Safety of intraoperative hypothermia for patients: meta-analyses of randomized controlled trials and observational studies

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Abstract

Background: Previous studies have shown that intraoperative hypothermia was associated with higher risks of clinical adverse events, but we found otherwise from recent evidences. This study aims to synthesize the existing evidence evaluating safety of intraoperative hypothermia.

Methods: Articles, reviews, ongoing trials and grey literatures were retrieved from PubMed, The Cochrane Library, Clinical Trials and CNKI (a Chinese national database) till February 2nd, 2019. Both randomized controlled trials and observational studies compared incidences of all sorts of intra- and post-operative consequences between hypothermia and normothermia were included. Researches comparing different warming systems were excluded. We also examined risks of hypothermia using lowered standards (35.5 °C and 35 °C) from a Chinese trial (ChiCTR-IPR-17011099).

Results: A total of 9 RCT studies and 11 observational studies were included. RCT-synthesized results showed that intraoperative hypothermia was associated with higher risks of bleeding (MD = 131.90, 95%CI: 117.42, 146.38), surgical site infection (RD = 0.14, 95%CI: 0.06, 0.21) and shivering (RD = 0.32, 95%CI: 0.06, 0.58) but with no significant differences in duration of surgery, hospital stay or mortality. Observational study-synthesized evidences showed that intraoperative hypothermia did not result in higher risks in any of these adverse events. Results didn’t change even if the standard of hypothermia was lowered by 0.5–1.0 °C.

Conclusions: The study indicates that the synthesized risks resulted by intra-operative hypothermia might be overestimated and the eligibility of 36 °C to define hypothermia is not sensitive enough. Given body-temperature protection has not been popularized in China, it is still critical to normalize the hypothermia prevention at this stage.

Research in Context

Evidence before this study

The safety and clinical effects of intraoperative warming have been extensively studied and reviewed. Individual studies have reported significantly increased risks of surgical site infection, blood loss, chills/shivering, and pain as well as a longer duration of surgery and longer stays in the post-anesthesia care unit (PACU) and hospital. However, no systematic comparison of postoperative outcomes in patients with and without intraoperative hypothermia has been performed to date. Therefore, we searched the English and Chinese literature published before February 2019 to identify relevant research articles and registered clinical trials on this topic using four databases: Cochrane Library, PubMed, Clinical Trials (ClinicalTrials.gov), and China National...
Intraoperative hypothermia is widely known operative risk that requires careful monitoring during surgical procedures. Using meta-analytical techniques, we provide evidence that the detrimental effects of intraoperative hypothermia are likely to be overestimated. Analysis of RCTs showed that the hypothermic group had significantly higher risks of surgical site infection, chills/shivering, and blood loss than did the normothermic group; however, no statistically significant difference was found in the duration of surgery, length of stay, or mortality. Furthermore, when the definition of intraoperative hypothermia was lowered to < 35.5 °C or < 35.0 °C, there was not reach statistical significance in the risk of other events except shivering. The difference between our findings and the current consensus is partly explained by the heterogeneity in the meta-analysis results, but it may also be attributable to the gaps in the causal chain from intraoperative hypothermia to adverse events, resulting in uncertainties, and to potential confounding effects that cannot be eliminated from RCTs (e.g., impact of other protective clinical practices that lead to reduced harm).

Implications of all the available evidence
Under the current definition of intraoperative hypothermia as well as the tentatively lowered criteria for hypothermia, the evidence synthesized from the RCTs showed significantly higher intraoperative blood loss and incidences of surgical site infection and postoperative chills/shivering in the hypothermic than normothermic group. However, no significant differences were found in risks of other adverse events. Furthermore, evidence from observational studies also found no statistically significant difference in any postoperative adverse event. Therefore, the clinical harm reported in the studies evaluated herein appears lower than would be expected from the current consensus. These findings raise a question regarding the benefit of practices to prevent intraoperative hypothermia. Our findings are limited by the relatively small sample size and experimental designs. For more thorough assessment, future works should include larger-scale real-world studies and incorporate control over other medical practices (e.g., postoperative management that may offset the impact of intraoperative hypothermia).

Background
Intraoperative hypothermia (core temperature of < 36 °C) is a common complication during surgery complications OR fluids infused OR duration of surgery OR [1]. Normal body temperature is maintained at approximately 37 °C by neurohumoral regulation to ensure stable physiological functions [2]. However, during surgery hypothermic events may occur as a result of multiple factors such as anesthesia, the operating room temperature, intraoperative warming practices, and infusions of fluids or blood product [3]. While many vital signs (e.g., blood pressure, heart rate, respiratory rate, and pulse) are routinely monitored during surgery, [4, 5] body temperature was commonly neglected until the past two decades, during which prevention of intraoperative hypothermia has become gradually accepted globally. Many organizations such as the American Society of Peri-Anesthesia Nurses, National Institute for Health and Care Excellence, Association of Peri-Operative Registered Nurses, and the Chinese Society of Anesthesia now recommend pre-warming before the operation, continuous intraoperative temperature monitoring and warming, and active warming in case of hypothermic events preoperatively or intraoperatively [3, 6–9].

