Original Article

# The effects of hypothermia in thrombosis: a systematic review and meta-analysis

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**Background:** Systemic therapeutic hypothermia is commonly used in patients with craniocerebral injury, cardiopulmonary resuscitation, and high fever, but its effect is still controversial that some reported hypothermia is helpful for thrombosis while someothers thought it had limited effects on thrombosis. In order to explore the effect of intraoperative hypothermia on patients, we analyzed the role of hypothermia in promoting thrombosis, in order to guide the implementation of corresponding countermeasures and timely intervention.

**Methods:** The databases of PubMed, Embase, Cochrane database, and China National Knowledge Infrastructure (CKNI) were used to retrieve relevant studies. The selected literatures were evaluated with Review Manager 5.2. Forest plots, sensitivity analysis, and bias analysis were used to analyze the included studies.

**Results:** A total of 2,053 patients in 8 trials (762 patients were randomly divided into hypothermia group and 1,191 patients in normothermia group) were included in the meta-analysis. High quality randomized evidence suggested that therapeutic hypothermia is associated with thrombosis and high mortality in critically ill patients. Although therapeutic hypothermia may still be beneficial in specific environments, it is best to avoid the routine application of therapeutic hypothermia outside the circumstances specified in the international guidelines (adult cardiac arrest and neonatal hypoxic ischemic encephalopathy).

**Discussion:** This study shows that intraoperative hypothermia is more likely to cause thrombosis, massive hemorrhage, and even death in comparison to routine nursing.

**Keywords:** Intraoperative; thrombus; hypothermia

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## Introduction

Thrombotic diseases are life threatening and seriously threaten human health. They include many common diseases such as coronary heart disease, myocardial infarction, ischemic stroke, venous thrombosis, and pulmonary thromboembolism (1-3). The incidence rate, disability rate, and mortality rate of thrombotic diseases are very high. Thrombus is mainly divided into white thrombus, mixed thrombus, red thrombus, and transparent thrombus. It can be prevented by taking part in physical activities, increasing high-density lipoprotein (HDL), and medication (4-6).

A thrombus is a small clot of blood formed on the surface of a vessel or repair of the internal surface of the cardiovascular system. Variable fluid-dependent type clots are composed of insoluble fibrin, deposited platelets, accumulated white blood cells, and trapped red blood cells (7-9). Thrombosis is a multifactorial process in which a group of genetic and environmental factors interact and influence each other. The most common clinical characteristics of patients with thrombosis are hereditary, recurrent, severe symptoms, abnormal thrombosis sites, and younger onset time.

The normal body temperature of a healthy person generally fluctuates between 36.5 and 37.5 ℃ in a healthy state, which is a relatively constant value. It is regulated by the body temperature center in the hypothalamus (10,11). The heat generated by the human body usually maintains a balance with the heat emitted; however, during surgery, this balance is destroyed for various reasons, resulting in hypothermia (34–36 ℃). Studies have shown that intraoperative hypothermia is very harmful to patients. It is linked with an increased infection rate of surgical incision, affects the body's coagulation, cardiovascular, and central nervous system function, and metabolism (12,13).

The correlation between hypothermia and thrombosis (14,15). To address these concerns, we conducted this meta-analysis to evaluate the relationship between hypothermia and thrombosis. This research analyzed more indicators than previous similar meta-analysis and update this topic since we include several recent articles. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1925).

## Methods

### Search strategy

We performed an electronic search for original articles, clinical trials, reviews, and meta-analyses published between 2000 and 2020. We searched the databases of PubMed, Embase, the Cochrane database, and China National Knowledge Infrastructure (CNKI), using the keywords: (I) low temperature; (II) thrombosis. Boolean operators OR and AND Boolean operators are used to search for combining words with different meanings. To achieve the maximum sensitivity of the search strategy and identify all studies, we manually screened the reference lists of all retrieved articles to identify potentially relevant studies further.

### Eligibility criteria

The inclusion criteria were as follows: (I) considered to be randomized trials or controlled studies; (II) the hypothermia group was compared with the normothermia group; (III) complications that occurred during the treatment were clearly recorded; (IV) no overlapping data. The exclusion criteria were as follows: (I) other health problems were the research subject; (II) patients received other diagnostic technology; (III) there was a lack of available data on the research. The title and abstract of the articles were independently evaluated by two researchers to determine whether they met the inclusion and exclusion criteria. When there was a difference in opinion on a document, the two authors resolved the problem through mutual discussion and requested help from a third author if necessary.

