

## Sequential vs simultaneous revascularization in patients undergoing liver transplantation: A meta-analysis

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### Abstract

**AIM:** We undertook this meta-analysis to investigate the relationship between revascularization and outcomes after liver transplantation.

**METHODS:** A literature search was performed using MeSH and key words. The quality of the included studies was assessed using the Jadad Score and the Newcastle-Ottawa Scale. Heterogeneity was evaluated by the  $\chi^2$  and  $I^2$  tests. The risk of publication bias was assessed using a funnel plot and Egger's test, and the risk of bias was assessed using a domain-based assessment tool. A sensitivity analysis was conducted by reanalyzing the data using different statistical approaches.

**RESULTS:** Six studies with a total of 467 patients were included. Ischemic-type biliary lesions were significantly reduced in the simultaneous revascularization group compared with the sequential revascularization group (OR = 4.97, 95%CI: 2.45-10.07;  $P < 0.00001$ ), and intensive care unit (ICU) days were decreased (MD = 2.00, 95%CI: 0.55-3.45;  $P = 0.007$ ) in the simultaneous revascularization group. Although warm ischemia time was prolonged in simultaneous revascularization group (MD = -25.84, 95%CI: -29.28-22.40;  $P < 0.00001$ ), there were no significant differences in other outcomes between sequential and simultaneous revascularization groups. Assessment of the risk of bias showed that the methods of random sequence generation and blinding might have been a source of bias. The sensitivity analysis strengthened the reliability of the results of this meta-analysis.

**CONCLUSION:** The results of this study indicate that simultaneous revascularization in liver transplantation may reduce the incidence of ischemic-type biliary lesions and length of stay of patients in the ICU.

**Key words:** Revascularization; Liver transplantation; Outcomes; Biliary complications; Meta-analysis

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**Core tip:** The current methods of revascularization in liver transplantation can be divided into two main groups. We carried out this meta-analysis in order to study the relationship between revascularization and outcomes after liver transplantation. Ischemic-type biliary lesions were significantly reduced in the simultaneous revascularization group compared with the sequential revascularization group ( $P < 0.00001$ ), and intensive care unit days were decreased ( $P = 0.007$ ) in the simultaneous revascularization group. There were no significant differences in other outcomes between sequential and simultaneous revascularization groups, such as blood transfusions, hospital days, graft failure and mortality in one month and one year, operation time.

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## INTRODUCTION

Sequential portal and arterial revascularization (SeqR) and simultaneous portal and arterial revascularization (SimR) have been advocated to improve outcomes after liver transplantation<sup>[1-5]</sup>. In SeqR, the liver graft is sequentially reperfused by portal and arterial reperfusion. By contrast, in SimR, the liver graft is simultaneously reperfused by the portal vein and the hepatic artery. Because the portal vein contributes approximately three fourths of the blood supply to the liver and is easily anastomosed to shorten the warm ischemia time (WIT) and the anhepatic phase during the operation, SeqR is the more widely performed sequence of revascularization<sup>[6]</sup>. However, the primary disadvantage of SeqR is the potential increased risk of arterial ischemic injury to the bile ducts, which depend solely on the arterial blood supply<sup>[7]</sup>. Therefore, some authors have recommended the use of SimR for its reduction of the risk of arterial ischemic damage to biliary epithelial cells, which are more susceptible to ischemia-reperfusion injury than hepatocytes<sup>[8,9]</sup>. However, the disadvantage of SimR is that it prolongs the WIT and the anhepatic phase, which can be detrimental to patient mortality and morbidity related to the graft<sup>[10]</sup>. The better method of revascularization in liver transplantation remains controversial.

Although some meta-analyses have been conducted to compare the incidence of total biliary complications between SimR and SeqR in liver transplantation<sup>[1,2]</sup>, the method that results in a greater reduction in the

incidence of ischemic-type biliary lesions (ITBLs) and other outcomes remains unclear. The primary purpose of this meta-analysis was to investigate the relationship between revascularization and ITBLs. In addition, we also evaluated other outcomes, such as blood transfusions, hospital days, graft failure and mortality in one month and one year, operation time.

## MATERIALS AND METHODS

This systematic review and meta-analysis were conducted according to the PRISMA statement<sup>[11]</sup>.

### Literature search

To identify relevant studies, a search of the literature was performed in MEDLINE, the Cochrane database, the Science Citation Index (SCI), PLOS ONE, Wiley Online Library, Springer, and China National Knowledge Infrastructure (CNKI) without restrictions on the year or language. We performed a systematic search using both "MeSH" and "key words" protocols. More specifically, the following terms retrieved from the MeSH browser provided by PubMed were utilized: ["liver" (All Fields) OR "hepatic" (All Fields)] AND "transplantation" (All Fields) AND "revascularization" (All Fields) OR "reperfusion" (MeSH). A multiple "key words" search was performed with the terms "liver transplantation" AND "revascularization".

### Eligibility criteria

**Types of studies:** Clinical studies conducted comparing SimR and SeqR in liver transplantation were included regardless of blinding, publication status, or sample size. Further, these clinical studies had to contain sufficient data about outcomes after liver transplantation. Literature on animal experiments, reviews, letters to the editor and clinical studies conducted without control groups were excluded.

**Types of participants:** Patients undergoing SeqR or SimR in liver transplantation were included regardless of age, gender, nationality, or reason for liver transplantation.

**Types of interventions:** Studies with comparisons between SeqR and SimR were included regardless of whether piggy-back or conventional orthotopic liver transplantation was performed.

**Types of outcomes:** (1) ITBLs; (2) blood transfusions (units of blood and plasma); (3) Hospital days [intensive care unit (ICU) and total hospital days]; (4) graft failure and mortality in one month and one year; and (5) Operation time (total operation and WIT).