Early studies of intraoperative hypothermia found the incidence ranged from 50 to 90% [10]. Improvements in the standardization of clinical practices and temperature-protective equipment has reduced this incidence. Recent studies have reported rates of 54% in distal gastrectomy [11], 37% in gastroenterological surgery [12], and 17% in hip fracture fixation [13]. An epidemiological survey conducted from 2014 to 2015 in China revealed an incidence of 44% [6]. The study found that patients who developed intraoperative hypothermia did not have a significantly increased risk of surgical site infection, a longer duration of intensive care unit (ICU) stay, or a higher 30-day mortality rate compared with patients who did not develop intraoperative hypothermia [6]. This unexpected finding was also supported by other studies. A randomized controlled trial (RCT) conducted from 2017 to 2018 in China (ChiCTR-IPR-17011099) showed a significantly lower incidence of intraoperative hypothermia in patients given active intraoperative warming than in patients who received regular passive warming during the operation [odds ratio (OR),
0.07; 95% confidence interval (CI), 0.04–0.14); however, no significant difference was found in the incidences of intraoperative or postoperative adverse events [postoperative surgical site infection: OR = 1.11; 95% CI: 0.39–3.17; ICU admission: OR = 0.67; 95% CI: 0.38–1.21; postoperative blood loss: OR = 0.24; 95% CI: 0.03–2.14; duration of hospital stay: mean difference (MD) in days was –1.25; 95% CI, –6.15–4.31]. These findings raise questions regarding the impact of intraoperative hypothermia on clinical outcomes in the current clinical setting. Specifically, we asked whether such efforts translate into clinical benefits given the increasing development and use of intraoperative temperature protective techniques [14, 15].

The purpose of this study was to conduct a meta-analysis to synthesized evidence from published studies to assess the clinical harms of intraoperative hypothermia. Additionally, we explored the association between intraoperative hypothermia and the clinical harm, tested the differences in clinical injury under different hypothermia criteria, and discussed the possible factors underlying the lack of significance of hypothermia-induced harm.

Methods
Data from RCTs and observational studies on the risks of adverse effects in patients with and without intraoperative hypothermia were identified and analyzed. Importantly, the findings were combined with data from a recently completed randomized controlled trial (RCT) to examine whether different hypothermia definition might alter the outcomes.

Literature search
Evidence of studies related to surgical hypothermia was identified by searching four databases: Cochrane Library, PubMed, Clinical Trials (ClinicalTrials.gov), and China National Knowledge Infrastructure (CNKI). CNKI is currently the largest database of academic publications (e.g., research articles, dissertations, newspapers, conference proceedings, annals, and reference books) published in China. All information entered into the databases prior to February 2019 was included. References from identified studies were also evaluated for possible inclusion. In addition, results from an unpublished RCT is also included (see section 4, Methods).

Databases were searched using the keywords “intraoperative hypothermia” and “adverse events” in both English and Chinese. The resulting articles were reviewed to identify other potential search terms. The following keywords were commonly used in the articles: “surgical site infection,” “chill,” “shivering,” “complications,” “mortality,” “infusion,” “blood loss,” “pain,” “duration of surgery,” “duration of anesthesia,” “duration of PACU,” “length/days of stay,” and “readmission.”

New searches were conducted using the following terms: ((hypothermia) AND normothermia) AND (surgical site infection OR mortality OR blood loss OR pain OR chill OR shivering OR complications OR infusion OR duration of surgery OR duration of anesthesia OR duration of PACU OR length of stay OR readmission) AND (randomized controlled trial OR non-randomized OR non-randomised OR cohort OR observational OR investigation OR retrospective OR cross-sectional OR case control).

Studies meeting all of the following criteria were included: 1) inclusion of at least a hypothermic group and a normothermic group, 2) hypothermia defined as < 36 °C, and 3) reporting one or more of the following 12 adverse events: intraoperative blood loss/blood transfusion; surgical site infection; intraoperative or postoperative chills/shivering; complications; infusion; postoperative pain; duration of surgery; duration of anesthesia; duration of postanesthesia care unit (PACU) stay; duration/days of hospitalization; mortality; and readmission.

