the measure temperature at a different moment. Did you check this with an epidemiologist?

Response: *We have sought advice with regards to the epidemiological aspects raised from Professor Ziyad Riyad Mahfoud, Professor of Research in Population Health Sciences, Population Health Sciences, Weill Cornell Medical College, Qatar and Director of Health Quantitative Sciences in the Institute for Population Health and Associate Director of the Biostatistics, Epidemiology, and Biomathematics Core at WCM-Q.*

Professor Mahfoud advised that it is appropriate to combine the 3 studies but also to do a sensitivity analysis of the 2 studies which had similar characteristics. We have done this and present our findings in the results section, and further elaborate this issue in our limitations section (see lines 258-268 and 284-286).

Perioperative hypothermia is associated with increased 30-day mortality in hip fracture patients in the United Kingdom. A systematic review and meta-analysis

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Conflicts of Interest and Source of Funding: No conflicts of interest and source of funding to declare by all authors.

1 **Perioperative hypothermia is associated with increased 30-day mortality in hip fracture**
2 **patients in the UK. A systematic review and meta-analysis**

3

4

ABSTRACT

5 **Introduction/Objectives:** Peri-operative hypothermia is common in trauma and surgical patients.

6 The aim of this study was to undertake a systematic review and meta-analysis to determine the
7 relationship between perioperative hypothermia and mortality following surgery for hip fracture.

8

9 **Materials and methods:** A systematic literature search of Medline, EMBASE, CINAHL, and
10 Cochrane CENTRAL databases was performed using the Cochrane methodology for systematic
11 reviews. The identified studies were assessed and compared against predetermined inclusion and
12 exclusion criteria. Data extraction and quality appraisal was performed on selected articles. A
13 meta-analysis was conducted using a random-effects model.

14

15 **Results:** The literature search identified 1016 records. After removing duplicates and those not
16 meeting inclusion criteria, 3 studies measuring 30-day mortality were included. All included
17 studies were carried out in the UK. The mortality rate was higher in the hypothermic groups as
18 compared to the normothermic group in all the studies, with the difference being significant in two
19 of the studies ($p < 0.0001$). The meta-analysis showed that low body temperature was associated
20 with an increased mortality risk (estimated OR: 2.660; 95%CI:1.948-3.632, $P < 0.001$) in patients
21 undergoing surgery for hip fracture.

22

23 **Conclusions:** This study shows that low body temperature in hip fracture patients is associated
24 with an increased 30-day mortality risk in the UK. Randomised control trials are required to
25 determine whether the association between perioperative hypothermia in hip fracture patients and
26 mortality is causal. Nevertheless, based on this analysis we urge the maintenance of normal body
27 temperature in the peri-operative period to be included in national hip fracture guidelines.

28

29 **Key words:** body temperature, hypothermia, hip fracture, mortality

30

31

INTRODUCTION

32

33 Inadvertent perioperative hypothermia, defined as a body temperature $<36.0^{\circ}\text{C}$, has been reported
34 in 10-90% of patients undergoing major surgery (1-3). According to National Institute for Health
35 and Care Excellence (NICE), inadvertent hypothermia may occur during the preoperative,
36 intraoperative or postoperative phase (4). It is associated with increased mortality, life-threatening
37 arrhythmias (5), altered antibody and cell-mediated immunity and tissue hypoxia, and an increased
38 risk of surgical site infections (6). In a meta-analysis by Mahoney et al. perioperative hypothermia
39 during various major surgical procedures was associated with an increased length of stay and an
40 increased incidence of myocardial infarction, infections and mortality (7).