### Literature selection and data extraction

Two independent reviewers (Wang JL, Lu L) evaluated each title, abstract, citation, and selected relevant studies according to the eligibility criteria. Disagreements

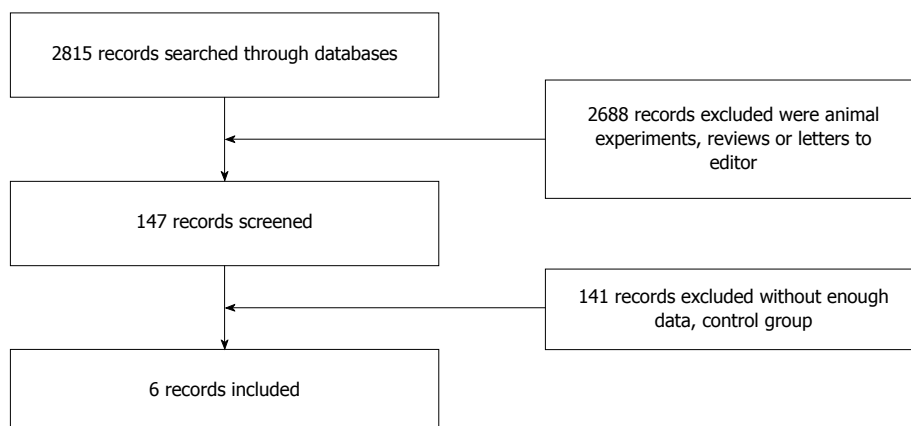


Figure 1 Flow diagram of the included studies.

were resolved by another reviewer (Lu HW). Data were extracted separately from the included studies, and a reviewer (Lu HW) reviewed and confirmed the accuracy of the extracted data. Data from the included studies were recorded as follows: (1) authors, country, year; (2) publication; (3) number of participants in the SimR and SeqR groups; and (4) outcomes after liver transplantation.

### Quality assessment of studies

The methodological quality of each randomized controlled trials (RCTs) was independently assessed using the Jadad score. This five-point quality scale includes points for randomization (0-2 points), double blinding (0-2 points), and withdrawals and dropouts (0-1 points). Total scores of 0-2 were considered indicative of low quality, whereas studies with total scores  $\geq 3$  were defined as high quality. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of each retrospective study. The NOS contains 8 items, which are divided into three categories: selection (4 items), comparability (1 item), and exposure for case-control studies (3 items). A star system was used to allow for a semi-quantitative assessment of study quality. A study can be awarded a maximum of one star for each item within the selection and exposure categories. A maximum of two stars can be given for comparability. Studies were defined as high quality if they had more than seven stars; as medium quality if they had between four and six stars; and as poor quality if they had fewer than four stars.

### Statistical analysis

The statistical methods of this study were reviewed by Deyu Meng from the Faculty of Mathematics and Statistics, Xi'an Jiaotong University. Data were analyzed by the statistical software Review Manager 5.2 (The Cochrane Collaboration) using a fixed effects model. The results of continuous and discontinuous data were reported as MD with 95%CI and as OR with 95%CI, respectively.  $P < 0.05$  was considered to indicate a statistically significant difference. The

heterogeneity of the included studies was evaluated by the  $\chi^2$  and  $I^2$  tests (Review Manager 5.2), and  $P < 0.10$  or  $I^2 > 25\%$  was defined as indicating heterogeneity. A funnel plot (Review Manager 5.2) and Egger's test (Stata 10.0) were used to assess the risk of publication bias, and  $P < 0.10$  indicated statistical publication bias. The risk of bias in the studies was assessed by two independent reviewers (Wang JZ, Li YM) using a domain-based assessment tool recommended by the Cochrane collaboration. Two methods of sensitivity analysis were conducted by comparing the effect size between a fixed effects model and a random effects model; the fixed effect model was applied after excluding the greatest weight study.

## RESULTS

### Flow diagram of the included studies

We screened the title and abstract of 2815 studies after performing the database search. Then, 2688 studies were excluded because they were animal experiments, reviews, or letters to the editor, and 141 clinical studies did not meet our criteria due to their lack of a control group or insufficient data on outcomes after liver transplantation. A total of six studies were included<sup>[12-17]</sup>, comprising a total of 467 patients (Figure 1).

### Study characteristics

Six studies with a total of 467 patients were included. Two studies were RCTs<sup>[16,17]</sup>, with a total of 120 patients; the other studies were retrospective, with a total of 347 patients<sup>[12-15]</sup>. The included studies were conducted in five countries: two in Italy, one in China, one in the United States, one in Brazil, and one in the Netherlands. None of the six studies was considered low quality (Table 1).

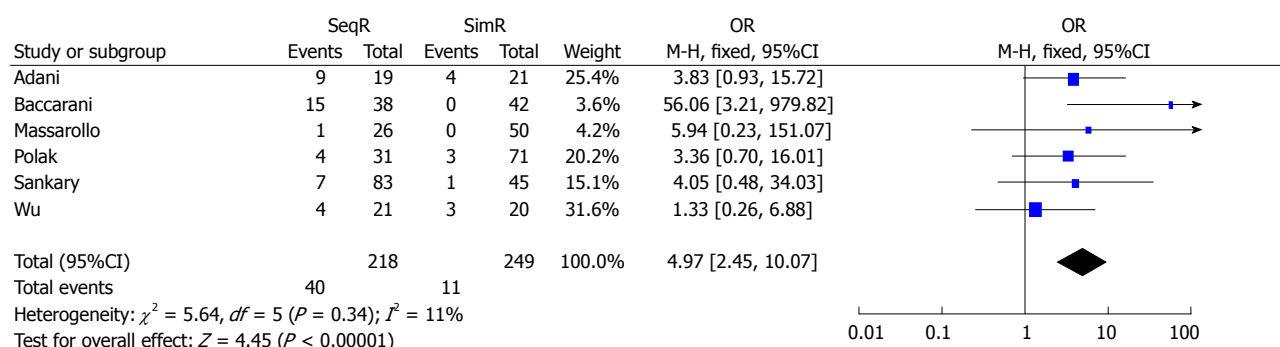
### Synthesis of outcomes and assessments of heterogeneity

**Simultaneous revascularization reduced the incidence of ITBLs:** The incidence of ITBLs was significantly reduced in the SimR group compared to

**Table 1** Characteristics of the included studies

Study	Year	Country	No. of SeqR/ SimR	Type of study	Jadad score	NOS
Sankary <i>et al</i> <sup>[12]</sup>	1995	United States	83/45	Retrospective study	-	6
Massarollo <i>et al</i> <sup>[13]</sup>	1998	Brazil	26/50	Retrospective study	-	7
Polak <i>et al</i> <sup>[14]</sup>	2005	the Netherlands	71/31	Retrospective study	-	7
Wu <i>et al</i> <sup>[15]</sup>	2006	China	21/20	Retrospective study	-	6
Adani <i>et al</i> <sup>[16]</sup>	2011	Italy	19/21	RCT	3	-
Baccarani <i>et al</i> <sup>[17]</sup>	2012	Italy	38/42	RCT	3	-

RCT: Randomized controlled trial; NOS: Newcastle-Ottawa scale.