Studies meeting any of the following conditions were excluded: 1) inappropriate group division (e.g., grouping by use/non-use of warming practices with inadequate reporting of actual occurrence/absence of intraoperative hypothermia), 2) incomplete data (e.g., lack of standard deviation), 3) induction of hypothermia for treatment purposes (e.g., accidental cerebral injuries, myocardial conditions), 4) duplicate publication, 5) study reported in languages other than English or Chinese, or 6) unavailable full text.

Information screening, retrieval, and quality assessment
The primary clinical harm of intraoperative hypothermia is the development of intraoperative and postoperative adverse events. Two researchers independently read all included studies for information screening, retrieval, and quality assessment. Disagreements were resolved by discussion or introduction of a third reviewer. The following items were retrieved: author name, year of publication, location where study was performed, population, study type, sample size, and outcomes. RCTs were assessed with the Cochrane risk-of-bias tool for quality of research methodology [16]. Observational studies were assessed with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [17], because of the lack of a universally accepted criterion on data quality, the studies were ranked according to the number of items reported and grouped around the median value to ensure that the sample was balanced.

Statistical analysis
The risk difference (RD) and mean difference (MD) were used to calculate effect sizes. To determine if
heterogeneity was present across the studies the Cochran Q test as estimated by the $\chi^2$ test ($\alpha = 0.05$) and the $I^2$ statistic ($I^2 \geq 50\%$: substantial heterogeneity) was used. In case of minor heterogeneity ($I^2 < 50\%$), a fixed-effects model was used for the meta-analysis ($\alpha = 0.05$). Otherwise, the source of the heterogeneity was further analyzed. If it was not possible to determine differences across the papers based on methodological and clinical factors, a random-effects model was used for the meta-analysis. When clinical or methodological factors contributed substantially to the heterogeneity, a subgroup analysis or sensitivity analysis was used or, alternatively, only qualitative description was performed. Statistical analysis was performed in Review Manager 5.3.5 (Cochrane Collaboration, www.cc-ims.net/RevMan).

Impact of hypothermia definition on rates of adverse events

When intraoperative definition of hypothermia was evaluated < 36.0 °C, < 35.5 °C, or < 35.0 °C, the incidences of adverse events were analyzed from the data reported in a recently completed RCT (ChiCTR-IPR-17011099) in China and compared with the results from other studies. The RCT included 240 patients who underwent esophagectomy or pancreatectomy at Peking Union Medical College Hospital from 11 October 2016 to 28 March 2018. The patients were randomized to receive passive or active warming practices and were monitored for intraoperative hypothermia and adverse events (Table 1 shows the mean sample information). After the start of the operation, the temperatures of the eardrum and nasopharynx were measured every 30 min; if the temperature decreased to < 36 °C at any time during the operation, the patient was considered to have developed intraoperative hypothermia. Incidences calculated with the three tentative hypothermic definitions were analyzed with R 3.6.0 ($\alpha = 0.05$) (R Foundation for Statistical Computing; www.r-project.org).

### Table 1 Baseline characteristics of patients

|                | Experimental group (n = 122) | Control group (n = 118) | $P$-value $^a$ |
|----------------|-----------------------------|------------------------|---------------|
| Age (years)    | 61.23 (9.79)                | 56.97 (11.23)          | 0.002         |
| Sex            |                             |                        |               |
| Male           | 67.2% (82)                  | 68.6% (81)             | 0.812         |
| Female         | 32.8% (40)                  | 31.4% (37)             |               |
| Ethnic group   |                             |                        |               |
| Han            | 92.6% (113)                 | 94.1% (104)            | 0.654         |
| Other          | 7.4% (9)                    | 5.9% (7)               |               |
| Body mass/kg   | 66.05 (11.89)               | 65.45 (10.79)          | 0.963         |
| Height/cm      | 167.80 (7.70)               | 167.68 (7.24)          | 0.870         |
| Profession     |                             |                        |               |
| Regular employee | 18.9% (23)                  | 26.3% (31)             | 0.481         |
| Short-time employee | 0% (0)                  | 0% (0)               |               |
| Part-time employee | 0% (0)                  | 0% (0)               |               |
| Self-employed  | 3.3% (4)                    | 5.1% (6)               |               |
| Retiree        | 41.8% (51)                  | 33.1% (39)             |               |
| Student        | 0% (0)                      | 0.8% (1)               |               |
| Farmer         | 16.4% (20)                  | 11.9% (14)             |               |
| Unemployed     | 19.7% (24)                  | 22.9% (27)             |               |
| Medical insurance coverage |             |                        |               |
| Urban employee | 41.8% (51)                  | 49.2% (58)             | 0.098         |
| Urban resident | 7.4% (9)                    | 5.9% (7)               |               |
| New rural cooperative | 32.8% (40)              | 38.1% (45)             |               |
| Free medical care | 6.6% (8)                 | 1.7% (2)               |               |
| Commercial insurance | 0% (0)                 | 0% (0)                |               |
| Student insurance | 0% (0)                   | 0% (0)                |               |
| Other          | 5.7% (7)                    | 1.7% (2)               |               |
| None           | 5.7% (7)                    | 3.4% (4)               |               |
| Monthly income/RMB | 3377.78 (1545.30)        | 3277.19 (1474.63)      | 0.617         |
| Diabetes       |                             |                        |               |
| Yes            | 11.5% (14)                  | 12.7% (15)             | 0.769         |
| No             | 88.5% (108)                 | 87.3% (103)            |               |
| Other diseases |                             |                        |               |
| Yes            | 65.6% (80)                  | 57.6% (68)             | 0.206         |
| No             | 34.4% (42)                  | 42.4% (50)             |               |
| Smoking        |                             |                        |               |
| Non-smoker     | 54.1% (66)                  | 50.8% (60)             | 0.642         |
| Quitter        | 17.2% (21)                  | 18.6% (22)             |               |
| Smoker         | 28.7% (35)                  | 30.5% (36)             |               |
| American Society of Anesthesiologists Classification |          |                        |               |
| I              | 11.5% (14)                  | 22.9% (27)             | 0.059         |
| II             | 82.0% (100)                 | 70.3% (83)             |               |
| III            | 6.6% (8)                    | 6.8% (8)               |               |

