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

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Corresponding Author:	Charalambos P. Charalambous, BSc, MBChB, MSc, MD, FRCS(Tr&Orth) Blackpool Teaching Hospitals NHS Foundation Trust Blackpool, Lancashire UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Blackpool Teaching Hospitals NHS Foundation Trust
Corresponding Author's Secondary Institution:	
First Author:	Thomas J Mroczek, MD
First Author Secondary Information:	
Order of Authors:	Thomas J Mroczek, MD
	Apostolos D Prodromidis, MD, MSc
	Adrian Pearce, BSc, MBChB
	Rayaz A Malik, MBChB, PhD
	Charalambos P. Charalambous, BSc, MBChB, MSc, MD
Order of Authors Secondary Information:	
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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

Authors:

1. Thomas J. Mroczek MD[1]
2. Apostolos D. Prodromidis MD, MSc[2]
3. Adrian Pearce BSc, MBChB, MRCS[3]
4. Rayaz A Malik, MBChB, PhD, Professor of Medicine[4,5]
5. Charalambos P. Charalambous, BSc, MBChB, MSc, MD[1,6]

Affiliations:

1. Blackpool Teaching Hospitals NHS Foundation Trust, Trauma & Orthopaedics, Blackpool, United Kingdom
2. Leeds Teaching Hospitals NHS Foundation Trust, Trauma & Orthopaedics, Leeds, United Kingdom
3. Salford Royal NHS Foundation Trust, Trauma & Orthopaedics, Salford, United Kingsdom
4. Weill Cornell Medicine, Doha, Qatar
5. University of Manchester, Manchester, United Kingdom
6. School of Medicine, University of Central Lancashire, Preston, United Kingdom

Corresponding author:

Charalambos P. Charalambous BSc, MBChB, MSc, MD.

Trauma & Orthopaedics, Blackpool Victoria Hospital

Whinney Heys road, Blackpool, Lancashire, FY3 8NR, UK.

Email: mr.charalambous@nhs.net

Telephone number: +441253655983.

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

ABSTRACT

Introduction/Objectives: Peri-operative hypothermia is common in trauma and surgical patients. The aim of this study was to undertake a systematic review and meta-analysis to determine the relationship between perioperative hypothermia and mortality following surgery for hip fracture.

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

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

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

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

INTRODUCTION

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

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

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

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

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

MATERIALS AND METHODS

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

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

1. hip AND fracture AND temperature
2. femur AND fracture AND temperature
3. femur AND hypothermia
4. hip AND hypothermia

Inclusion/Exclusion criteria

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

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

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

Data extraction

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

Data analysis – Statistical analysis

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

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

Assessment of methodological quality of studies and quality of evidence

The methodological quality of the included studies was assessed according to each study design. The revised and validated version of Methodological Index for Non-Randomised Studies (MINORS criteria) was used for all the retrospective comparative studies (18). Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used by two reviewers (ADP, CPC) independently to assess the quality of evidence of the review (19). GRADE grades the quality of evidence as high, moderate, low, or very low based on risk of bias, directness, consistency, precision, and reporting of bias. Observational studies are considered low quality evidence but may be downgraded or upgraded according to GRADE recommendations.

RESULTS

Findings of the database searches

As per the Preferred Reporting Items for Systematic reviews and meta-analyses (PRISMA) flow diagram used for identification of eligible studies (20), the searches identified 1016 records by title in total. The screening process led to the initial selection of 206 titles based on information gathered from the titles; 130 duplicates were removed, and 76 abstracts were reviewed, resulting in the exclusion of 63 articles. A full-text review of the remaining 13 articles and a thorough search

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

Characteristics of included studies

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

Definition of body temperature

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

30-day mortality rates

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

Assessment of methodological quality of studies and quality of evidence

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

Quality of evidence

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

Meta-analysis

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

DISCUSSION

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

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

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

Low body temperature in patients with a hip fracture may be attributed to fracture patients lying on the floor for long periods before hospital admission with delays in transfer from A&E to the ward and from ward to theatre without communicating their experience of feeling cold. Hip fracture surgery per se also requires exposure of the whole lower part of the body and general anesthesia which alters thermoregulatory mechanisms impairing the normal body response to a low ambient temperature. Indeed, low body temperature is highly prevalent amongst hip fracture patients in the UK, with 38% having a temperature <36.5 ^{0}C and 10-14% having a temperature of

<36 ^{0}C in this analysis. With about 65,000 hip fractures occurring annually in the UK, low body temperature could affect a large number of patients.

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

NICE in England recommends maintaining the patients' temperature above 36 ^{0}C during the pre-, intra- and post- operative phases with active warming in the pre-operative phase (emergency department, ward), adequate patient cover and warming of intravenous fluids and blood products and at least one cotton sheet plus two blankets or forced-air warming to maintain body temperature above 36 ^{0}C (4). A meta-analysis of randomised controlled trials in abdominal, orthopaedic, spinal and obstetrical surgeries demonstrated that active body surface warming can maintain physiological normothermia in the perioperative period and decreases wound infection, and the need for blood transfusion (29).