### Data collection and quality assessment

We carefully read the full text of the article and extract features from each study. The data extracted from these studies include the first author's name, country, year of publication, gender, language, sample age, sample size, and the research period of each article. Then, we used the revised Cochrane bias risk assessment tool to assess the overall quality of the included studies tool (https://methods.cochrane.org/risk-bias-2).

### Statistical analysis

All the meta-analyses were performed with the software Review Manager 5.2 (RevMan, The Cochrane Collaboration, 2013) and bias analysis of the studies were conducted to examine the quality of articles. A funnel plot was used to estimate publication bias. Review Manager was used to evaluate the overall results between the hypothermia group and the normothermia group. The odds ratio (OR) of 95% confidence interval (CI) was calculated to estimate the relationship between intraoperative hypothermia group and normothermia group on complications. When $I^2>50\%$, we considered that there was heterogeneity and selected the random effects model; otherwise, the fixed effects model was selected for analysis. For all statistical comparisons, a P value of less than 0.05 was considered statistically significant.

## Results

### Study selection

The preliminary result of our electronic search is 892

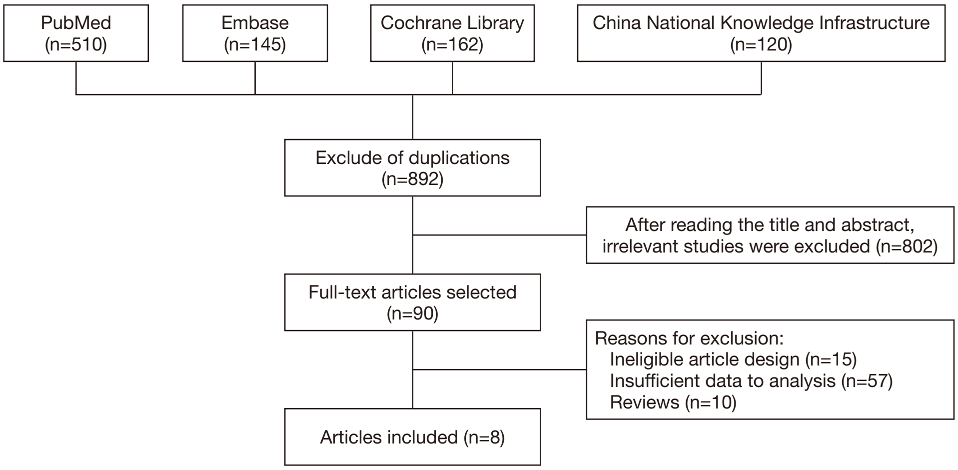


**Figure 1** Flow diagram of the study selection.

**Table 1** Characteristics of studies included in the meta-analysis

| Study | Year | Language | Country | No. of patients (male/female) | Age range (mean) | No. of hypothermia group | No. of normothermia group | Years of onset |
|---|---|---|---|---|---|---|---|---|
| Achim | 2014 | English | Switzerland | 32/11 | 57.1±12.2 | 22 | 21 | January 2011 to March 2013 |
| Andremon | 2017 | English | France | 400/201 | 60.6±15.1 | 89 | 512 | August 2012 to November 2014 |
| Dae | 2017 | English | America | 250/67 | 65±13.2 | 157 | 160 | January 2003 to August 2010 |
| Garcıa | 2018 | English | Spain | 124/21 | 59.8±11.7 | 105 | 40 | May 2005 to July 2016 |
| Joffre | 2014 | English | France | 166/42 | 60.3±12.3 | 55 | 153 | August 2000 to January 2012 |
| Moellhoff | 2020 | English | Germany | 343/272 | 51.9±27.8 | 271 | 244 | June 2012 to March 2019 |
| Nichol | 2015 | English | America | 46/8 | 57.3±8.7 | 28 | 26 | January 2013 to January 2014 |
| Zhang | 2019 | English | China | 56/14 | 62.7±6.8 | 35 | 35 | March 2013 to June 2017 |

articles. After careful reading, 90 papers meet the primary standards. In further screening, 82 articles were excluded due to inconsistent research design, insufficient data and inconsistent article types. Finally, eight papers are selected for analysis. *Figure 1* shows a flowchart of identification, inclusion, and exclusion.