41

42 Conversely, in a randomised control trial (RCT) preservation of normothermia in the perioperative
43 period was associated with reduced mortality and incidence of ventricular tachycardia in patients
44 undergoing abdominal, thoracic, or vascular surgical procedures (8). In a large series of 8871
45 patients undergoing various orthopaedic surgical procedures the incidence of perioperative

46 hypothermia was 11.4%, and although it was not associated with SSIs, urinary tract infections,
47 respiratory tract infections or cardiac and cerebral events, it was associated with increased 30-day
48 mortality (9). In a recent study of patients undergoing shoulder arthroplasty, 52.7% developed
49 intraoperative hypothermia, but this was not associated with SSI or any other perioperative
50 complications (10).

51
52 A recent meta-analysis identified that malignancy, nursing home residence, time to surgery,
53 pulmonary disease, diabetes, and cardiovascular disease significantly increased the risk of
54 mortality after hip fracture surgery (11, 12). Increasing age and lower BMI are major risk factors
55 for hip fracture and perioperative hypothermia and a significant drop in the body temperature and
56 intraoperative hypothermia has been reported in up to a third of patients undergoing surgery for
57 hip fracture (12, 13). However, there are limited studies on the impact of perioperative
58 hypothermia in this high risk population (14).

59
60 The aim of this study was to carry out a systematic review and meta-analysis to determine the
61 relationship between perioperative hypothermia and mortality in patients undergoing surgery for
62 hip fracture.

63
64

65 **MATERIALS AND METHODS**

66
67 For this systematic review, the Cochrane methodology for systematic reviews was followed (15).

68 The work was conducted with reference to a predefined protocol, which was registered with the
69 PROSPERO database (CRD42021256606). A literature search of the following electronic
70 bibliographic databases was conducted in January 2021 with no publication year limit: MEDLINE
71 (Interface: OvidSP); Embase (Interface: OvidSP); CINAHL (Interface: EBSCOhost); and Central
72 (Interface: Cochrane Library). Only studies available in the English language were included. The
73 search in all databases was performed with a combination of the keywords: “hip”, “femur”,
74 “fracture”, “temperature”, and “hypothermia”. Keywords were combined with the Boolean
75 operator AND in 4 separate searches and results were combined. The 4 searches were:

- 76 1. hip AND fracture AND temperature
- 77 2. femur AND fracture AND temperature
- 78 3. femur AND hypothermia
- 79 4. hip AND hypothermia

80

81 Inclusion/Exclusion criteria

- 82 • *Population*: The population included patients of any age with a hip fracture.
- 83 • *Intervention/Exposure/Comparators*: The exposure was the body temperature in patients with
84 hip fractures; patients with low body temperature were compared to those without low body
85 temperature.
- 86 • *Outcomes*: Mortality rate.
- 87 • *Study designs*: Any comparative study design was eligible. This included randomized
88 controlled studies, prospective cohort studies, case-control studies, and retrospective
89 comparative studies. Excluded study designs included case reports, reviews, editorials,

90 commentaries, personal opinions, surveys, and case series. The methodology of each study
91 was classified for the purposes for this review according to Mathes and Pieper (2017) (16).

92 Based on these inclusion and exclusion criteria, the titles of studies identified by the searches were
93 screened for inclusion. Duplicate studies were removed. The abstracts of potential studies were
94 then further screened, and when a decision regarding eligibility for inclusion could not be made
95 from the title and abstract, the full manuscripts were retrieved. The reference lists of all selected
96 articles were examined for any additional articles not identified through the database search. Two
97 reviewers assessed the search outputs independently. Any disagreements for inclusion were
98 discussed between reviewers and, if still unresolved, with a senior author.

99

100 Data extraction

101 Two reviewers extracted relevant data from the included studies using a standardised data
102 extraction form and inputted onto an Excel spreadsheet. Where necessary, results were discussed
103 with the senior author to decide for extraction. Extracted data included characteristics of the study
104 and study population, definitions used for low body temperature and mortality, patients'
105 temperature measurements, including techniques and values, as well as the rates of complications.