**Figure 2** Meta-analysis results of incidence of ischemic-type biliary lesions. The occurrence of incidence of ischemic-type biliary lesions was significantly reduced in the SimR group over the SeqR group (OR = 4.97, 95%CI: 2.45-10.07,  $P < 0.00001$ ). SeqR: Sequential revascularization; SimR: Simultaneous revascularization.

the SeqR group according to this meta-analysis (OR = 4.97, 95%CI: 2.45-10.07;  $P < 0.00001$ ). Furthermore, the results of the  $\chi^2$  and  $I^2$  tests did not indicate heterogeneity ( $P = 0.34$ ,  $I^2 = 11\%$ ) (Figure 2).

**Simultaneous revascularization did not increase blood transfusions:** Two and three studies, respectively, were conducted to compare units of blood cell and plasma transfusions between SeqR and SimR. There were no significant differences in units of blood cell transfusions (MD = 0.55, 95%CI: -0.84-1.94;  $P = 0.44$ ) and plasma transfusions (MD = -416.71, 95%CI: -997.01-163.59;  $P = 0.16$ ). The results of the  $\chi^2$  and  $I^2$  tests were  $P = 0.21$  ( $I^2 = 37\%$ ) and  $P = 0.08$  ( $I^2 = 66\%$ ), respectively (Figure 3).

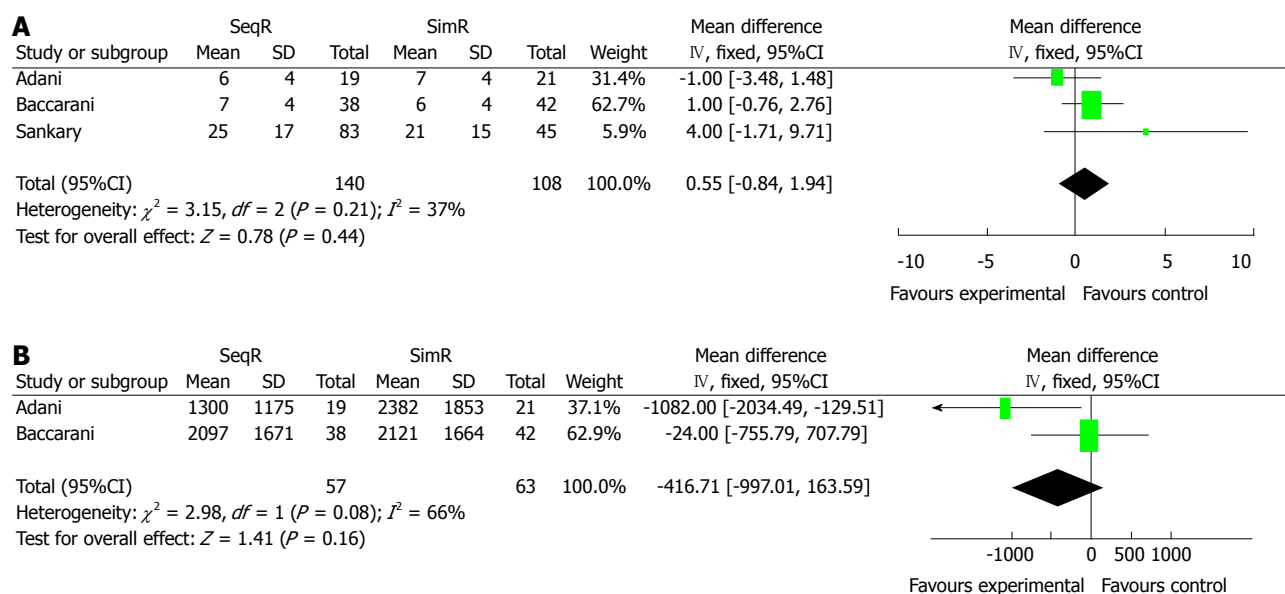
**Simultaneous revascularization decreased ICU days:** Two studies were conducted to compare ICU and total hospital days. SimR significantly decreased ICU days (MD = 2.00, 95%CI: 0.55-3.45;  $P = 0.007$ ), while no significant difference was shown in total hospital days (MD = 0.46, 95%CI: -1.99-2.90;  $P = 0.71$ ). The results of the  $\chi^2$  and  $I^2$  tests did not indicate heterogeneity ( $P = 1.00$ ,  $I^2 = 0\%$  and  $P = 0.23$ ,  $I^2 = 31\%$ ), respectively (Figure 4).