### *Study characteristics*

*Table 1* summarizes the types of studies reported and the total number of patients associated with each group, including author, year of publication, language, country, gender, age, sample size and collection time (16-23). A total of 2,053 samples were collected from 2000 to 2019, and 8 articles were published, with sample sizes of 43–615. The participants included 1,417 women and 636 men.

### *Risk of bias in studies*

The quality of the studies was assessed though the risk of bias table in the Review Manager 5.2 Tutorial (24), and the evaluation is shown in *Figures 2,3*. The assessment revealed limited bias among the included articles. Only 1 study showed the problem of selection bias. From the summary of deviations, there were no problems in selection deviation, performance deviation, loss deviation, and reporting deviation. Generally speaking, there were 2 trials with risk of bias and 6 trials without risk.

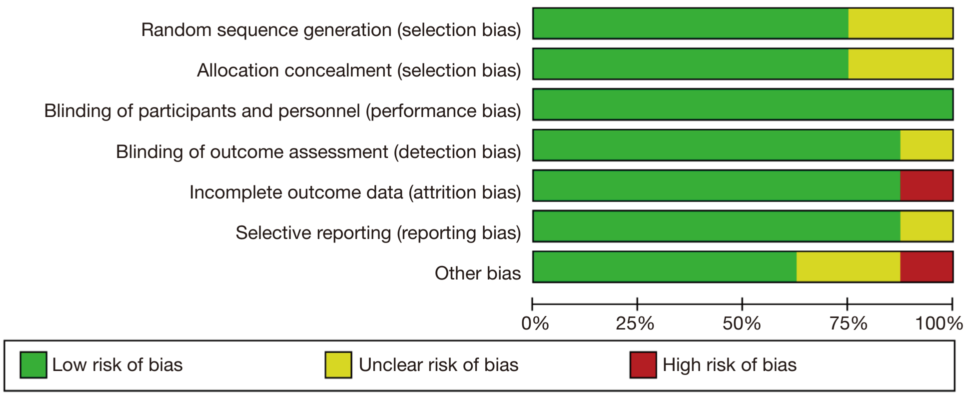


**Figure 2** Assessment of the quality of the included studies: green indicates a low risk of bias, yellow an unclear risk of bias, and red indicates a high risk of bias.


**Figure 3** Quality assessment of included studies.

### *Results of individual studies*

*Figure 4* shows the forest map of intraoperative thrombosis in the hypothermia group and normothermia group participants. A total of 8 studies were involved in the analysis. The analysis showed that there were differences between the two groups. The probability of intraoperative thrombosis in the hypothermia group was higher than that in the normothermia group (OR =1.89, 95% CI: 0.87 to 4.13, P=0.0003, $I^2$=74%).

*Figure 5* shows a forest plot of intraoperative mortality in patients in the hypothermia and normothermia groups. A total of 5 studies were involved in the analysis. The analysis showed that there were differences between the two groups. The probability of intraoperative death in the hypothermia group was higher than that in the normothermia group (OR =2.84, 95% CI: 0.61 to 13.27, P<0.00001, $I^2$=89%).

*Figure 6* shows a forest plot of the probability of massive intraoperative bleeding in participants in the hypothermia and normothermia groups. A total of 6 studies were involved in the analysis, and it was revealed that there were differences between the two groups. The probability of massive intraoperative bleeding in the hypothermia group was higher than that in the normothermia group (OR =1.81, 95% CI: 0.85 to 3.83, P<0.0001, $I^2$=81%).

### *Results of sensitivity analysis and publication bias*

Sensitivity analysis was performed to test the stability of the results. After eliminating the relative outliers, the sensitivity of or value of heterogeneity decreased from 74% to 35%. The results showed that this heterogeneity was mainly due to the study by Moelhoff *et al.* in 2020. A forest map without the article by Moelhoff *et al.* is shown in *Figure 7*.