106

107 Data analysis – Statistical analysis

108 An initial brief descriptive analysis of the studies was performed, presenting study characteristics,
109 populations, outcomes and measurements. Meta-analysis was conducted using a random-effects
110 model, due to the inherent heterogeneity expected in clinical studies (17). Risk ratios and 95%
111 confidence intervals (CIs) were calculated and reported. Heterogeneity was assessed using τ^2 , I^2 ,
112 Q and P values. No formal testing for funnel plot asymmetry was performed due to the small

113 number of studies analysed. Data were analyzed with Comprehensive Metaanalysis version 2
114 (Biostat, Englewood, NJ, USA).

115

116 Assessment of methodological quality of studies and quality of evidence

117 The methodological quality of the included studies was assessed according to each study design.

118 The revised and validated version of Methodological Index for Non-Randomised Studies

119 (MINORS criteria) was used for all the retrospective comparative studies (18). Grading of

120 Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used by

121 two reviewers (ADP, CPC) independently to assess the quality of evidence of the review (19).

122 GRADE grades the quality of evidence as high, moderate, low, or very low based on risk of bias,

123 directness, consistency, precision, and reporting of bias. Observational studies are considered low

124 quality evidence but may be downgraded or upgraded according to GRADE recommendations.

125

126

127 **RESULTS**

128

129 Findings of the database searches

130 As per the Preferred Reporting Items for Systematic reviews and meta-analyses (PRISMA) flow

131 diagram used for identification of eligible studies (20), the searches identified 1016 records by title

132 in total. The screening process led to the initial selection of 206 titles based on information

133 gathered from the titles; 130 duplicates were removed, and 76 abstracts were reviewed, resulting

134 in the exclusion of 63 articles. A full-text review of the remaining 13 articles and a thorough search

135 of their references were performed; 3 of these articles met the inclusion criteria and were used for
136 analysis.

137

138 Characteristics of included studies

139

140 Table 1 summarizes the characteristics of the 3 included studies, all were retrospective cohort
141 studies (21-23). All were conducted in the UK. The total number of participants included in the
142 analysis was 4,298. The inclusion and exclusion criteria of the participants in the 3 included
143 studies, along with the methods of patient warming are summarized in Table 2. None of the studies
144 used for analysis reported on the mechanism of injury of the patients with hip fractures, but one
145 study stated that polytrauma patients were excluded.

146

147 Definition of body temperature

148

149 One study defined normal body temperature (normothermia) as a temperature ≥ 36 degrees
150 Celsius, and hypothermia as a temperature < 36 degrees Celsius (23). The other two studies defined
151 normal body temperature (normothermia) between 36.5 and 37.5 degrees Celsius, and
152 hypothermia) as a temperature < 36.5 degrees Celsius (21, 22). The definitions of low body
153 temperature (hypothermia), along with temperature measurement techniques and the timings of
154 measurements for the studies are summarized in Table 3.

155

156 30-day mortality rates

157

158 All studies referred to 30-day mortality rate (21-23). The mortality rates in both normal body
159 temperature (normothermic) and low body temperature (hypothermic) groups of patients in the
160 studies are summarized in Table 4. The mortality rate was higher in the hypothermic groups as
161 compared to the normothermic group in all the studies, with the difference being significant in two
162 of the studies (21, 22).

163

164 Assessment of methodological quality of studies and quality of evidence

165

166 The MINORS criteria were used to assess the methodological quality of the included studies and
167 all scored high in the assessment (Table 5) (18). All studies had a clearly stated aim, included
168 consecutive patients, had baseline equivalence amongst the groups and performed adequate
169 statistical analysis.

170

171 Quality of evidence

172

173 The GRADE approach was used to assess the overall quality of evidence in this study and the
174 following ratings are reported (19). The review included only retrospective cohort studies, so the
175 starting rating of the study was ‘low quality’ evidence. The study had inconsistency with a
176 variation in the definition of hypothermia, but no inconsistency for methodological and clinical
177 heterogeneity and baseline equivalence of patient groups. Based on this assessment, evidence is
178 rated as ‘low quality’. Overall, there were no concerns for publication bias and imprecision. Based
179 on this assessment, evidence is rated as ‘low quality’.