**Simultaneous revascularization increased WIT:** Although there was no significant difference in total operation time (MD = 22.59, 95%CI: -4.79-49.96;  $P = 0.11$ ), SimR significantly prolonged WIT (MD = -25.84,

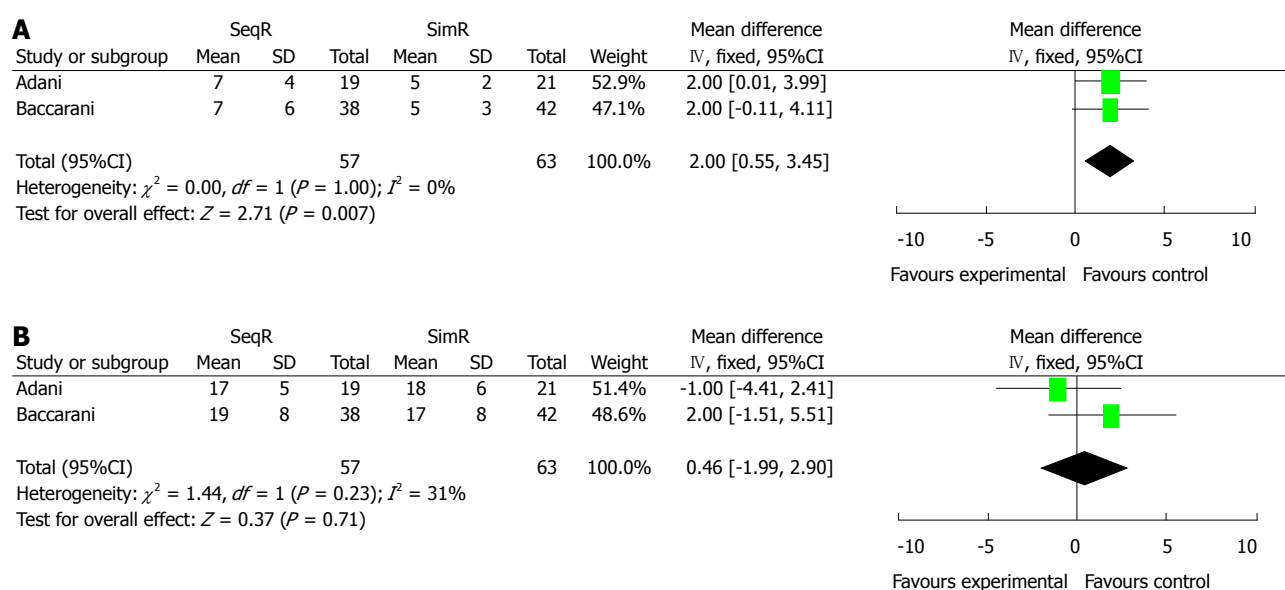
95%CI: -29.28-22.40;  $P < 0.00001$ ). However, the results of  $\chi^2$  and  $I^2$  tests in WIT showed heterogeneity ( $P = 0.05$ ,  $I^2 = 75\%$ ), which was not indicated in total operation time ( $P = 0.86$ ,  $I^2 = 0\%$ ) (Figure 5).

**Simultaneous revascularization did not increase patient mortality and graft failure in one month and one year:** There were two and three studies comparing graft failure and mortality in one month and one year between SeqR and SimR, respectively. There were no significant differences in patient graft failure and mortality in one month (OR = 1.19, 95%CI: 0.50-2.81;  $P = 0.70$ ; OR = 1.44, 95%CI: 0.57-3.68,  $P = 0.44$ ), or in one year (OR = 1.31, 95%CI: 0.57-3.04,  $P = 0.53$ ; OR = 0.83, 95%CI: 0.39-1.78,  $P = 0.64$ ). All results of  $\chi^2$  and  $I^2$  tests did not indicate heterogeneity ( $P = 0.59$ ,  $I^2 = 0\%$ ;  $P = 0.23$ ,  $I^2 = 30\%$ ;  $P = 0.60$ ,  $I^2 = 0\%$ ;  $P = 0.67$ ,  $I^2 = 0\%$ ) (Figure 6).

**Publication bias and risk of bias and sensitivity analyses** Although the funnel plot was not strictly symmetrical, Egger's test did not show publication bias ( $P = 0.136$ ) (Figure 7). The analyses indicated that random sequence generation and blinding, which were not properly described in these studies, might have been a source of bias (Figure 8). The sensitivity analysis showed the same effect sizes among a fixed effect model ( $P < 0.00001$ ), a random effect model ( $P = 0.002$ ) and a fixed effect model after excluding the largest weight study ( $P < 0.00001$ ) (Figure 9).



**Figure 3** Meta-analysis results of blood cell and plasma transfusions. A: Three studies were conducted to compare units of blood cell (MD = 0.55, 95%CI: -0.84-1.94,  $P = 0.44$ ); B: Two studies were conducted to compare plasma transfusions (MD = -416.71, 95%CI: -997.01-163.59,  $P = 0.16$ ).



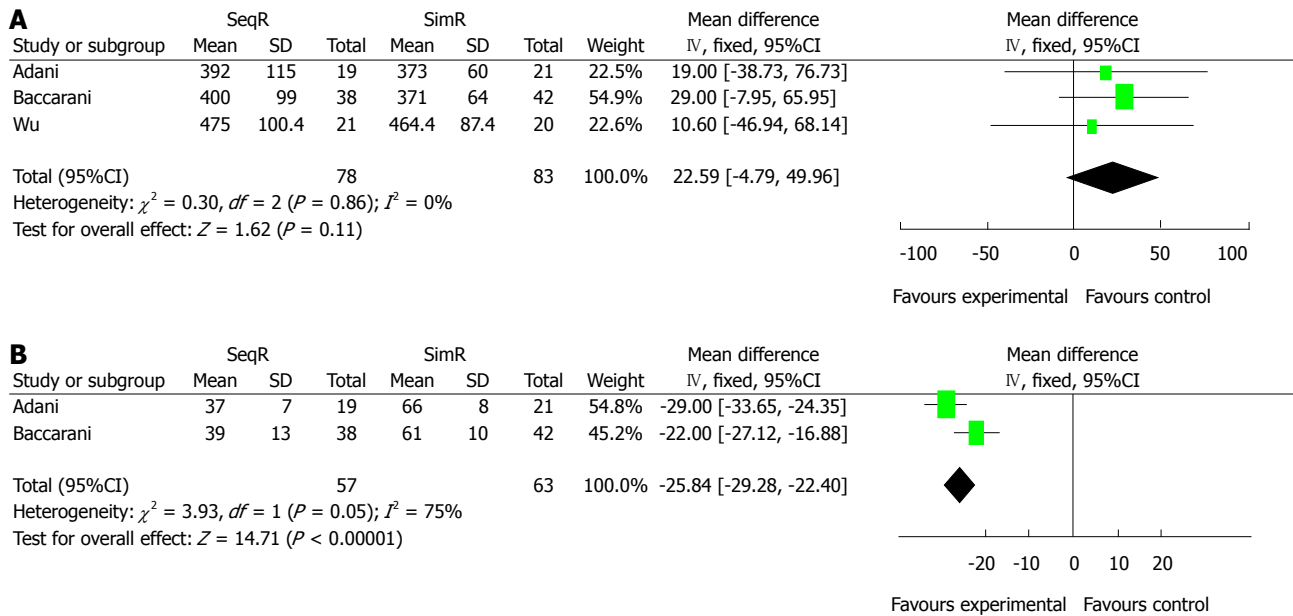
**Figure 4** Meta-analysis results of intensive care unit and total hospital days. A: SimR significantly decreased intensive care unit days (MD = 2.00, 95%CI: 0.55-3.45,  $P = 0.007$ ); B: No significant difference was shown in total hospital days (MD = 0.46, 95%CI: -1.99-2.90,  $P = 0.71$ ).