$^a$Chi-square test for categorical variables, T-test or rank sum test for continuous variables
Table 1 below describes the demographic characteristics of patients who were evaluated in a RCT examining the effects of passive or active warming.

**Results**

The database search identified 614 publications RCTs and 818 related to observational studies [817 articles, 1 unpublished RCT (ChiCTR-IPR-17011099) after re-adjustment of grouping] related to surgical hypothermia. After applying inclusion and exclusion criteria, a total of 9 RCTs and 11 observational studies were included in the quantitative analysis (Fig. 1).

**Basic features of the included studies**

The basic features included in the study are shown in Table 2.

**Meta-analysis of adverse events**

Figure 2 depicts the risks of adverse events in the hypothermic and normothermic groups. Results from the RCT studies, two adverse events (intraoperative/postoperative chills and length of stay) had substantial heterogeneity across the studies. Because only three RCTs were identified, a random-effects model was used instead of a subgroup analysis estimate the odds of these two outcomes. The meta-analysis of results reported that compared with the normothermic group, the hypothermic group had higher intraoperative blood loss (MD, 131.90 ml; 95% CI, 117.42–146.38) and higher incidences of surgical site infection (RD, 0.14; 95% CI, 0.06–0.21) and postoperative chills/shivering (RD, 0.32; 95% CI, 0.06–0.58). It should be noted that the difference here point to the differences of statistical instead of a clinical one, which means whether the adverse events need to be treated, should be based on the actual situation. The incidence of other adverse events (duration of surgery(h), length of stay(d), mortality) were not significantly different between the two groups. Results from the observational studies indicated the presence of heterogeneity; thus, they were analyzed by subgroup analyses according to the study quality. Studies of higher quality were observed to have lower heterogeneity, but no statistically significant differences in outcomes were detected.