180 Meta-analysis

181 Meta-analysis of the 3 studies comparing mortality rates showed that peri-operative hypothermia
182 was associated with a higher 30-day mortality (estimated OR: 2.660; 95% CI:1.948-3.632,
183 $P<0.001$; heterogeneity: $\tau^2=0.00$, $I^2=0.00$, $Q=1.77$, $P=0.41$, see forest plot in Figure 1).
184 Sensitivity analysis including only the 2 studies that assessed body temperature on presentation to
185 the A&E showed similar results (estimated OR: 2.900; 95% CI:2.051-4.101, $P<0.001$;
186 heterogeneity: $\tau^2=0.00$, $I^2=0.00$, $Q=0.51$, $P=0.48$).

187

188

189

DISCUSSION

190

191 Our study shows that lower peri-operative body temperature in patients undergoing surgery for hip
192 fracture is associated with a 2.7-fold increased 30-day mortality risk compared to patients with
193 normal body temperature. These results are consistent with studies showing that body temperature
194 impacts on outcomes from a variety of surgical interventions. Billeter et al. demonstrated a 4-fold
195 increase in mortality and a doubling of the risk for stroke and sepsis in patients with perioperative
196 hypothermia after elective surgery for gastrointestinal, pancreatic and hepatobiliary conditions,
197 joint replacement, spinal, vascular, neurosurgical, thoracic, gynecological, and urological
198 pathologies (24). A systematic review and meta-analysis conducted by Kiekkas et al. showed that
199 peri-operative hypothermia during abdominal aortic aneurysm repair, coronary artery bypass -
200 grafting, emergency laparotomy, and thoracotomy was associated with increased mortality (25).
201 Hypothermia has also been shown to increase the incidence of morbid cardiac outcomes, surgical
202 blood loss, and need for blood transfusion. Frank et al. showed that high-risk patients experiencing

203 1.3°C core hypothermia were three times more likely to experience adverse myocardial outcomes
204 (8). Although the relationship between perioperative hypothermia and mortality is well
205 documented in other surgical specialties and surgical patient groups, assessing this relationship
206 specifically in a hip fracture population helps to give a more robust message to guide clinical
207 practise.

208
209 At a cellular and molecular level, hypothermia is associated with a threefold increase in plasma
210 norepinephrine concentrations, which may augment cardiac irritability, predisposing to ventricular
211 arrhythmias and cardiac dysfunction (26, 27). It may also cause hypertension in elderly patients
212 and in those at high risk of cardiac complications. Mild perioperative hypothermia may impair
213 platelet function and reduce the release of thromboxane A₂, accounting for the derangements in
214 coagulation and increased need for transfusion. Hypothermia may also induce changes in
215 monocyte activity with reduced HLA-DR surface expression, delayed TNF- α clearance, and
216 increased IL-10 release, potentially increasing the risk of surgical site infections (28).

217
218 Low body temperature in patients with a hip fracture may be attributed to fracture patients lying
219 on the floor for long periods before hospital admission with delays in transfer from A&E to the
220 ward and from ward to theatre without communicating their experience of feeling cold. Hip
221 fracture surgery per se also requires exposure of the whole lower part of the body and general
222 anesthesia which alters thermoregulatory mechanisms impairing the normal body response to a
223 low ambient temperature. Indeed, low body temperature is highly prevalent amongst hip fracture
224 patients in the UK, with 38% having a temperature <36.5 °C and 10-14% having a temperature of

225 <36 °C in this analysis. With about 65,000 hip fractures occurring annually in the UK, low body
226 temperature could affect a large number of patients.

