

# Safety of Albumin and Hydroxyethyl Starch as Priming Fluid for Cardiopulmonary Bypass in Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials

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## Research article

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# Abstract

**Introduction:** Hydroxyethyl starch (HES) has been widely used for volume expansion, but its safety as priming fluid for cardiopulmonary bypass has been questioned recently. The aim of this meta-analysis is to compare the safety of albumin and hydroxyethyl starch as priming fluid for cardiopulmonary bypass.

**Methods:** Pubmed, Embase database and Cochrane Library were searched for randomized controlled trials (RCTs) involving patients who received HES or albumin as priming fluid for cardiopulmonary bypass in cardiac surgery published up to October 2019. Two reviewers independently extracted the valid data, including the length of ICU stay, ventilator time, the length of hospital stay, crystal volume, fresh frozen plasma, platelet input, blood loss, blood platelet count, hemoglobin value, fibrin, APTT, PT, urea, creatinine and urine volume. Meta-analysis was performed with revman version 5.3.

**Results:** Total 9 RCTs involving 452 patients were included in this meta-analysis. Compared with albumin, HES had similar effects on the length of ICU stay (MD = 0.70; 95% CI: -0.14 to 1.55; P = 0.10; I<sup>2</sup> = 89%); ventilation time (MD = 2.31; 95% CI: -3.93 to 8.55; P = 0.47; I<sup>2</sup> = 60%); the length of hospital stay (MD = -0.31; 95% CI: -2.00 to 1.37; P = 0.71; I<sup>2</sup> = 0%); crystal volume (SMD = 0.26; 95% CI: -0.09 to 0.61; P = 0.15; I<sup>2</sup> = 0%); fresh frozen plasma (SMD = 0.25; 95% CI: -0.08 to 0.59; P = 0.66; I<sup>2</sup> = 0%); platelet input (SMD = -0.17; 95% CI: -0.59 to 0.26; P = 0.45; I<sup>2</sup> = 0%); blood loss (SMD = 0.31; 95% CI: -0.01 to 0.63; P = 0.06; I<sup>2</sup> = 29%); platelet count (SMD = -0.21; 95% CI: -0.54 to 0.11; P = 0.20; I<sup>2</sup> = 29%); hemoglobin value (SMD = 0.1; 95% CI: -0.15 to 0.36; P = 0.42; I<sup>2</sup> = 0%); fibrin (SMD = 0.12; 95% CI: -0.19 to 0.44; P = 0.45; I<sup>2</sup> = 0%); APTT (MD = 1.13; 95% CI: -2.06 to 4.32; P = 0.49; I<sup>2</sup> = 0%); PT (MD = 0.10; 95% CI: -0.21 to 0.40; P = 0.52; I<sup>2</sup> = 0%); creatinine (SMD = 0.09; 95% CI: -0.32 to 0.50; P = 0.66; I<sup>2</sup> = 51%); urine volume (SMD = 0.11; 95% CI: -0.26 to 0.48; P = 0.55; I<sup>2</sup> = 43%). but did not increase urea (SMD = -0.46; 95% CI: -0.81 to -0.11; P = 0.01; I<sup>2</sup> = 0%).

**Conclusions:** HES was safe and effective compared to albumin as priming fluid for cardiopulmonary bypass because it did not affect renal function, coagulation function, liquid input, or the length of ICU stay and ventilation time of patients.

## Introduction

Currently, cardiopulmonary bypass (CPB) is an important adjunct to cardiac surgery because it improves the success of cardiac surgery. By providing low blood flow perfusion, CPB prolongs the safe operation time and provides basic blood flow supply for various organs of the human body. However, CPB can lead to blood dilution, decrease plasma osmotic pressure, damage vascular endothelial cells (VEC), increase vascular permeability, and cause systemic complications such as postoperative tissue edema, cardiac insufficiency, pulmonary exudation, infection, liver and renal insufficiency<sup>[1]</sup>. At present, how to select priming fluid for CPB is a focus of controversy.

CPB priming solution directly affects the change of colloid pressure and the incidence of VEC damage after cardiac operation. Albumin has become the preferred fluid for patients undergoing CPB in many centers. Compared with other liquids, albumin is a natural colloid that effectively provides plasma colloid osmotic pressure [2], protects vascular endothelium, delays fibrinogen adhesion in circulation pipeline, and reduces surface activation and platelet adhesion [3]. Large randomized controlled trials comparing albumin with other fluids have not been conducted in patients undergoing cardiac surgery. Engelman et al. [4] reported that preoperative hypoalbuminemia ( $< 25 \text{ g}\cdot\text{L}^{-1}$ ) is an independent risk factor for various adverse outcomes after cardiac surgery. Fritz et al. [5] found that hypoalbuminemia was even better than EuroSCORE score in predicting mortality after cardiac surgery, and the cut-off point for hypoalbuminemia was  $18 \text{ g}\cdot\text{L}^{-1}$ . Several other studies have evaluated the effectiveness of albumin as priming fluid for CPB. A retrospective cohort study by Sedrakyan et al. [6] enrolled 19,578 CABG patients, the results showed that compared with the older generation of artificial colloid, albumin was associated with a reduction in mortality (OR = 0.8, 95% CI: 0.67 to 0.96), and compared to crystal liquids, the albumin group required less priming fluid. In addition, the use of albumin as priming fluid can reduce postoperative blood loss. Onorati et al. [7] retrospectively compared low dose albumin with pure crystal as priming fluid solution in 377 patients, and patients who received albumin need less blood transfusion and had less blood loss after surgery.