Funnel plot analysis was used to analyze the probability of thrombosis in the hyperthermia group and normothermia

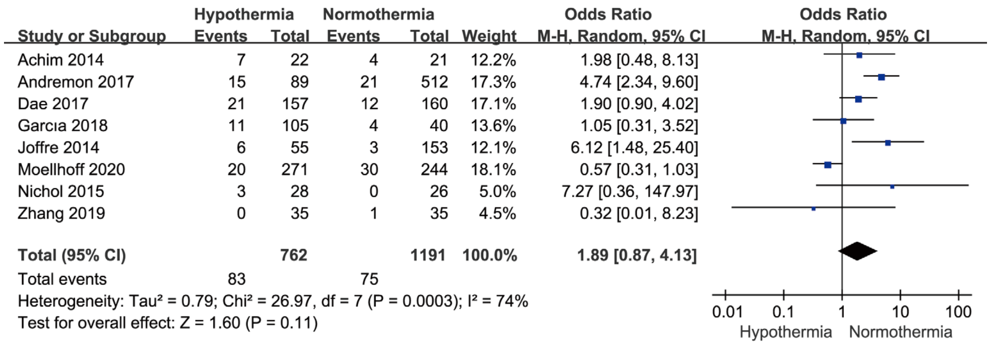


**Figure 4** Forest plot of the incidence of thrombus in patients with intraoperative hypothermia.

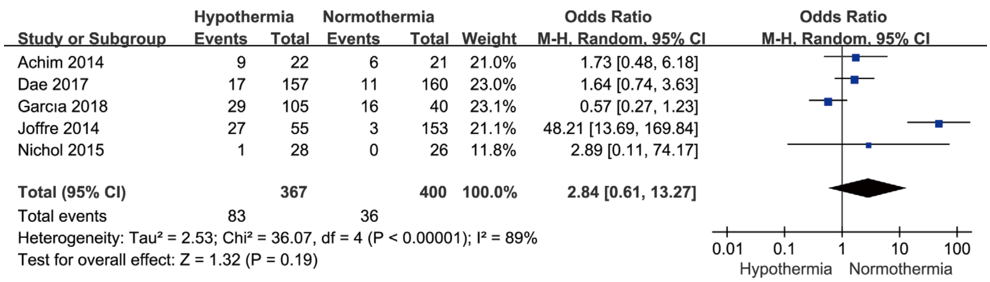


**Figure 5** Forest plot of mortality of patients with hypothermia during operation.

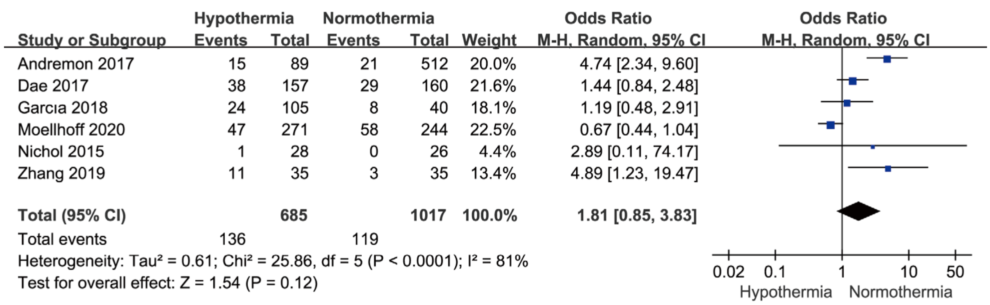


**Figure 6** Forest plot of the incidence of massive hemorrhage in patients with intraoperative hypothermia.

group. All 8 studies were included in the plot. To some extent, the results showed that there was limited publication bias due to the good symmetry of funnel plot (*Figure 8*).