227

228 There are several techniques to maintain normal body temperature in the perioperative period
229 including passive methods to minimise heat loss (such as airway heating and humidification,
230 control of ambient temperature, intravenous fluid warming, cutaneous insulation by cotton
231 blankets, reflective “space” blankets, surgical drapes) and active warming methods (such as
232 forced-air warming blankets, resistive heating mattresses).

233

234 NICE in England recommends maintaining the patients’ temperature above 36 °C during the pre-
235 , intra- and post- operative phases with active warming in the pre-operative phase (emergency
236 department, ward), adequate patient cover and warming of intravenous fluids and blood products
237 and at least one cotton sheet plus two blankets or forced-air warming to maintain body temperature
238 above 36 °C (4). A meta-analysis of randomised controlled trials in abdominal, orthopaedic, spinal
239 and obstetrical surgeries demonstrated that active body surface warming can maintain
240 physiological normothermia in the perioperative period and decreases wound infection, and the
241 need for blood transfusion (29).

242

243 Increased mortality risk in hip fracture patients has been associated with a number of factors
244 including surgical delay (>48 hours), comorbidities, male sex, and advanced age (30). Indeed, hip
245 fracture management is highly standardised through the National Hip Fracture Database in
246 England, Wales and Northern Ireland and the Scottish Hip Fracture Audit (SHFA) in Scotland
247 (31). NHS trusts have incentivised recommendations using a pay-for-performance initiative to

248 reduce mortality in elderly patients with hip fractures (32). In line with this, a meta-analysis by
249 Klestil et al. demonstrated a 20% lower 12-month mortality rate in hip fractures patient who were
250 operated on within 48 hours (33). Similarly, Moja et al. showed that hip fracture patients
251 undergoing surgery within 24 to 48 hours of admission had a lower mortality (34). Despite the
252 mortality associated with perioperative hypothermia being higher, there has been no unified
253 enforcement by NHS trusts to maintain normal body temperature in patients undergoing surgery
254 for hip fracture.

255
256 This interpretation of the outcomes of this study has limitations given the small number of include
257 studies and heterogeneity with regards to the definition of low body temperature (hypothermia)
258 and the methods and timing of temperature recording during the peri-operative period. **There were**
259 **only 3 studies eligible for inclusion, but we feel that by combining these in a meta-analysis the**
260 **message is more robust than the results of any one individual study in isolation. Two studies**
261 **recorded temperature in the Accident and Emergency department and one post surgery. In any**
262 **meta-analysis a decision is made as to what methodological heterogeneity may be accepted when**
263 **it comes to inclusion criteria. In this review we aimed to analyse the effect of one documented**
264 **episode of hypothermia in the peri-operative period hence the inclusion of all studies.**
265 **Nevertheless, a sensitivity analysis including only the 2 studies that recorded temperature in the**
266 **Accident and Emergency department was performed and yielded similar results to the overall**
267 **analysis with all 3 studies included. It could also be argued that including all 3 studies allows**
268 **diversity in the examined settings, hence so more generalizability.** Furthermore, there were only
269 retrospective cohort studies with no randomised trials available. In addition, although we have

270 identified a significant association between low body temperature and increased mortality after
271 surgery for hip fracture, a causal effect cannot be established.

272
273 Despite the limitations, this systematic review and meta-analysis clearly shows that a low
274 perioperative body temperature is associated with an increased 30-day mortality risk, which far
275 exceeds the increase in mortality risk associated with a delay in surgery. RCTs are required to
276 determine whether the association between perioperative hypothermia in hip fracture patients and
277 mortality is causal, and whether correcting body temperature can reduce mortality. Given the
278 potential ethical considerations, future RCTs may compare advanced warming techniques to
279 current standard practise. Nevertheless, whilst more information from RCTs is awaited, the current
280 analysis supports the inclusion of guidance to maintain normal body temperature in national hip
281 fracture guidelines and best practice tariffs.

282
283
284 **Acknowledgements:** We would like to thanks Professor Ziyad Riyad Mahfoud, Professor of
285 Research in Population Health Sciences, Population Health Sciences, Weill Cornell Medical
286 College, Qatar for his advice with regards to epidemiological aspects of this study.