Hydroxyethyl Starch (HES) is another plasma substitute widely used in the clinic practice since 1960s, which is made of high molecular weight amylopectin through degradation, hydroxyethylation and further processing. HES is mainly used to prevent or treat intraoperative hypotension and hemodilution [8,9]. On June 14, 2013, due to safety concerns, the European Medicines Agency (EMA) and Drug Risk Assessment Committee (PRAC) recommended the delisting of HES. At the end of June 2013, U.S. officials pointed out that HES may increase the death rate of patients, cause the decline of hemostatic function of patients [10] and have serious negative effects on the kidneys [11], and issued a warning to HES [12]. A meta-analysis by Myburgh et al. [13] showed that HES can increase the amount of blood transfusion during reoperation due to bleeding. These negative effects are not directly related to the average molecular weight and substitution level of HES. However, a recent study showed that the use of artificial colloid as priming fluid for CPB has not raised the risk of organ injury [14]. Moreover, many randomized controlled clinical studies showed that for patients undergoing cardiac surgery with normal organ function and coagulation function, the use of artificial colloid as priming fluid for CPB has not raised the risk of organ injury. At present, artificial colloidal fluids are still widely used for priming fluid of CPB, but there is no definite clinical evidence to support the safety or even superiority of artificial colloid priming fluid of CPB. Therefore, we performed this meta-analysis to compare the safety of albumin and HES as priming fluid for CPB to provide reference for clinical application.

## Materials And Methods

### 1.1 inclusion criteria and exclusion criteria

**1.1.1 Included in the study:** The types of literature included in the study are randomized controlled trial (RCT) regardless of whether blind method and allocation concealment are used. The language is limited to English.

**1.1.2 The inclusion criteria were:** (1) RCTs;(2) The subjects of the study were heart disease patients;(3) HES was used in the test group and albumin was used in the control group.(4) All were extracorporeal circulation operations.

**1.1.3 The exclusion criteria were:** (1) Summary, review, case report, clinical observation and unpublished data;(2) No statistical ;(3) Repeated detection or repeated published research;(4) No mention of research type;(5) Unable to obtain full text;(6)Coagulopathy;(7)Anemia; (8)Hepatic dysfunction, (9)Reoperation.

**1.1.4 Interventions:** The colloidal liquid in the experimental group was HES. The colloidal solution in the control group was human serum albumin.

**1.1.5 Outcome indicators included:** the length of ICU stay, ventilator time, the length of hospital stay, crystal volume, fresh frozen plasma, platelet input, blood loss, blood platelet count. hemoglobin value, fibrin, APTT, PT, urea, creatinine and urine volume.

## 1.2 Search strategies

PubMed, Embase and the Cochrane Library were searched using the following key words and related free words: 'cardiopulmonary bypass', 'albumin', 'Hydroxyethyl Starch'. The relevant clinical trials were those published before October 2019 that met the above criteria. The search was limited to 'randomized controlled trials', 'human', and the language was restricted to English.

## 1.3 Study selection and data extraction

Two reviewers (Ye and Zang) independently screened the search results and obtained the full texts according to the inclusion and exclusion criteria, and independently extracted the valid data. Data extraction and analysis were performed under the supervision of an experienced statistician (Mo).

## 1.4 Quality assessment

Risk of bias assessment was performed using the 'Risk of bias' tool in the Cochrane Handbook for Systematic Reviews of Interventions<sup>[15]</sup>. We assessed each study according to the quality domains of random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other bias.

## 1.5 statistical analysis

Data were analyzed by Review Manager (5.3 RevMan, Cochrane Collaboration). The continuous effect data were assessed by mean difference (MD). When median and extreme values were presented in the original articles, these data were converted into mean and standard deviation according to relevant

formulas<sup>[16]</sup>. Non-continuous data were assessed by the risk ratio (RR). Statistical heterogeneity of the data was analyzed quantitatively by the I<sup>2</sup>-test<sup>[17]</sup>. The decision of to use fixed effect or random effect is based on whether we believe that the true effect is the same in all studies, i.e. all of the studies are identical and the true effect size is the same across all studies. If this is believed to be true (which is a very strong assumption, rarely found), then fixed effect should be used; if not, random effect should be used instead. Publication bias was tested by funnel plots. Two-sided tests were performed with a significant difference defined at P <0.05.

## Results

### 2.1 Literature search and study selection

Figure 1 showed the flow chart of the literature search, and we identified total 665 articles, from which 452 were excluded after reading the titles, abstracts and full texts. Finally, 9 RCTs were included in this meta-analysis. Figure 1

### 2.2 The characteristics of the 9 RCTs

The 9 RCTs included 452 patients treated with CPB. The characteristics of intervention measures, outcome indicators, and number of participants of 9 RCTs were shown in Table 1.

Table 1. Characteristics of the included RCTs.