## DISCUSSION

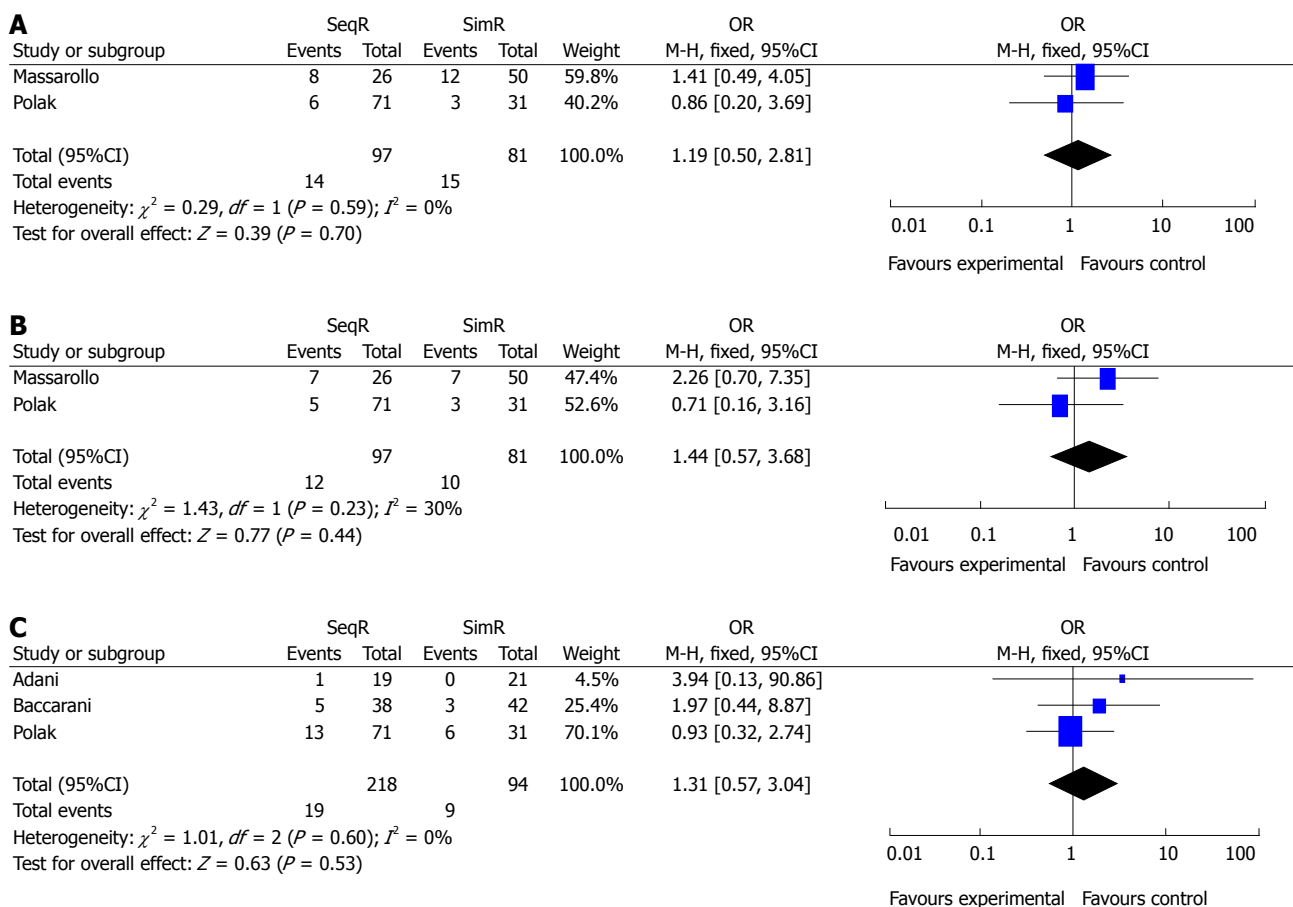
The current methods of revascularization in liver transplantation can be divided into two main groups according to whether the liver graft is reperfused sequentially or simultaneously. In SeqR cases, the first reconstructed vessel of the liver graft is one of the portal vein, the hepatic artery, or the inferior vena cava, followed by subsequent revascularization of the remaining vessels. By contrast, in SimR cases, the graft is simultaneously reperfused *via* the portal vein and the hepatic artery<sup>[3]</sup>. Although the best method of revascularization in liver transplantation remains