287 **Conflicts of interest:** No conflict of interest to declare.

288 **Sources of funding:** No sources of funding to declare.

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292

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390 **Figures:**

391 **Figure 1.** Comparison of 30-day mortality rates between patients with normal and low peri-
392 operative body temperature.

Table 1. Characteristics of included studies.

Lead author (Year)	Study design, Level evidence, Country	Sample/Patient groups	ASA grade		Gender	Age (years)	Management	Outcomes
			Normal body temp	Low body temp				
Uzoigwe (2014) (21)	Retrospective cohort Level of evidence: III UK	Normal body temp: 449 Low body temp: 300 Total: 781	III/IV : I/II: 1.5 : 1 (ratio)	III/IV : I/II: 2.3 : 1 (ratio)	199M:582F	Mean: 80	96% had surgery	Mortality (30-day)
Faizi (2014) (22)	Retrospective cohort Level of evidence: III UK	Normal body temp: 612 Low body temp: 407 Total: 1066	Not reported	Not reported	273M:793F	Mean: 81	Not available	Mortality (30-day)
Williams & Ashworth (2018) (23)	Retrospective cohort Level of evidence: III UK	Normal body temp: 837 Low body temp: 92 Total: 929	Mean +/- SD: 2.69 +/- 0.66	Mean +/- SD: 2.76 +/- 0.60	271M:658F	Mean: 84.9	All patients had surgery	Mortality (30-day)

UK: United Kingdom, **ASA:** American Society of Anaesthesiologists, **temp:** temperature, **M:** Males, **F:** Females

Table 2. Inclusion criteria, exclusion criteria, and patient warming methods of included studies.

Lead author (Year)	Inclusion Criteria	Exclusion Criteria	Patient Warming Methods
Uzoigwe (2014) (21)	All hip fracture patients presenting to authors' institution between June 2011 and May 2012.	Not reported.	Not reported. *
Faizi (2014) (22)	All hip fracture patients presenting to authors' institution between June 2011 and May 2012.	Poly-trauma patients (ISS \geq 16).	Not reported. *
Williams & Ashworth (2018) (23)	Patients who underwent hip fracture surgery at authors' institution between June 2015 and July 2017.	Patients <65 years of age and patients with missing temperatures.	Various methods of patient warming including; blanket, forced air blanket, fluid warmer, heated mattress.

ISS: Injury Severity Score

* Studies measured temperatures on admission to the Emergency Department.

Table 3. Definitions and temperature measurement techniques of the included studies.

Lead author	Definition of hypothermia	Temperature measurement technique	Timing of temperature measurement
Uzoigwe (21)	< 36.5 °C	Tympanic / Axillary	On presentation to A&E
Faizi (22)	< 36.5 °C	Tympanic	On presentation to A&E
Williams & Ashworth (23)	< 36.0 °C	Tympanic	Post-op (upon entering recovery)

°C: degrees Celsius

Table 4. 30-day mortality rates.

Lead author	30-day mortality		Statistical analysis
	Normal body temperature	Low body temperature	
Uzoigwe (21)	23/449 (5.1%)	46/300 (15.3%)	Chi-square test P<0.0001
Faizi (22)	32/612 (5.2%)	51/407 (12.5%)	Chi-square test P<0.0001
Williams & Ashworth (23)	52/837 (6.2%)	10/92 (10.9%)	Chi-square test P=0.093