Author	% of male	Location	Age (Y)	Sample Size		Follow-up time	Type of heart disease	Intervention	Outcome assessment
				HES	HA				
Miao 2014	38	China	0.67±0.23	30	30	6 hours after surgery	CHD	6% HES 130/0.4 or 3.3% albumin	the length of ICU stay, ventilator time, crystal volume, fresh frozen plasma, urine volume
patel 2016	64	India	1.33±1.13	35	35	24 hours after surgery	CHD	albumin or HES130/0.4 6%	urine volume, ventilator time, the length of ICU stay, blood platelet count, hemoglobin value, urea, creatinine
saunders 1983		America	60.7±9.24	10	10	After Bypass After arrival on ICU until first postoperative morning	aortocoronary bypass	HES or 25% albumin	urine volume, fibrinogen
Philippe 2013	52	America	5.2±7.40	31	30		CHD	6% HES 130/0.4 or 5% human albumin	fresh frozen plasma, Platelet input, amount of bleeding, fibrinogen, APTT, hemoglobin value, urea, creatinine
Kuitunen 2004	90	Finland	60±20	15	15	2 hours after surgery	aortocoronary bypass	HES 120; molecular weight 120,000 daltons or 4% human	the length of ICU stay, the length of hospital stay, crystal volume, amount of bleeding, blood platelet count, hemoglobin value, urine
Cho 2014	63	Korea	60.5±15.33	18	18	24 hours after surgery	complex valvular heart disease	6% hydroxyethyl starch (HES) 130/0.4 or albumin	the length of ICU stay, the length of hospital stay, amount of bleeding, blood platelet count, APTT, PT
Palanzo 1982		America	57.6±8.59	37	42	24 hours after surgery	patients undergoing myocardial revascularization	25% albumin or 6% hetastarch	fresh frozen plasma, Platelet input, blood platelet count, fibrinogen, APTT, PT, hemoglobin value
Mahmood 2015	63	Iran	63.96±9.13	30	30	24 hours after surgery	aortocoronary bypass	5% Albumin or 6% Hydroxyethyl Starch 130/0.4	amount of bleeding, creatinine
CHOI 2010	30	Korea	54.5±12.86	18	18	24 hours after surgery	patients undergoing mitral valvular heart surgery	5% Albumin or 6% Hydroxyethyl Starch 130/0.4	urine volume, crystal volume, amount of bleeding, blood platelet count, APTT, PT, hemoglobin value

According to Cochrane's systematic evaluation manual, the methodological quality of the 9 clinical studies included in the study was evaluated for items such as random method, allocation concealment, blind method, withdrawal from missed visits and selective reporting (Figure 2).

## 2.3 Results of meta-analysis

**2.3.1 The length of ICU stay.** Four RCTs reported the length of ICU stay. There was no statistical heterogeneity among the studies ( $P = 0.10$ ;  $I^2 = 89\%$ ), and the random effect model was selected for the analysis. The results showed no significant difference in the length of ICU stay between the HES group and the albumin group (MD = 0.70; 95% CI -0.14 to 1.55;  $P = 0.10$ ) (Figure 3A). Therefore, the use of albumin and HES as priming fluid for CPB in cardiac surgery had a similar effect on the length of stay in ICU. (Figure 3A).

**2.3.2 Ventilation time.** Two RCTs reported the ventilation time. There was no statistical heterogeneity among the studies ( $P = 0.12$ ;  $I^2 = 60\%$ ), and the random effect model was selected for analysis. The results showed no significant difference between the HES group and the albumin group (MD = 2.31; 95% CI -3.93 to 8.55;  $P = 0.47$ ) (Figure 3B). Therefore, the use of albumin and HES as priming fluid for CPB in cardiac surgery had a similar effect on ventilation time. (Figure 3B)

**2.3.3 The length of hospital stay.** Two RCTs reported the length of hospital stay. Two was statistical heterogeneity among the studies ( $P = 0.48$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed no significant difference between the HES group and the albumin group (MD = -0.31; 95% CI: -2.00 to 1.37;  $P = 0.71$ ) (Figure 3C).

**2.3.4 Crystal volume.** Three RCTs reported crystal volume. There was no statistical heterogeneity among the studies ( $P = 0.60$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed no significant difference between the HES group and the albumin group (MD = 0.26; 95% CI: -0.09 to 0.61;  $P = 0.15$ ) (Figure 3D).

**2.3.5 Fresh frozen plasma.** Three RCTs reported fresh frozen plasma. There was statistical heterogeneity among the studies ( $P = 0.66$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (SMD = 0.25; 95% CI -0.08 to 0.59;  $P = 0.14$ ) (Figure 3E).

**2.3.6 Platelet input.** Two RCTs reports platelet input. There was no statistical heterogeneity among the studies ( $P = 0.75$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (MD = -0.17; 95% CI -0.59 to 0.26;  $p = 0.45$ ) (Figure 3F).

**2.3.7 Blood loss.** Five RCTs reports blood loss. There was no statistical heterogeneity among the studies ( $P = 0.23$ ;  $I^2 = 29\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (MD = 0.31; 95% CI -0.01 to 0.63;  $p = 0.06$ ) (Figure 4A).

