

Short-term and long-term outcomes of liver transplantation using moderately and severely steatotic donor livers

A systematic review

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Abstract

Background: The aim of this study was to perform a systemic review of the studies addressing the use of moderately and severely steatotic donor livers for liver transplantation.

Methods: We searched the following electronic databases from January 1, 1989, to August 1, 2017: PubMed, EMBASE, Science Citation Index Expanded, and the Cochrane Library. In addition, reference lists were scanned to identify any additional reports. The quality of published papers was assessed. The main outcomes of the use of moderately and severely steatotic donor livers for liver transplantation, including primary nonfunction, short-term mortality, and long-term mortality, were extracted for pooled analysis.

Results: Literature searches identified 16 studies that met the inclusion criteria. There were no randomized controlled studies, and all of the studies were retrospective or prospective case series. From a total of 3226 subjects (532 moderately and severely steatotic donor livers and 2694 controls), we found a significant increase in primary nonfunction [odds ratio (OR): 2.47, 95% confidence interval (95% CI): 1.44–4.27], and a trend of increase in 1-month patient mortality (OR: 1.90, 95% CI: 0.98–3.71) with the use of moderately and severely steatotic donor livers, whereas the 1-year mortality was relatively less influenced.

Conclusion: The use of moderately and severely steatotic livers is associated with unfavorable short-term outcomes, but long-term outcomes are relatively less influenced.

Abbreviations: CI = confidence interval, NA = not available, OR = odd ratio, PNF = primary nonfunction.

Keywords: liver transplantation, outcome, steatosis

1. Introduction

Fatty liver (hepatic steatosis) is one of the most common hepatic parenchymal disorders in developed countries, affecting 20% to 30% of individuals in the general population and up to 74% of obese individuals.^[1,2] Hepatic steatosis has also become a significant public health concern in developing countries.^[1,3] Steatosis can be caused by various reasons, such as obesity, alcohol abuse, malnutrition, hyperalimentation, diabetes, pregnancy, and hepatitis.^[4,5] Due to an increased susceptibility to ischemia/reperfusion injury, hepatic steatosis is regarded as a

major risk factor for liver surgery and transplantation.^[5,6] The use of steatotic donor livers for liver transplantation is also associated with an increased risk for poor outcomes after surgery.^[7,8]

Steatosis can be quantitatively classified as mild (< 30%), moderate (30–60%), or severe (>60%) grade according to the percentage of hepatocytes containing cytoplasmic fat droplets.^[9] With an increase in transplantation techniques and increasing demand for donor organs, more and more steatotic donor livers are used in liver transplantation. Recent clinical studies have observed that the use of mildly steatotic donor livers in liver transplantation did not significantly increase the risk for poor outcomes after the transplantation.^[10] However, whether moderately and severely steatotic donor livers are suitable for liver transplantation remains controversial in the literature.^[11–13]

The aim of this study was to perform a systemic review of the studies addressing the use of moderately and severely steatotic donor livers for liver transplantation.

2. Material and methods

2.1. Systematic literature search

For the electronic search, published studies were found using PubMed, EMBASE, Science Citation Index Expanded, and the Cochrane Library for the query “(fatty liver OR steatotic liver OR hepatic steatosis OR steatotic donor) AND (liver transplantation)”. In addition, the references of the articles were verified, and the PubMed link “related articles” were used to identify additional papers. The literature search was carried out for

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studies from January 1, 1989, to August 1, 2017, and required the availability of an English-language abstract or paper for review. There were no country restrictions. All abstracts were reviewed for appropriateness on the research issue by the authors, and, if so, the article was retrieved.

Ethical approval was not required due to the nature of this study, which is a systematic review.

2.2. Study selection

Two authors independently performed the study selection. Any disagreements were resolved by consensus or arbitration by a third party. Studies that met the following criteria were included: studies that provided raw data dealing with the clinical use of moderately and severely steatotic donor livers for liver transplantation; the information about the patients, including sample sizes and observation periods, were clearly demonstrated; and steatosis was graded as mild (< 30%), moderate (30–60%), or severe (>60%), and outcomes of the use of the different grades of steatotic donor livers for liver transplantation could be extracted.

Duplicate publications, letters, editorial materials, and review articles were excluded. Case series involving fewer than 15 cases were excluded because we believed that studies addressing fewer than 15 cases would not generate enough meaningful data that could be used to assess the quality. Studies were also excluded if relevant data were not extractable or if the grades of steatosis were unclassified or not clearly classified.

2.3. Data collection and quality assessment

Post-transplantation outcomes of patients who received moderately and severely steatotic donor livers (defined as the observation group) were compared with patients who received lean and mildly steatotic donor livers (defined as the control group). For each study, information was collected concerning the demographic information of the subjects, study design, incidence of primary nonfunction (PNF), short-term mortality (≤ 4 months), and long-term mortality (≥ 1 year) and was

analyzed. Data extraction was performed by 2 independent reviewers. Sections of the Methods and Results were coded to blind reviewers to the above information. The methodological quality of studies included was assessed using a validated quality checklist^[14] with a maximum score of 32. A score ≥ 12 (38%) was considered to have acceptable quality.^[15]

2.4. Statistical analysis

The pooled estimate of each variable of interest was calculated and presented as a mean. The cumulative rate of each outcome of interest was calculated. Statistical heterogeneity was analyzed with Chi-squared distribution, Cochran Q -test, and I -squared statistics. A fixed-effects model (Mantel–Haenszel) was applied for meta-analysis if the I -squared statistic was under 50% and/or the Q -test was not significant at $P < .05$. On the contrary, we choose the random effect model. $P < .05$ was considered statistically significant.