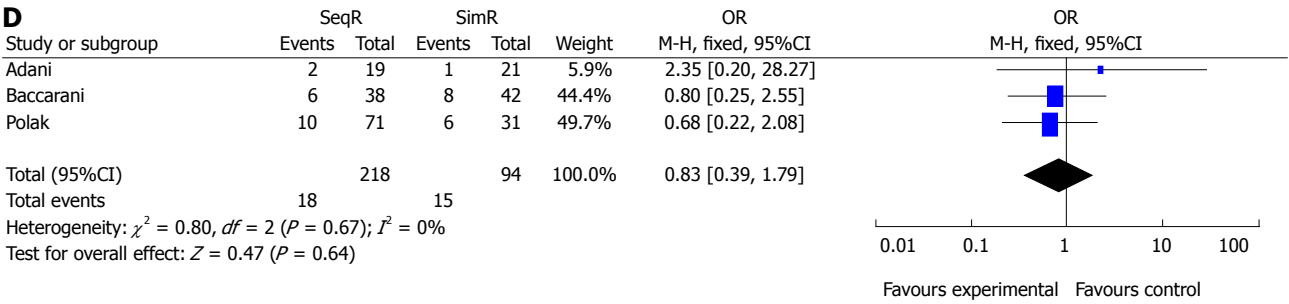
debatable<sup>[18]</sup>, the most commonly used procedure for the revascularization of liver grafts is SeqR<sup>[19]</sup>. Theoretically, there are some potential advantages to SeqR: (1) the portal vein contributes approximately 3/4 of the blood supply and 1/2 of the oxygen supply to the liver; (2) the portal vein is easily anastomized to shorten the WIT and anhepatic phase during the operation; and (3) the arterial anastomosis is performed under better technical conditions, without retrograde bleeding from the graft hepatic artery and in a surgical field free of hemorrhages<sup>[20]</sup>. However, SeqR increases warm ischemic injury to the bile ducts, which depend on the hepatic artery. Because ischemic



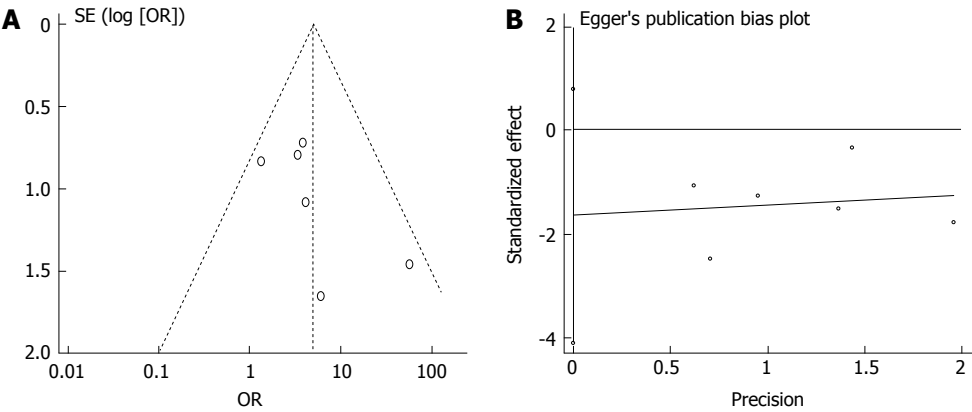


**Figure 5 Meta-analysis results of total operation time and warm ischemia time.** A: There was no significant difference in total operation time (MD = 22.59, 95%CI: -4.79-49.96,  $P = 0.11$ ); B: SimR significantly prolonged warm ischemia time (WIT) (MD = -25.84, 95%CI: -29.28-22.40,  $P < 0.00001$ ). However, the results of  $\chi^2$  and  $I^2$  tests in WIT showed heterogeneity ( $P = 0.05$ ,  $I^2 = 75\%$ ).