**2.3.8 Platelet count.** Five RCTs reported platelet count. There was no statistical heterogeneity among the studies ( $P = 0.18$ ;  $I^2 = 37\%$ ), and the random effect model was selected for analysis. The results showed

no statistical difference between the HES group and the albumin group (MD =-0.21;95% CI: -0.54 to 0.11; p = 0.20) (Figure 4B).

**2.3.9 Hemoglobin value.** Five RCTs reported hemoglobin value. There was no statistical heterogeneity among the studies ( $P = 0.96$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (MD =0.1;95% CI: -0.15 to 0.36;  $P = 0.42$ ) (Figure 4C).

**2.3.10 Fibrin.** Three RCTs reported fibrin. There was no statistical heterogeneity among the studies ( $P = 0.91$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (MD =0.12;95% CI: -0.19 to 0.44;  $P = 0.45$ ) (Figure 4D).

**2.3.11 APTT.** Four RCTs reported APTT. There was no statistical heterogeneity among the studies ( $P = 0.83$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (MD =1.13;95% CI: -2.06 to 4.32;  $P = 0.49$ ) (Figure 4E).

**2.3.12 PT.** Three RCTs reported PT. There was no statistical heterogeneity among the studies ( $P = 0.10$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (MD =0.10;95% CI: -0.21 to 0.40;  $P = 0.52$ ) (Figure 4F).

**2.3.13 Urea.** Two RCTs reported hemoglobin urea. There was no statistical heterogeneity among the studies ( $P = 0.58$ ;  $I^2 = 0\%$ ), and the random effect model was selected for analysis. The results showed statistical difference between the HES group and the albumin group (MD =-0.46;95% CI: -0.81 to -0.11;  $P = 0.01$ ) (Figure 5A).

**2.3.14 Creatinine.** Three RCTs reported creatinine. There was no statistical heterogeneity among the studies ( $P = 0.09$ ;  $I^2 = 51\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (MD =0.09;95% CI: -0.32 to 0.50;  $P = 0.66$ ) (Figure 5B).

**2.3.15 Urine volume.** Five RCTs reported urine volume. There was no statistical heterogeneity among the studies ( $P = 0.14$ ;  $I^2 = 43\%$ ), and the random effect model was selected for analysis. The results showed no statistical difference between the HES group and the albumin group (MD =0.11;95% CI: -0.26 to 0.48;  $P = 0.55$ ) (Figure 5C).

## Discussion

The use of HES in priming solution for CPB is still controversial. This meta-analysis included 9 RCTs that met the inclusion criteria to compare the impact of albumin and HES on the prognosis of patients. The

results showed that compared with albumin, HES group had no statistical difference in the length of ICU stay, ventilator time, the length of hospital stay, crystal volume, fresh frozen plasma, platelet input, blood loss, blood platelet count, hemoglobin value, fibrin, APTT, PT, creatinine and urine volume, while HES group had lower urea than the control group.

The effects of HES on renal function were reported in the included studies, but the renal function test indexes were different, including blood creatinine, glomerular filtration rate, urine volume, urea, renal replacement therapy and other indexes. Because urea, blood creatinine and urine volume were common indexes reported in previous studies, we chose urea, blood creatinine and urine volume for analysis. Previous basic research and clinical trials have shown that HES has potential nephrotoxicity. A study found that HES was an independent risk factor for acute kidney injury after cardiac surgery [27]. However, other studies suggested that HES as priming fluid for CPB had no side effect on renal function [28]. Our results showed that HES had no different effects on serum creatinine and urine volume compared to albumin. The inconsistent results may be due to the molecular weight of HES. In their study they used macromolecular HES [29]. As the molecular weight of HES decreases, its effect on renal function becomes less. These data suggest that low molecular HES is safe for priming solution during CPB. But HES group had lower urea than the control group, may be the sample size included in this meta-analysis is relatively small.

HES may change the coagulation function in vivo and in vitro by prolonging the coagulation time, reducing the intensity of blood clots, and increasing blood loss of patients [30-31]. However, this meta-analysis found that HES had no different effect on fibrinogen value, platelet input, platelet count, APTT, PT and did not increase blood loss compared with albumin. It may be related to the new generation HES130/0.4 used in the most of studies enrolled in this meta-analysis. It was reported that the third generation HES130/0.4 did not increase blood loss [32], because its molar replacement ratio was less than 0.5 and it was a rapidly degradable HES solution [33]. However, the sample size included in this meta-analysis is relatively small, and our conclusion needs to be confirmed by large-sample RCT study.

There was no difference between HES group and albumin group in the amount of liquid required during the operation, indicating that the volume expansion effect of HES was not different from that of albumin. However, large sample RCT studies are needed to confirm these results. Our results also found that HES group had no significant difference in the length of ICU stay and ventilation time compared with albumin group, indicating that HES treatment could not shorten the hospitalization time of patients. Since our data were estimated from the original data, our conclusion remains to be confirmed.