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

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

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

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

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

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REFERENCES

1. Alfonsi P, Bekka S, Aegerter P. Prevalence of hypothermia on admission to recovery room remains high despite a large use of forced-air warming devices: Findings of a non-randomized observational multicenter and pragmatic study on perioperative hypothermia prevalence in France. PLoS One. 2019;14(12):e0226038.
2. Chalari E, Intas G, Zyga S, Fildissis G, Tolia M, Toutziaris C, et al. Perioperative inadvertent hypothermia among urology patients who underwent transurethral resection with either TURis or transurethral resection of the prostate method. Urologia. 2019;86(2):69-73.
3. Mendonça FT, Ferreira JDS, Guilardi VHF, Guimarães GMN. Prevalence of Inadvertent Perioperative Hypothermia and Associated Factors: A Cross-Sectional Study. Ther Hypothermia Temp Manag. 2021.
4. (NICE) NIfHaCE. Hypothermia: prevention and management in adults having surgery Clinical guideline [CG65]: NICE; 2008 [Available from: https://www.nice.org.uk/guidance/cg65.
5. Dietrichs ES, McGlynn K, Allan A, Connolly A, Bishop M, Burton F, et al. Moderate but not severe hypothermia causes pro-arrhythmic changes in cardiac electrophysiology. Cardiovasc Res. 2020;116(13):2081-90.
6. Bu N, Zhao E, Gao Y, Zhao S, Bo W, Kong Z, et al. Association between perioperative hypothermia and surgical site infection: A meta-analysis. Medicine (Baltimore). 2019;98(6):e14392.
7. Mahoney CB, Odom J. Maintaining intraoperative normothermia: a meta-analysis of outcomes with costs. Aana j. 1999;67(2):155-63.
8. Frank SM, Fleisher LA, Breslow MJ, Higgins MS, Olson KF, Kelly S, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. Jama. 1997;277(14):1127-34.
9. Yamada K, Nakajima K, Nakamoto H, Kohata K, Shinozaki T, Oka H, et al. Association Between Normothermia at the End of Surgery and Postoperative Complications Following Orthopedic Surgery. Clin Infect Dis. 2020;70(3):474-82.
10. Jildeh TR, Okoroha KR, Marshall NE, Amato C, Trafton H, Muh SJ, et al. The Effect of Intraoperative Hypothermia on Shoulder Arthroplasty. Orthopedics. 2018;41(4):e523-e8.
11. Chang W, Lv H, Feng C, Yuwen P, Wei N, Chen W, et al. Preventable risk factors of mortality after hip fracture surgery: Systematic review and meta-analysis. Int J Surg. 2018;52:320-8.
12. Gurunathan U, Stonell C, Fulbrook P. Perioperative hypothermia during hip fracture surgery: An observational study. J Eval Clin Pract. 2017;23(4):762-6.
13. Frisch NB, Pepper AM, Jildeh TR, Shaw J, Guthrie T, Silverton C. Intraoperative Hypothermia During Surgical Fixation of Hip Fractures. Orthopedics. 2016;39(6):e1170-e7.
14. Arkley J, Taher S, Dixon J, Dietz-Collin G, Wales S, Wilson F, et al. Too Cool? Hip Fracture Care and Maintaining Body Temperature. Geriatr Orthop Surg Rehabil. 2020;11:2151459320949478.
15. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane: Cochrane; 2021. Available from: www.training.cochrane.org/handbook.

16. Mathes T, Pieper D. Clarifying the distinction between case series and cohort studies in systematic reviews of comparative studies: potential impact on body of evidence and workload. BMC Med Res Methodol. 2017;17(1):107.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015;45(Pt A):139-45.
18. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73(9):712-6.
19. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
21. Uzoigwe CE, Khan A, Smith RP, Venkatesan M, Balasubramanian S, Isaac S, et al. Hypothermia and low body temperature are common and associated with high mortality in hip fracture patients. Hip Int. 2014;24(3):237-42.
22. Faizi M, Farrier AJ, Venkatesan M, Thomas C, Uzoigwe CE, Balasubramanian S, et al. Is body temperature an independent predictor of mortality in hip fracture patients? Injury. 2014;45(12):1942-5.
23. Williams M, Ng M, Ashworth M. What is the incidence of inadvertent hypothermia in elderly hip fracture patients and is this associated with increased readmissions and mortality? J Orthop. 2018;15(2):624-9.
24. Billeter AT, Hohmann SF, Druen D, Cannon R, Polk HC, Jr. Unintentional perioperative hypothermia is associated with severe complications and high mortality in elective operations. Surgery. 2014;156(5):1245-52.
25. Kiekkas P, Fligou F, Igoumenidis M, Stefanopoulos N, Konstantinou E, Karamouzos V, et al. Inadvertent hypothermia and mortality in critically ill adults: Systematic review and meta-analysis. Aust Crit Care. 2018;31(1):12-22.
26. Sessler DI. Complications and treatment of mild hypothermia. Anesthesiology. 2001;95(2):531-43.
27. Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, Sitzmann JV, et al. The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. A randomized clinical trial. Anesthesiology. 1995;82(1):83-93.
28. Qadan M, Gardner SA, Vitale DS, Lominadze D, Joshua IG, Polk HC, Jr. Hypothermia and surgery: immunologic mechanisms for current practice. Ann Surg. 2009;250(1):134-40.
29. Balki I, Khan JS, Staibano P, Duceppe E, Bessissow A, Sloan EN, et al. Effect of Perioperative Active Body Surface Warming Systems on Analgesic and Clinical Outcomes: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Anesth Analg. 2020;131(5):1430-43.
30. Dailiana Z, Papakostidou I, Varitimidis S, Michalitsis S, Veloni A, Malizos K. Surgical treatment of hip fractures: factors influencing mortality. Hippokratia. 2013;17(3):252-7.
31. (NICE) NIfHaCE. Hip fracture: management Clinical guideline [CG124]: NICE; 2011 [updated 10 May 2017. Available from: https://www.nice.org.uk/guidance/cg124.
32. Metcalfe D, Zogg CK, Judge A, Perry DC, Gabbe B, Willett K, et al. Pay for performance and hip fracture outcomes: an interrupted time series and difference-in-differences analysis in England and Scotland. Bone Joint J. 2019;101-b(8):1015-23.