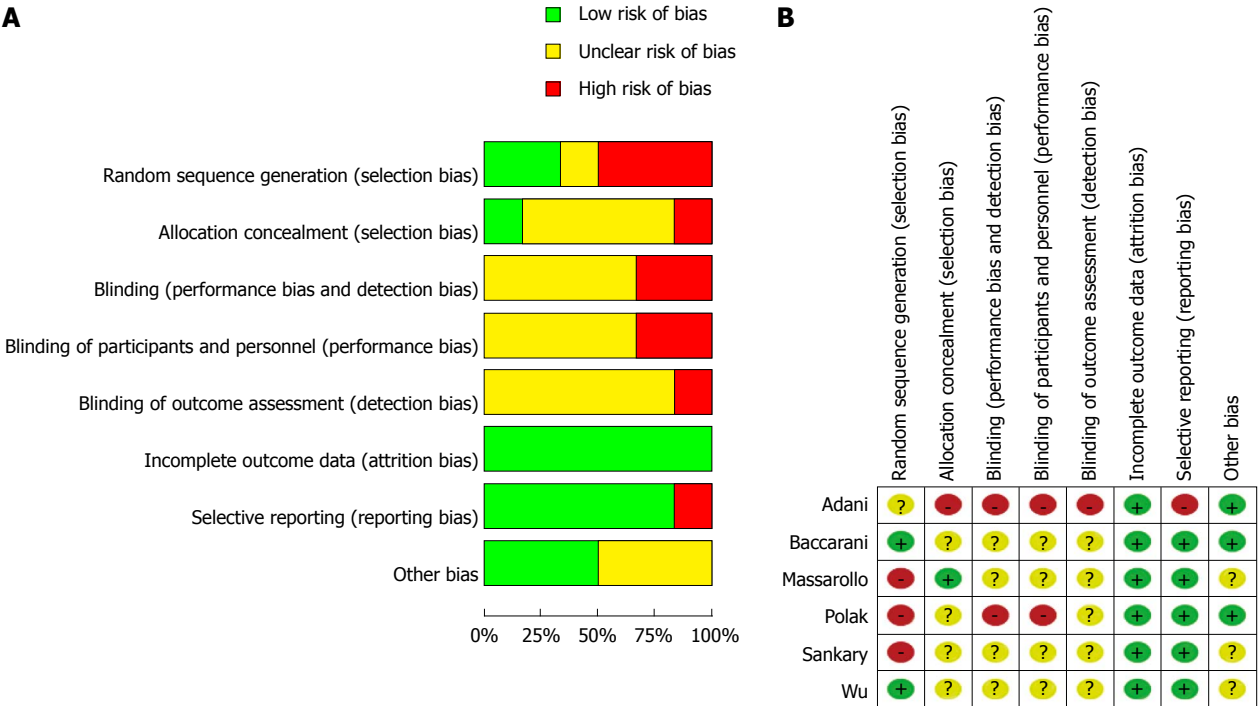




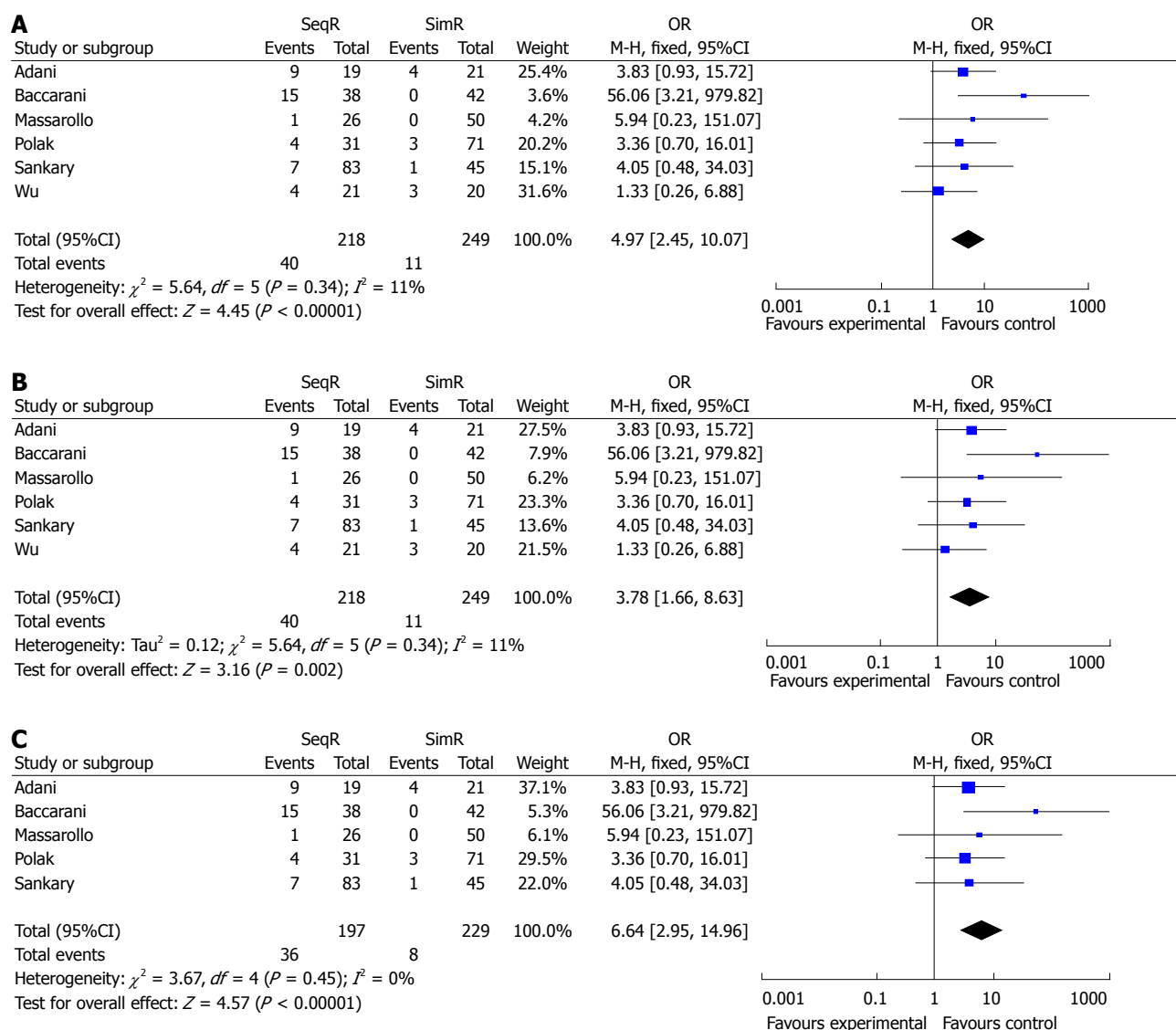
**Figure 6** Meta-analysis results of graft failure and mortality in one month and one year. A: There were no significant differences in graft failure in one month (OR = 1.19, 95%CI: 0.50-2.81,  $P = 0.70$ ); B: There were no significant differences in mortality in one month (OR = 1.44, 95%CI: 0.57-3.68,  $P = 0.44$ ); C: There were no significant differences in graft failure in one year (OR = 1.31, 95%CI: 0.57-3.04,  $P = 0.53$ ); D: There were no significant differences in mortality in one year (OR = 0.83, 95%CI: 0.39-1.78,  $P = 0.64$ ).



**Figure 7** Funnel plot and Egger's test of studies on incidence of ischemic-type biliary lesions. A: Funnel plot was not strictly symmetrical; B: Egger's test did not show publication bias ( $P = 0.136$ ).



**Figure 8** Risk of bias graph: review authors' judgments regarding each risk of bias item for each included study.



**Figure 9 Sensitivity analysis of this meta-analysis.** The sensitivity analysis showed the same effect sizes among different models. A: A fixed effects model ( $P < 0.00001$ ); B: A random effects model ( $P = 0.002$ ); C: A fixed effects model after excluding the greatest weight study ( $P < 0.00001$ ).

injuries to the bile ducts account for a majority of cases of morbidity, mortality, and graft failure in patients after liver transplantation<sup>[21-25]</sup>, some researchers have advocated the use of SimR. Although some meta-analyses have demonstrated that SeqR increases total biliary complications<sup>[1,2]</sup>, including anastomotic biliary complications and nonanastomotic biliary complications (*i.e.*, ITBLs)<sup>[26,27]</sup>, little is known about the relationship between revascularization and ITBLs.

We comprehensively reviewed the literature on the relationship between revascularization and ITBLs. The results of this meta-analysis on ITBLs imply that SimR reduces the incidence of ITBLs after liver transplantation, which is in accordance with previous clinical studies<sup>[12,13]</sup>. In addition, the heterogeneity tests did not show heterogeneity, and the sensitivity analysis showed the same effect sizes, which strengthened the confidence that can be placed in these results.