This meta-analysis is designed and implemented according to the requirements of Cochrane Collaboration Network. We strictly followed the inclusion criteria and exclusion criteria. Two independent authors chose articles, collected data and evaluated bias risks. Although this meta-analysis tried to use high-quality studies such as RCTs, we cannot completely eliminate the confounding and bias in independent studies, which inevitably lead to certain bias in the results. For example, some studies did not use blind methods, some studies did not report the hidden schemes and the generation of random

sequences in detail, and some articles cannot trace other bias sources. In addition, only English literatures were included in this study, which may have publication bias. Moreover, the dosage of HES need to be considered, because the dosage used in different studies was different. In addition, the sample size of some studies was small. More RCTs with large samples and multiple centers are needed to confirm our conclusion.

Taken together, HES had no obvious side effects on renal function, coagulation function and did not prolong the length of ICU stay and ventilation time of patients. These results indicate that HES may be safe to be used as priming fluid for CPB. Even with some problems such as insufficient samples, different follow-up time and different dosage of HES, we think that the evidence is credible and the quality grade is judged as medium quality because all the included studies are RCTs, most of the studies used the random grouping and concealment methods, reported complete outcome indicators, had little heterogeneity among the experiments, and had consistent conclusions for all indicators.

## **Conclusion**

This meta-analysis provides evidence that HES as priming fluid for CPB in cardiac surgery will not damage renal function, coagulation function or increase bleeding volume and intraoperative infusion volume as well as the length of ICU stay and ventilation time of patients, compared with albumin.

## **Declarations**

### **Author Contributions**

Xuming Mo, Zhaocong Yang conceived and designed the study. Mingtang Ye edited the manuscript text and performed the statistical analyses. Xiaodong Zang, Peicheng Ding analyzed and interpreted the data. Ruonan Wang collected data. Feng Chen, Jirong Qi prepared tables and figures. All authors read and approved the final version of the manuscript.

### **Conflicts of Interest**

The authors declare that they have no competing interests.

### **Ethics Approval and consent to participate**

Not applicable

### **Consent for Publication**

Not applicable

### **Availability of supporting data**

Not applicable

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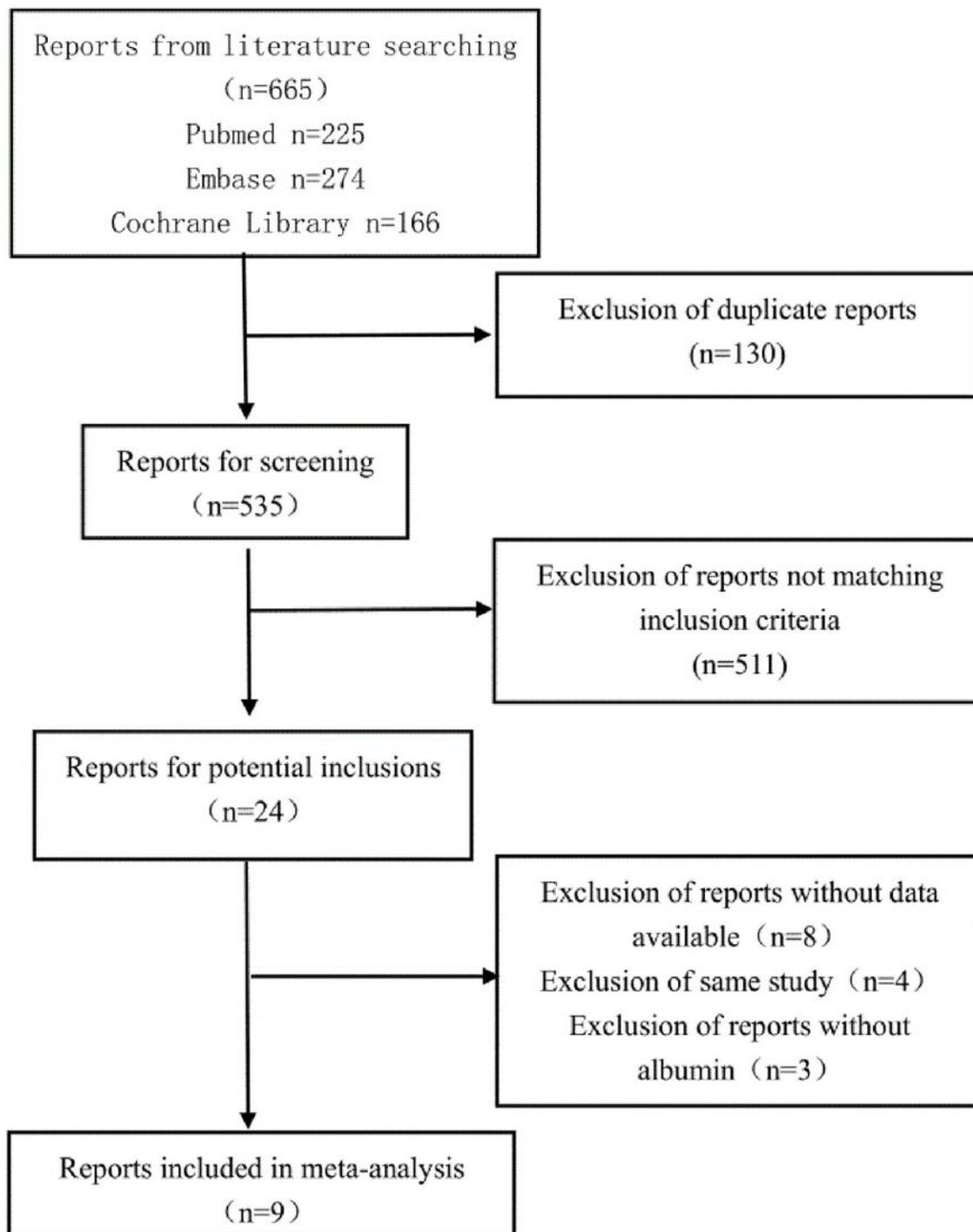
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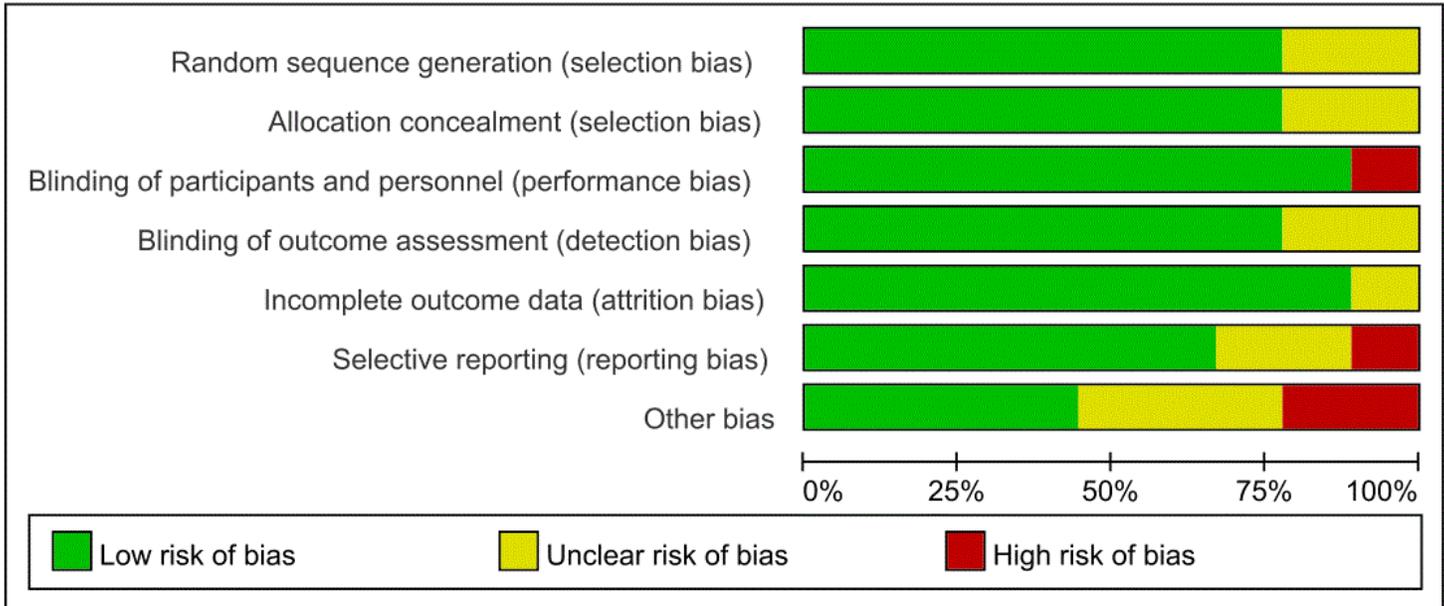
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## Figures