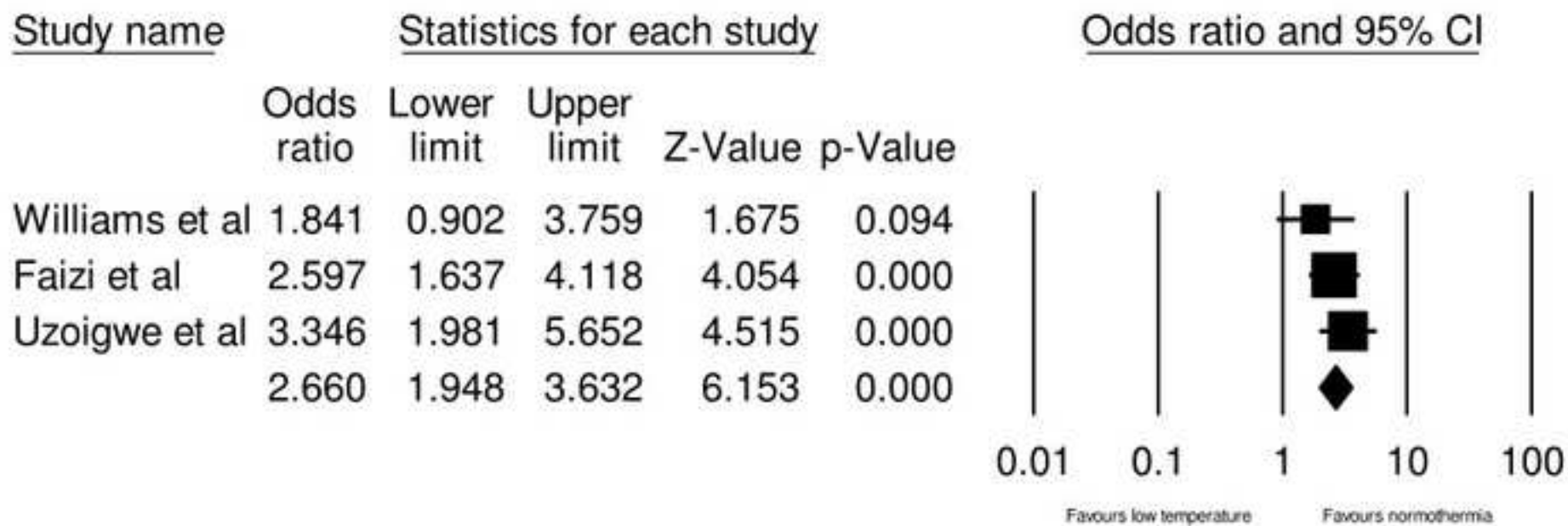
Table 5. Assessment of methodological quality of the retrospective cohort studies using MINORS criteria (18).

<u>Criteria</u>	Uzoigwe (21)	Faizi (22)	Williams (23)
A clearly stated aim	2	2	2
Inclusion of consecutive patients	2	2	2
Prospective collection of data	2	2	1
Endpoints appropriate to the aim of study	2	2	2
Unbiased assessment of the study endpoint	0	0	2
Follow-up period appropriate to the aim of study	2	2	2
Loss to follow-up <5%	1	1	1
Prospective calculation of the study size	2	2	0
Adequate control group	2	2	2
Contemporary group	2	2	2
Baseline equivalence of groups	2	2	2
Adequate statistical analysis	2	2	2
TOTAL	21	21	20

MINORS: Methodological Index for Non-randomized Studies (18).

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate).

Maximum possible score being 24 for comparative studies.



Meta Analysis



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pages 1,2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 2,3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 4,5
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 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4, Table 1
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.	Pages 4,5
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 5
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 5
	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.	N/A
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 6
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 5
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 4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	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 statistical heterogeneity, and software package(s) used.	Pages 5,6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
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.	Pages 6-7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/R
Study characteristics	17	Cite each included study and present its characteristics.	Page 7 Tables 1, 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8 Table 5
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.	Pages 7,8 Table 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8
	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 9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 9-11
	23b	Discuss any limitations of the evidence included in the review.	Page 12
	23c	Discuss any limitations of the review processes used.	N/A
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12-13
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 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
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.	Available upon request



PRISMA 2020 Checklist

For more information, visit: <http://www.prisma-statement.org/>