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**Fig. 1** Flowchart illustrating screening of publications based on randomized controlled trials. *Databases and number of publications retrieved: PubMed (n = 753); The Cochrane Library (n = 507); CNKI(n = 165); clinical trial (n = 4)
| Studies          | country  | Population                                                                 | Study type                             | Participants | Outcome indicators                      | Risk Difference (95%CI) | Mean Difference (95%CI) |
|-----------------|----------|----------------------------------------------------------------------------|----------------------------------------|--------------|-----------------------------------------|-------------------------|-------------------------|
| Yu et al (2010) | China    | patients undergoing opening radical resection of distal gastric cancer age: EG:60±20, CG:59±13 | Randomised, controlled trial           | 32 54        | Surgical site infection                 | 0.15 [0.01, 0.29]        |                         |
|                 |          |                                                                            |                                        |              | Intraoperative bleed                    |                         |                         |
| Zhang et al (2009) | China | patients undergoing radical resection for carcinoma of esophagus age: EG:59±6, CG:59±7 | Randomised, controlled trial           | 10 10b       | Shivering (EG vs CG1)                   | 0.30 [-0.10, 0.70]       |                         |
| Todd et al (2009) | America | patients undergoing clipping of intracranial aneurysms after subarachnoid hemorrhage | Randomised, controlled trial           | 499 501      | mortality                               | -0.01 [-0.04, 0.02]      |                         |
| Nathan et al (2004) | Canada | patients undergoing elective coronary artery surgery with cardiopulmonary bypass aged over 60 years age: EG:58±6, CG:70±7 | Randomised, controlled trial           | 71 73        | Length of stay                          | -0.20 [-1.11, 0.71]      |                         |
| Frank et al (1997) | America | patients undergoing abdominal, thoracic, or vascular surgical procedures aged 71±1 years | Randomised, controlled trial           | 158 142      | Intraoperative bleed                    |                         | 130.00 [115.16, 144.84] |
|                 |          |                                                                            |                                        |              | Length of surgery                       |                         | -0.20 [-0.43, 0.03]     |
|                 |          |                                                                            |                                        |              | Shivering                               |                         |                         |
|                 |          |                                                                            |                                        |              | mortality                               |                         |                         |
| Lenhardt et al (1997) | America | patients undergoing elective major abdominal surgery age: EG:55±16, CG:56±17 | Randomised, controlled trial           | 76 74        | Length of surgery                       | -0.20 [-0.57, 0.17]      |                         |
| Kurz et al (2) (1996) | America | patients undergoing elective colorectal resection age: EG:59±14, CG:61±15 | Randomised, controlled trial           | 96 104       | Surgical site infection                 | 0.13 [0.04, 0.22]        |                         |
|                 |          |                                                                            |                                        |              | Length of stay                          | 2.60 [1.05, 4.15]        |                         |
| Schmied et al (1996) | Austria | patients undergoing unilateral total hip arthroplasties aged 63±10 years    | Randomised, controlled trial           | 30 30        | Intraoperative bleed                    | 230.00 [64.89, 395.11]   |                         |
### Table 2 Basic features of the included studies (Continued)

| Studies          | country     | Population                                                                 | Study type                          | Participants | Outcome indicators | Risk Difference (95%CI) | Mean Difference (95%CI) |
|------------------|-------------|-----------------------------------------------------------------------------|--------------------------------------|--------------|--------------------|--------------------------|--------------------------|
| Kurz et al (1996) | America     | patients undergoing elective colon surgery averagely aged 58 years          | Randomised, controlled trial         | 35           | Length of surgery  | \                         | 0.20 [0.35, 0.75]        |
|                  |             | age : EG:59±14 CG:57±15                                                    |                                      | 39           |                    |                          |                          |
| Yamada et al (2019) | Japan       | patients undergoing orthopaedic surgery age : EG: 68.6 ± 16-6 CG: 65.8 ± 17.2 | Observational study                  | 1088         | Surgical site infection | -0.00 [0.01, 0.00]      | \                        |
|                  |             |                                                                             |                                      | 7833         | mortality          | 0.00 [0.00, 0.01]       | \                        |
| Xiehe (2018)     | China       | Patients undergoing esophageal/ pancreatic surgery age : EG: 60.6±96 CG: 58±11.4 | Observational study                  | 103          | Surgical site infection | -0.00 [-0.12, 0.00]     | \                        |
| Williams et al (2018) | England     | patients undergoing total joint arthroplasty age : EG:72.0 ± 10-0 CG: 71.3 ± 10.3 | Observational study                  | 240          | Length of surgery  | \                         | 0.00 [-2.35, 2.35]       |
|                  |             |                                                                             |                                      | 1815         | Length of stay     | -2.70 [-5.78, 0.38]     | \                        |
|                  |             |                                                                             |                                      |              | readmission        | -0.01 [-0.04, 0.01]     | \                        |
| Frisch et al (2017) | America     | patients undergoing total hip and knee arthroplasty age : EG: 66±1±10.7      | Observational study                  | 887          | Length of surgery  | \                         | 0.70 [-3.05, 3.45]       |
|                  |             |                                                                             |                                      | 1510         | Length of stay     | \                         | 0.10 [-0.09, 0.29]       |
|                  |             |                                                                             |                                      |              | readmission        | 0.00 [-0.02, 0.02]      | \                        |
| Henriksen et al (2016) | Denmark     | patients diagnosed of infections age : EG: 75.8 [71.9-79.7] CG: 72.8 [71.8-73.7] | Observational study                  | 64           | mortality          | 0.19 [0.07, 0.31]       | \                        |
| Frisch et al (2016) | America     | patients undergoing operative treatment of a hip fracture age : EG: 79.6± 11.9 CG: 77.2±14.6 | Observational study                  | 260          | Length of surgery  | \                         | -4.90 [-10.89, 0.90]     |
|                  |             |                                                                             |                                      | 1265         | Length of stay     | \                         | -0.50 [-1.39, 0.39]      |
|                  |             |                                                                             |                                      |              | readmission        | -0.02 [-0.07, 0.03]     | \                        |
| Tsuchida et al (2015) | Japan       | patients undergoing gastroenterologic surgery aged 15-92 years age : 61±2 ± 15.7 (15-92) | Observational study                  | 528          | Surgical site infection | -0.00 [0.04, 0.04]     | \                        |
Assessment of risk of bias