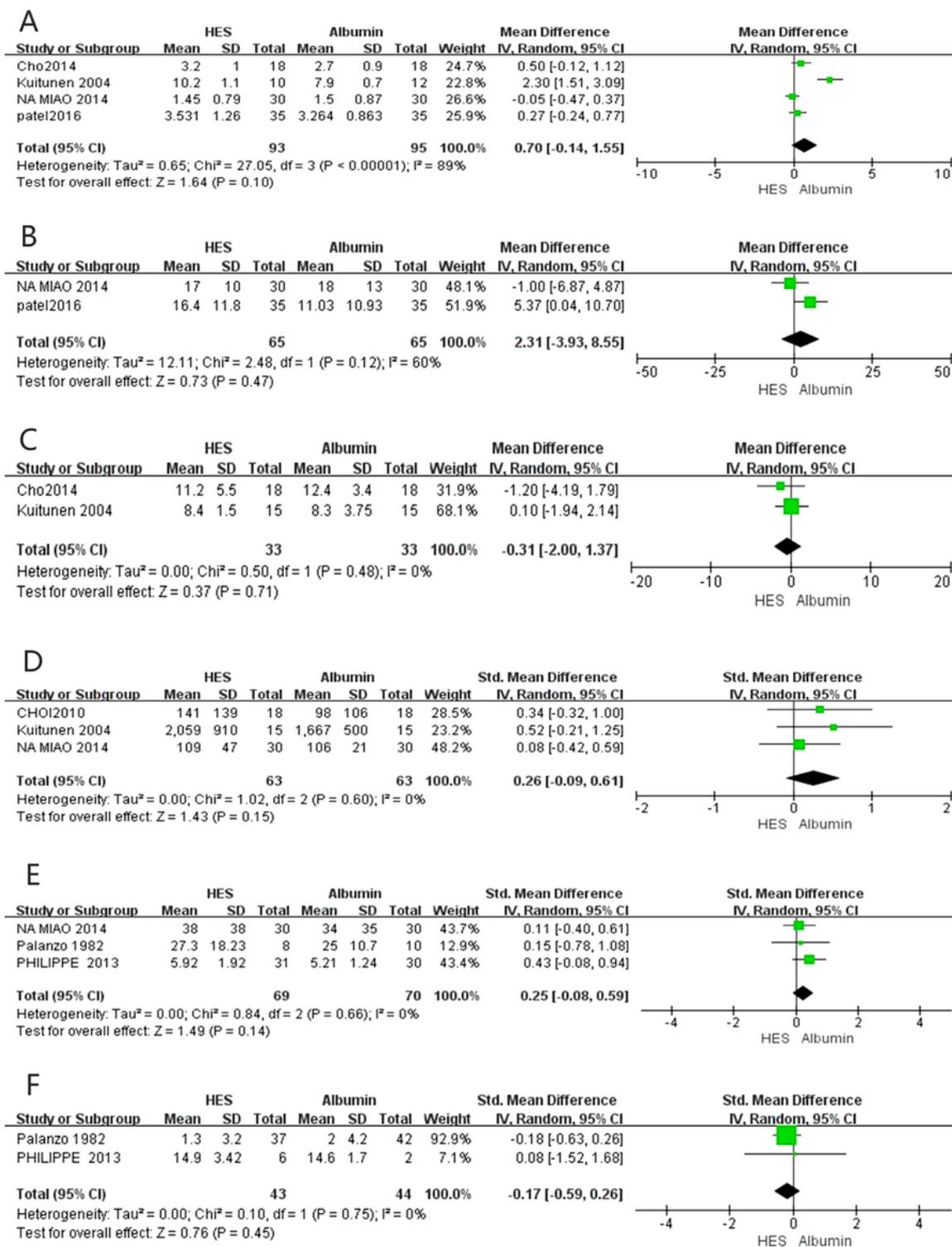
**Figure 1**

The flow chart of the literature search.