## Discussion

There are three factors of thrombosis include vascular wall injury, slow blood flow rate and hypercoagulable state. Problems in any of these three aspects can lead to thrombosis. Vascular wall damage is more common in patients with a history of venipuncture, deep venous catheterization or surgical injury of blood vessels, which can lead to thrombosis. Patients with coagulation factor disorder, hemophilia, thrombophilia or lack of coagulation factor can lead to early thrombosis after operation. There are also some factors, such as changes in blood flow status, long-term bed rest, malignant tumors, major surgery, severe blood loss after surgery, and more fluid loss after surgery, which can lead to slow blood flow and thrombosis (24-26). Intraoperative hypothermia increases the risk of incision infection and bleeding. We identified 8 studies that met the inclusion criteria to assess the effect

 

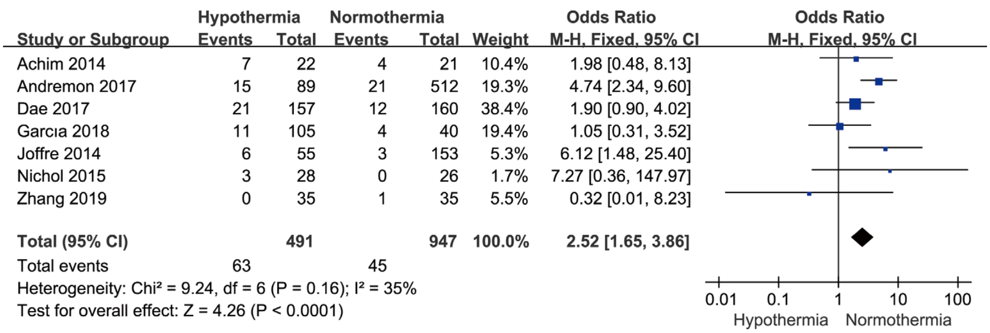


**Figure 7** Sensitivity analysis of the incidence of thrombosis in patients with intraoperative hypothermia.

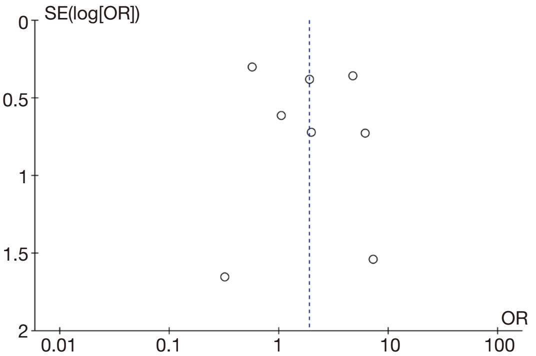


**Figure 8** Funnel plot of publication bias.

of intraoperative hypothermia on promoting thrombosis. These studies showed that the incidence of thrombosis and mortality in the hypothermia group were higher than those in the normothermia group. Active body temperature management can reduce the incidence of thrombosis and mortality, otherwise there is risk. Our results are consistent with the report by Jin *et al.* (24).

Thrombosis and thromboembolism are two kinds of diseases caused by pathological processes, and are clinically called thrombotic diseases (25-28). According to reports, thrombus can be divided into venous thrombosis, arterial thrombus and microthrombus according to the anatomical position. According to the thrombus composition, it can be divided into platelet thrombus, red blood cell thrombus, mixed thrombus and fibrin thrombus (29-31). Thrombotic diseases seriously threaten human health and life. Their incidence rate is the highest (1.35%) among various diseases and has been increasing gradually in recent years.

Thrombotic disease results from abnormal blood clots in the circulatory system (32,33), for which there are three causes: vascular damage, blood changes, and blood stasis. Thrombosis is a group of complications caused by many different diseases and causes. Due to the difference of various basic diseases and the location of thromboembolism, the clinical manifestations of thrombosis are also different.

The body dynamically balances heat production and heat dissipation through the thermoregulatory center, so as to maintain the core temperature at 36±0.4 ℃. Due to the large area and extended duration of exposure of internal organs or limbs during surgery, infusion of a large amount of room temperature liquid, repeated and prolonged washing of the operation area, and the inhibitive effect of anesthetics on the body's thermoregulatory function, the body temperature of patients falls below the normal range during surgery (34,35). Intraoperative hypothermia is very harmful to patients, especially the elderly and children, as it can increase oxygen consumption, increase heart rate, worsen coagulation function, damage immune function, and even endanger life.

In conclusion, the incidence of thrombosis and mortality in the hypothermia group were higher than those in normothermia group.

There were some limitations to this paper. First, comparisons between the same diseases were not considered, which should be evaluated in further studies (36-38). Second, the details of the complications were not included, which should also be evaluated in the future.

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## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1925

 

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1925). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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