Figure 3 shows the results of the risk-of-bias assessment of the included RCTs. Of the nine RCTs, five described the method of generating the random sequence, and the other four contained inadequate information for confirming the validity of randomization. Five RCTs were double-blinded and described allocation concealment, and three used blinded outcome assessment. Eight RCTs included reports of complete outcomes. Among the nine RCTs, bias of selective reporting could be neither confirmed nor rejected because of inadequate information. One RCT reported the presence of other biases. Table 3 shows the results of the risk-of-bias assessment of the included observational studies. The studies of the highest and lowest qualities reported 86-36% and 54-54% of the items in the checklist, respectively (median, 68-18%), indicating generally satisfactory quality.

Effects of hypothermia definition on occurrence of adverse events

Because the type of surgery affects clinical outcomes, the included studies were sub-grouped by the type of surgery and then analyzed assuming three definitions of intraoperative hypothermia: < 36.0 °C, < 35.5 °C, or < 35.0 °C (Table 4). The results showed that only when intraoperative hypothermia was defined as < 35.0 °C was the incidence of chills significantly higher ($p < 0.05$) in the hypothermic group undergoing esophagectomy than in the normothermic group.

Discussion

Clinical harm of intraoperative hypothermia is lower than expected

This analysis suggests that the risks of intraoperative hypothermia-associated adverse events are lower than the current consensus and other reports [19, 20, 26]. The difference may be partly attributable to when the

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| Studies     | Country   | Population                                    | Study type          | Participants | Outcome indicators | Risk Difference (95%CI) | Mean Difference (95%CI) |
|-------------|-----------|-----------------------------------------------|---------------------|--------------|--------------------|-------------------------|-------------------------|
| Billeter et al (2014) [30] | America   | patients undergoing elective operation age: EG: 61.3 ± 16-8 CG: 60.7 ± 16-3 | Observational study | 707 | Surgical site infection |
|             |           |                                               |                     | 698 | Length of stay                                 |
|             |           |                                               |                     |     | mortality                                     |
|             |           |                                               |                     |     | Length of ICU stay                             |
| Jeyadoss et al (2014) [31] | Australia | patients undergoing abdominal aortic aneurysm repair aged 71±6-9 years | Observational study | 66 | Surgical site infection |
|             |           |                                               |                     | 36 | Length of stay                                 |
|             |           |                                               |                     |     | mortality                                     |
|             |           |                                               |                     |     | Length of ICU stay                             |
| Kebrina et al (2012) [32] | England   | patients undergoing debulking surgery aged 63±9-117 years | Observational study | 81 | Surgical site infection |
|             |           |                                               |                     | 65 | Length of stay                                 |
|             |           |                                               |                     |     | mortality                                     |
|             |           |                                               |                     |     | readmission                                    |
| Williams et al (2) (2018) [33] | England   | patients undergoing hip fracture operations age: EG: 87-1 ±7-8 CG: 84-7 ±7-8 | Observational study | 92 | Surgical site infection |
|             |           |                                               |                     | 837 | Length of surgery                              |
|             |           |                                               |                     |     | Length of stay                                 |
|             |           |                                               |                     |     | mortality                                     |
|             |           |                                               |                     |     | Readmission                                     |
Fig. 2 Meta-analysis of incidences of adverse events in hypothermic versus normothermic group
studies were conducted and perhaps substantial variation in the type and duration of surgery. Other factors may have also contributed, such as the long causal chain from intraoperative to adverse events (e.g. mortality) and the confounding effects of medical practice. Surgical site infections are a key indicator of the quality of medical service [34]; therefore, surgeons may tend to be conservative in interpreting whether an infection is present, leading to a lower reported incidence in more modern times as compared to earlier decades.