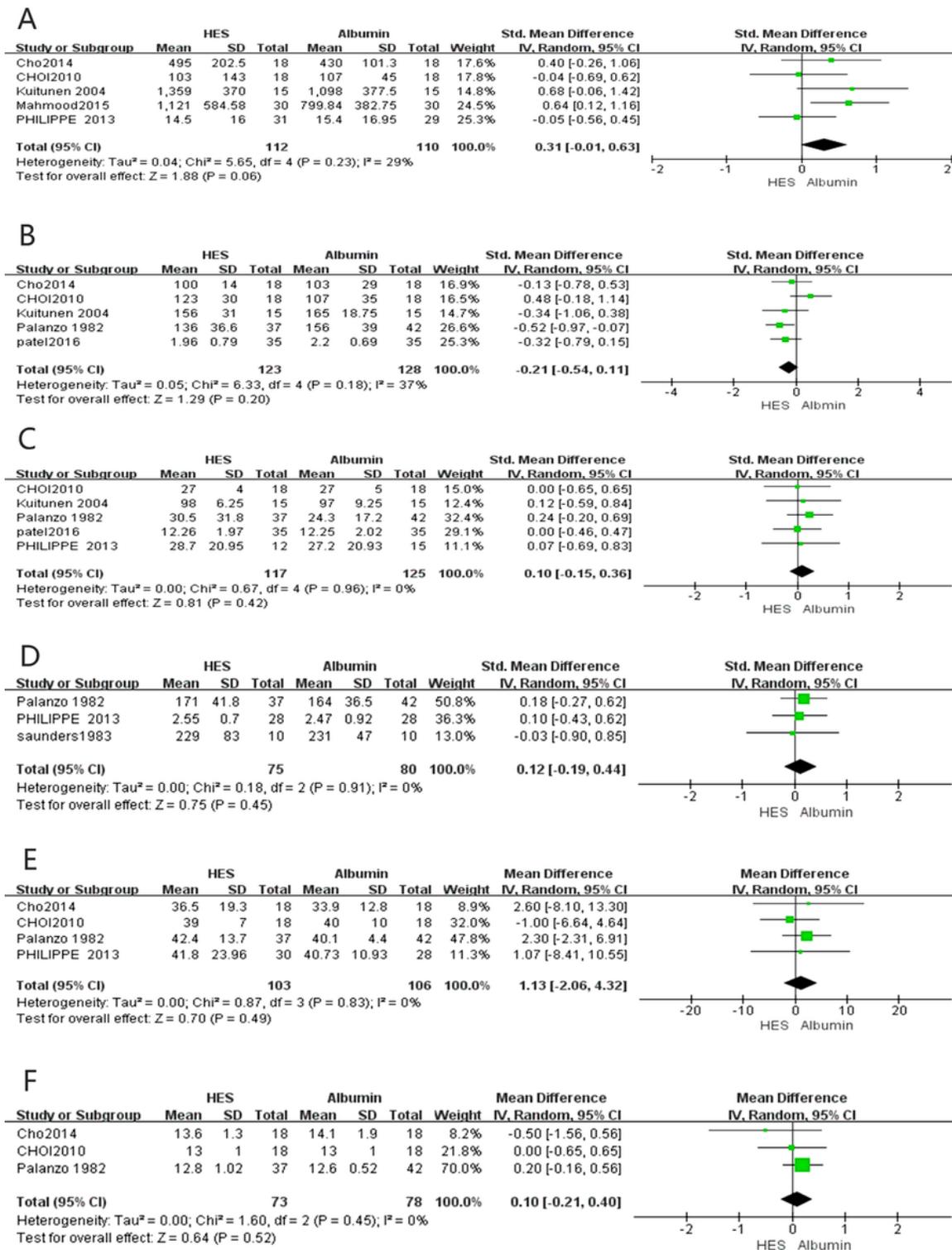
**Figure 2**

Quality of the included studies



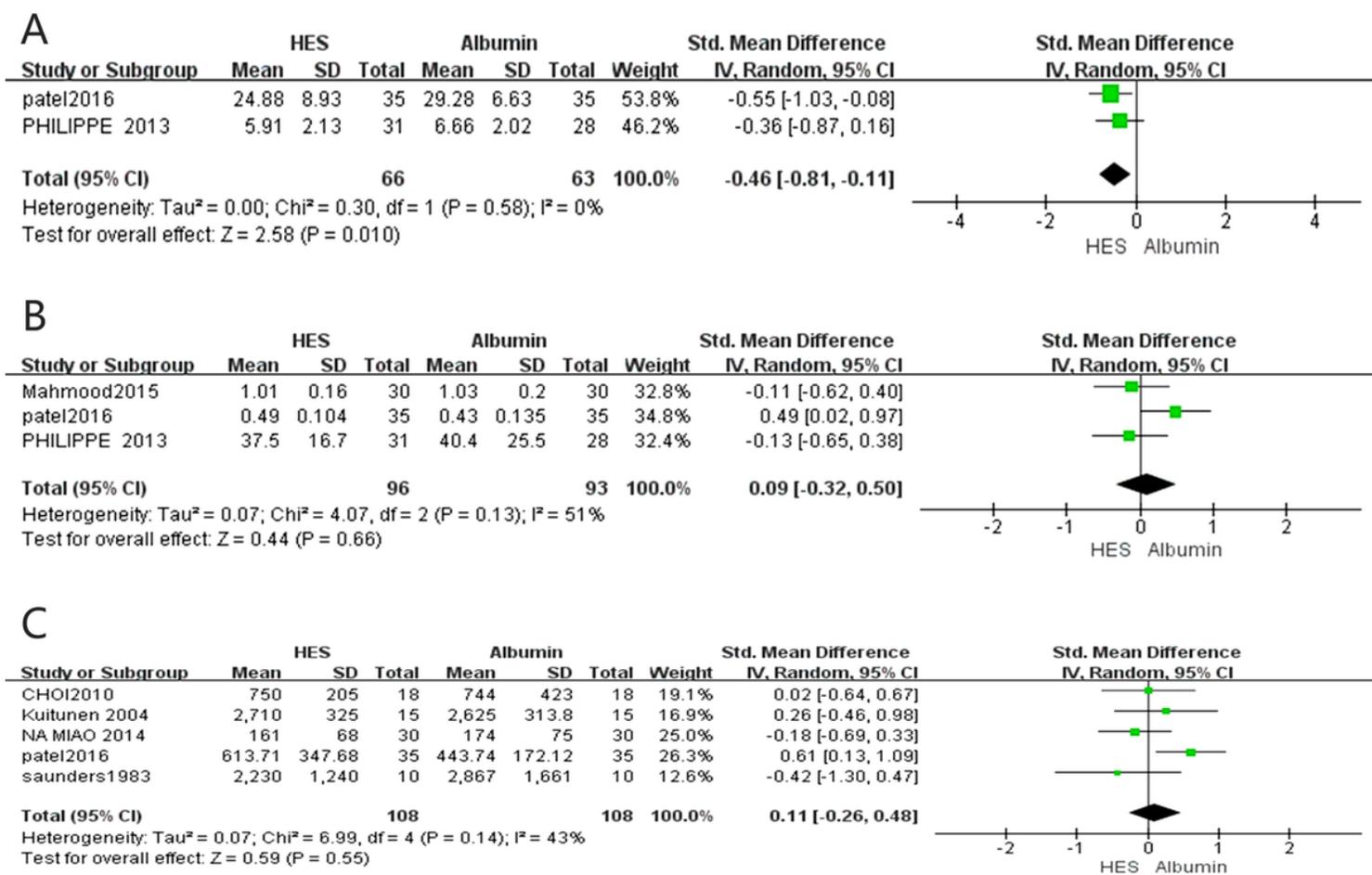
**Figure 3**

Forest plot of the meta-analysis (A) Length of ICU stay (B) Ventilation time. (C) Length of hospital stay. (D) Crystal volume. (E) Fresh frozen plasma. (F) Platelet input.



**Figure 4**

Forest plot of the meta-analysis (A) Blood loss, (B) Blood platelet count, (C) Hemoglobin value, (D) Fibrin, (E) APTT, (F) PT



**Figure 5**

(A) Urea, (B) Creatinine, (C) Urine volume.

## Supplementary Files

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