33. Klestil T, Röder C, Stotter C, Winkler B, Nehrer S, Lutz M, et al. Impact of timing of surgery in elderly hip fracture patients: a systematic review and meta-analysis. Sci Rep. 2018;8(1):13933.
34. Moja L, Piatti A, Pecoraro V, Ricci C, Virgili G, Salanti G, et al. Timing matters in hip fracture surgery: patients operated within 48 hours have better outcomes. A meta-analysis and meta-regression of over 190,000 patients. PLoS One. 2012;7(10):e46175.

Figures:

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

Table 1

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 ^{0}C	Tympanic / Axillary	On presentation to A&E
Faizi (22)	< 36.5 ^{0}C	Tympanic	On presentation to A&E
Williams & Ashworth (23)	< 36.0 ^{0}C	Tympanic	Post-op (upon entering recovery)

^{0}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).

Criteria	**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

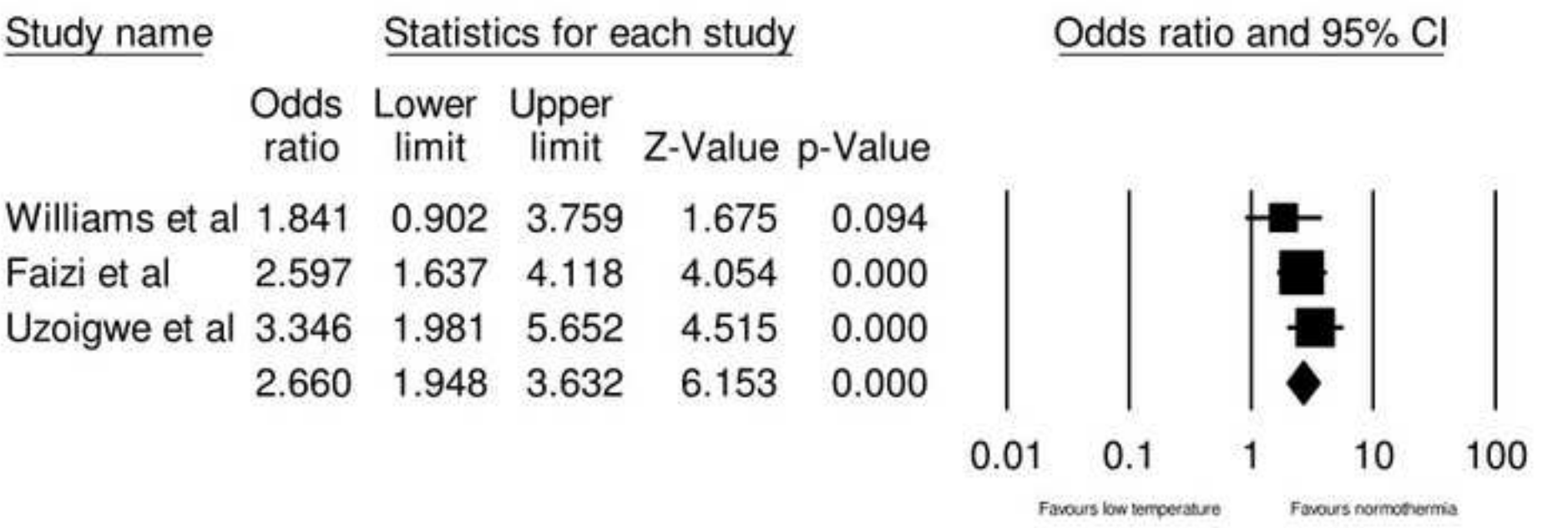
MINORS: Methodological Index for Non-randomized Studies (18).

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

Maximum possible score being 24 for comparative studies.

Figure 1

Click here to access/download;Figure;Figure 1.jpg



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

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA 2020 Checklist

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