Table 3 Quality assessment of observational studies

| Items                      | Yamada 2019 | Williams 2018 | Henriksen 2016 | Frisch 2016 | Williams 2018 | Frisch 2017 | Tsuchida 2015 | Billette 2014 | Jeyadoss 2013 | Kebria 2012 |
|----------------------------|-------------|---------------|----------------|-------------|---------------|-------------|---------------|---------------|---------------|-------------|
| Title and Abstract         | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Background/rationale       | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Objectives                 | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Study design               | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Setting                    | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Participants               | ✓           | x             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Variables                  | x           | x             | x              | x           | x             | x           | x             | x             | x             | x           |
| Data sources / measurement | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Bias                       | ✓           | x             | x              | x           | x             | x           | x             | x             | x             | x           |
| Study size                 | x           | x             | x              | x           | x             | x           | x             | x             | x             | x           |
| Quantitative variables     | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Statistical methods        | x           | x             | x              | x           | x             | x           | x             | x             | x             | x           |
| Participants               | ✓           | x             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Descriptive data           | ✓           | x             | ✓              | ✓           | x             | x           | x             | x             | x             | x           |
| Outcome data               | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Main results               | ✓           | x             | ✓              | ✓           | x             | x           | x             | x             | x             | x           |
| Other analyses             | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Key results                | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Limitations                | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Interpretation             | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Generalisability           | ✓           | ✓             | ✓              | ✓           | ✓             | ✓           | ✓             | ✓             | ✓             | ✓           |
| Funding                    | ✓           | x             | ✓              | ✓           | x             | x           | x             | x             | x             | x           |
| Percentage                 | 86.36%      | 54.55%        | 77.27%         | 68.18%      | 54.55%        | 72.72%      | 68.18%        | 59.09%        | 68.18%        | 54.54%      |
| Median                     | 68.18%      |               |               |             |               |             |               |               |               |             |
Both RCTs and observational studies reported the incidence of surgical infection, duration of surgery, duration of hospital stay, and mortality rate. Additionally, RCTs were more likely to have reported intraoperative blood loss and chills/shivering, whereas the observational studies focused on readmission rates and duration of ICU stays. The meta-analysis of RCTs found there was significantly higher intraoperative blood loss, surgical site infection, and intraoperative/postoperative chills/shivering in patients experiencing hypothermia than those who did not. In comparison, the high-quality observational studies showed no statistically significant differences in the incidences of adverse events between the two groups. The different findings from these two categories of studies in the present meta-analysis may be explained by their different experimental designs, patient characteristics, and types of surgery.

Is 36·0 °C an adequately sensitive criterion for intraoperative hypothermia?

Our analysis was based on the current consensus of the definition of intraoperative hypothermia (< 36·0 °C) and found fewer differences than other studies. This raised the question of whether < 36·0 °C is an adequately sensitive cut point for classifying intraoperative body temperature as normal or hypothermic. Our exploratory analyses showed persistent gaps between the expected and actual incidences of adverse events. Even assuming a tentative definition of intraoperative hypothermia of < 35·0 °C, except for chills the clinical risks of adverse events in the hypothermic group were not significantly higher than those in the normothermic group. This is partly explained by the unequal sizes of the two groups; however, it may also be related to the intrinsically moderate harm of intraoperative hypothermia. Several earlier studies have shown similar results. In a recent registry study of 7908 colorectal patients, Sessler et al. founded that intraoperative core temperature < 35·5 °C was associated with an increased odds ratio of serious infection, but superficial infection and duration of hospitalization were not significantly related to intraoperative core temperature. In the subgroup analysis of colorectal cancer patients, none of the above was related to intraoperative core temperature [35]. In 2007, Iwata et al. reported that when intraoperative hypothermia was defined as a body temperature of < 35·5 °C, the durations of surgery in the hypothermic and normothermic groups were not significantly different (396 ± 204 vs. 327 ± 97 min) [36]. Two other studies showed that when intraoperative hypothermia was defined as < 35·0 °C, the hypothermic group had a significantly longer duration of surgery than the normothermic group (396 ± 204 vs. 252 ± 180 min) [37] and a non-significantly higher mortality rate [12·5% (5/40) vs. 4·5% (3/67)] [38]. These data also support our finding that in current clinical practice, the harm induced by intraoperative hypothermia is less than previously established.

Do we still need to prevent intraoperative hypothermia?

The awareness of the potential for harm associated with intraoperative hypothermia has been increasing since the 1990s, with an increased focus on preventing hypothermia. However, the present study suggests that the current consensus on its harm is likely overestimated. Notably, this does not imply that the severe adverse effects of intraoperative hypothermia and its risk