Although the specific mechanisms of SimR

that reduce the incidence of ITBLs remain unclear, reduced arterial ischemic injury to the bile ducts may be the main reason. The peribiliary vascular plexus is composed of branches arising directly from the right and left hepatic arteries (and accessory hepatic arteries when present) and from their segmental branches as well as branches arising indirectly from the gastroduodenal artery *via* the arteries supplying the common bile duct<sup>[28]</sup>. In SeqR cases, the graft is exclusively perfused through the portal vein for at least 10 min until the completion of hepatic arterial anastomosis<sup>[29,30]</sup>. The delay of rearterialization in SeqR is associated with more pronounced microvascular disturbances and subsequent graft dysfunction, including ischemic injury to the bile ducts. In a rat model of liver transplantation, SimR resulted in the best microcirculatory perfusion of the graft. In addition, the authors found less leukocyte accumulation in the sinusoids and more abundant bile flow after



simultaneous reperfusion compared to SeqR<sup>[31]</sup>. Moreover, SimR also elicits a remarkable improvement in oxygen tension and the maintenance of tissue ATP compared to SeqR, which may be helpful for reducing the incidence of ITBLs<sup>[32]</sup>. Although there are some potential benefits of SimR, the main disadvantages of SimR are the prolonged WIT and anhepatic phase, which can be detrimental to postoperative graft function, survival, and morbidity<sup>[3]</sup>. However, Adani *et al.*<sup>[16]</sup> reported that delayed graft function was diagnosed in 10% vs 9% in SeqR and SimR, while Polak *et al.*<sup>[14]</sup> reported that primary nonfunction was diagnosed in 3% (SeqR) vs 1% (SimR) and the rate of retransplantation was 9% in SeqR and 7% in SimR, respectively. Vascular complications were absent except for one case of hepatic artery thrombosis (HAT) leading to retransplantation in SeqR<sup>[16]</sup>. Liver ischemia-reperfusion injury, resulting in ITBLs during liver transplantation, triggers a cascade of events leading to biliary apoptosis, necrosis, and cholangitis which may even lead to graft failure. The main cause of prolonged WIT in SimR may be the simultaneous reconstruction of the portal vein and hepatic artery, which is inevitable due to this particular surgical technique. However, interestingly, SimR did not significantly prolong the total operation time or increase the incidence of blood transfusions, graft failure or mortality (one month and one year) in this study. Therefore, this is a burning issue to find the answer in the worlds of liver transplantation.

Besides different kinds of revascularization, some donor factors affect ITBLs, such as ABO incompatibility, gender, cytomegalovirus (CMV) infection and metalloproteinase-2 (MMP-2) polymorphism. The incidence of ITBLs after ABO-incompatible liver transplantation in adults is much higher than in ABO-compatible liver transplantation<sup>[33]</sup>. MMP-2 genotype in both donor and recipient is strongly and independently related to the development of ITBLs within 4 years after liver transplantation<sup>[34]</sup>.

Although this systematic review and meta-analysis imply that SimR reduces the incidence of ITBLs after liver transplantation, there are undoubtedly some limitations: (1) the number of patients in the included studies ranged from 19 to 83; (2) although we do believe that our search strategy was sufficient, only six studies were included in this meta-analysis of ITBLs, which may lead to inaccurate conclusions<sup>[35,36]</sup>; and (3) assessment of risk of bias showed that the methods of random sequence generation and blinding, which were not properly described in these studies, might have been a source of bias, which may have led to an overstatement of the treatment effects of SimR<sup>[37]</sup>.

In conclusion, the present meta-analysis included all current relevant clinical studies from various countries through July 2014, and the findings indicate that SimR reduces the incidence of ITBLs and decreases ICU days. Additional randomized and blinded clinical trials with a sufficient number of participants are needed to adequately compare SimR and SeqR in liver

transplantation.

## COMMENTS

### Background

Sequential portal and arterial revascularization (SeqR) and simultaneous portal and arterial revascularization (SimR) have been advocated to improve outcomes after liver transplantation. However, little is known about the relationship between revascularization and ischemic-type biliary lesions (ITBLs). The authors undertook this meta-analysis to investigate the relationship between revascularization and outcomes after liver transplantation.

### Research frontiers

There are two main methods for revascularization of the liver graft: SimR and SeqR. The sequence of graft reperfusion may be relevant for the development of ITBLs. In some retrospective studies, the incidence of ITBLs in patients who underwent SimR of the graft was lower compared to patients who had SeqR. Some clinical studies are conducted to validate whether SimR is better than SeqR.

### Innovations and breakthroughs

Although some meta-analyses have been conducted to compare the incidence of total biliary complications between SimR and SeqR in liver transplantation, the method that results in a greater reduction in the incidence of ITBLs and other outcomes remains unclear. The current study demonstrated that ITBLs and ICU days were significantly reduced in the SimR group compared with the SeqR group.

### Applications

The present meta-analysis indicates that SimR reduces the incidence of ITBLs and may be more suitable to protect the integrity of the intrahepatic biliary tree.

### Terminology

In SimR, the liver graft is simultaneously reperfused by the portal vein and the hepatic artery. Some scientists have recommended the use of SimR for its reduction of the risk of arterial ischemic damage to biliary epithelial cells, which are more susceptible to ischemia-reperfusion injury than hepatocytes.

### Peer-review

This is a well written paper analyzing a hot topic in liver transplantation technique and its outcomes. This work is a meta-analysis concerning the aspect of sequential vs simultaneous portal and arterial reperfusion in liver transplantation. The authors performed a structured literature review with a final analysis of six studies including 467 patients overall. As expected, in patients with simultaneous reperfusion a significantly longer warm ischemic time was found. In contrast, ischemic-type biliary lesions were significantly reduced in the group of patients with simultaneous reperfusion. Graft failure and mortality were not different between both groups at one month and one year after liver transplantation.

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