| Table 4 Incidences of adverse events under intraoperative hypothermia definition of <36·0°C, <35·5°C, or <35·0°C |
|---------------------------------------------------------------|
| **36·0°C** | Normothermia | Hypothermia | P* | 35·5°C | Normothermia | Hypothermia | P* | 35·0°C | Normothermia | Hypothermia | P* |
|---------------------------------------------------------------|
| **Esophagectomy** | | | | | | | | | | | | |
| Intraoperative bleed ml | 285·19 (171·11) | 255·70 (144·24) | 0·297 | 273·29 (157·37) | 263·28 (160·52) | 0·511 | 279·24 (162·95) | 213·66 (109·77) | 0·108 |
| Length of stay d | 20·95 (16·40) | 21·60 (36·73) | 0·277 | 20·44 (14·97) | 22·95 (45·23) | 0·066 | 22·10± (30·76) | 16·29 (6·32) | 0·140 |
| Length of PACU min | 0·43 (0·09) | 0·39 (0·14) | 0·302 | 0·37 (0·16) | 0·38 (0·16) | 0·868 | 0·38 (0·17) | 0·37 (0·10) | 0·478 |
| Superficial Surgical Site Infection % | 2/58 | 0/62 | 0·232 | 2/80 | 0/40 | 0·552 | 2/103 | 0/17 | 1·000 |
| Shivering % | 0/58 | 2/62 | 0·496 | 0/80 | 2/40 | 0·109 | 0/103 | 2/17 | 0·019 |
| **Pancreatectomy** | | | | | | | | | | | | |
| Intraoperative bleed ml | 541·48 (434·55) | 542·71 (506·23) | 0·808 | 528·87 (416·52) | 615·73 (154·90) | 0·977 | 527·12 (421·15) | 1118·33 (1300·47) | 0·528 |
| Length of stay d | 23·82 (12·59) | 24·22 (11·75) | 0·844 | 23·20 (11·77) | 27·50 (14·42) | 0·273 | 23·75 (12·26) | 27·33 (12·58) | 0·533 |
| Length of PACU min | 0·46 (0·18) | 0·50 (0·18) | 0·272 | 0·46 (0·19) | 0·51 (0·25) | 0·166 | 0·46 (0·20) | 0·33 | 0·337 |
| Superficial Surgical Site Infection % | 2/79 | 1/41 | 1·000 | 2/102 | 1/18 | 0·389 | 3/117 | 0/3 | 1·000 |
| Shivering % | 0/79 | 0/41 | - | 0/102 | 0/18 | - | 0/117 | 0/3 | - |

*Chi-square test for categorical variables, T-test or rank sum test for continuous variables
can be ignored. In fact, practices to prevent intraoperative hypothermia are often initiated.

Currently, perioperative body temperature monitoring is not routinely performed in China, with passive measures used to prevent hypothermia [1]. Yi et al. reported that in China, only 10.7% of patients received active temperature monitoring and treatment and that the use of more economically efficient equipment was unpopular [39]. Nevertheless, economic factors should not be the principal consideration in prevention of intraoperative hypothermia. Instead, the focus should be aimed at improving the awareness of protecting body temperature as a critical life sign. Additionally, a full picture of the clinical and economic benefits of hypothermia prevention needs to be revealed under various definitions of hypothermia.

**Research novelty and limitations**

This meta-analysis addressed the harm of intraoperative hypothermia based on synthesizing evidence from multiple studies and thus overcomes the limitations from examining individual studies. The findings of this study provide new insight into the clinical value of intraoperative hypothermia and its prevention. We also examined the possibility of refining the current definition of intraoperative hypothermia. Evidence from multiple sources (analyses of data from studies adopting a lower temperature criterion, a recently completed RCT in China, and meta-analysis of publications) suggest that differences exist from pre-conceived notions of adverse events due to the surgical hypothermia.

The publications were categorized into RCTs and observational studies for separate meta-analyses, and the different findings of the two categories may be primarily attributed to heterogeneity within individual studies (e.g., surgery, procedures, and location of study) rather than the methodological design of the current meta-analysis (i.e., RCT vs. observational). Whether data from RCTs and observational studies can be directly combined for one analysis remains debatable [40, 41]; therefore, we separated them. We have tried to compare the heterogeneity of RCTs and observational studies as a whole and subgroups, and found that separating them can effectively reduce the heterogeneity. Because of the relatively small number of studies included, a subgroup analysis (e.g., by the type of surgery) is methodologically questionable. Therefore, we only performed analyses for uncertainty using an effects model and study quality, which may have affected the robustness of the meta-analysis findings.

**Conclusions**

The evidence from our research suggests that differences exist from pre-conceived notions of adverse events due to the surgical hypothermia, and 360°C is not an adequately sensitive criterion for intraoperative hypothermia. These findings may contribute to a better understanding of intraoperative hypothermia and its prevention in clinical practice in fields such as anesthesia and nursing. For more thorough assessment, future works should include larger-scale real-world studies and incorporate control over other medical practices.

**Abbreviations**

CI: Confidence interval; ICU: Intensive care unit; MD: Mean difference; OR: Odds ratio; PACU: Post anesthesia care unit; RCT: Randomized controlled trial; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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**Authors’ contributions**

WT conceptualized the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study design: AM, WT. Literature review: HX, ZW, YL, WT, XG. Data analysis: HX, ZW, YL. Drafting of manuscript: HX, WT. Critical revision of the manuscript: DM, JS. All authors have read and approved the manuscript.

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**Availability of data and materials**

The data that support the findings of this study are available from Peking Union Medical College Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Peking Union Medical College Hospital.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

We declare there is no competing interests.

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