3. Results

3.1. Studies characteristics

We initially screened 1658 potential relevant articles and excluded 1623 articles that did not obviously fulfill the inclusion criteria by reviewing their titles and abstracts. Of the 35 studies selected for further evaluation, 11 were excluded because the grade of donor liver steatosis was not appropriately defined,^[13,16–25] 4 were excluded because the sample size less than 15 in the observation group,^[12,26–28] 2 were excluded because of duplicated study subjects,^[29,30] and another 2 were excluded because the detailed data could not be extracted.^[31,32] Thus, 16 studies fulfilled the inclusion criteria in this study (Fig. 1).

All of the 16 studies were retrospective or prospective case series, and there were no randomized controlled trials. A total of 2694 subjects were included in the control group, and 532 subjects were included in the observation group. Detailed information and summarized data about the included studies are provided in Table 1.^[33–47]

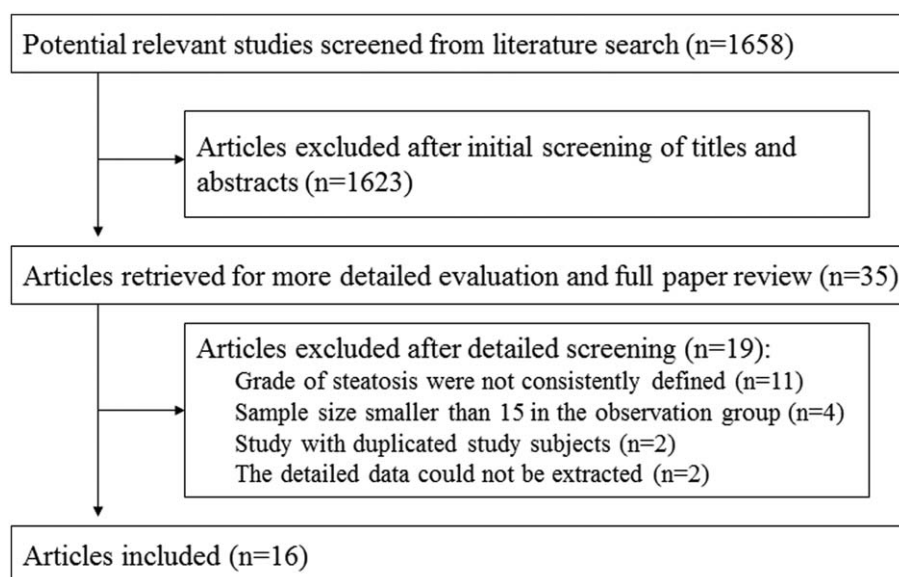


Figure 1. Identification of trials for inclusion.

Table 1
Characteristics of included studies.

Ref.	Country	Period	Study design	Drafts	PNF	1-mo patient death	1-y patient death	1-y graft death
Adam et al [7]	France	Nov 1986–Apr 1990	Retrospective	359 vs 31	8 vs 4	19 vs 8	NA	NA
Ploeg et al [35]	US	Jul 1984–Oct 1991	Retrospective	143 vs 15	7 vs 4	NA	NA	NA
Fishbein et al [33]	US	Aug 1992–Jan 1995	Retrospective	386 vs 40	20 vs 2	NA	78 vs 8	112 vs 9
Urena et al [36]	Spain	NA	Prospective	41 vs 31	0 vs 2	4 vs 3	NA	NA
Hayashi et al [37]	Japan	Jun 1990–Dec 1997	Retrospective	322 vs 16	NA	19 vs 1	67 vs 4	NA
Canelo et al [38]	Germany	NA	NA	55 vs 24	3 vs 3	NA	NA	NA
Verran et al [39]	Australia	Jan 1986–Dec 2000	Retrospective	395 vs 48	4 vs 1	NA	35 vs 21	73 vs 35
Perez-Daga et al [40]	Spain	1997–2004	Retrospective	259 vs 35	NA	NA	NA	NA
McCormack et al [34]	Switzerland	Jan 2002–Sep 2006	Retrospective	40 vs 20	0 vs 1	NA	7 vs 1	7 vs 1
Nikeghbalian et al [41]	Iran	Apr 1993–Jun 2006	Retrospective	140 vs 34	NA	22 vs 6	37 vs 9	NA
Angele et al [42]	Germany	Jan 1997–Feb 2005	Retrospective	175 vs 50	3 vs 2	9 vs 9	NA	NA
Gao et al [43]	China	May 2003–Jun 2005	Retrospective	24 vs 24	0 vs 0	NA	2 vs 4	NA
Briceño et al [44]	Spain	NA	Prospective	72 vs 48	NA	NA	13 vs 12	17 vs 15
Noujaim et al [45]	Brazil	May 2002–Mar 2008	Prospective	74 vs 44	2 vs 2	7 vs 7	20 vs 19	24 vs 19
Deroose et al [46]	Canada	Jan 2000–Dec 2004	Prospective	131 vs 34	NA	NA	15 vs 7	NA
Chavin et al [47]	US	Jun 1999–Dec 2001	Prospective	78 vs 38	3 vs 0	9 vs 3	18 vs 6	23 vs 7

NA=not available, PNF=primary nonfunction.

3.2. Primary nonfunction

PNF is the main poor post-transplantation outcome of the use of steatotic donor livers. Eleven studies reported the incidence of PNF. Among these, 2 reported an increased incidence of PNF

with the use of moderately and severely steatotic donor livers, and the remaining 9 reported that the incidence was not significantly different between the patients in the observation group and the control group. Pooled analysis showed that 5.75% (21/365) of

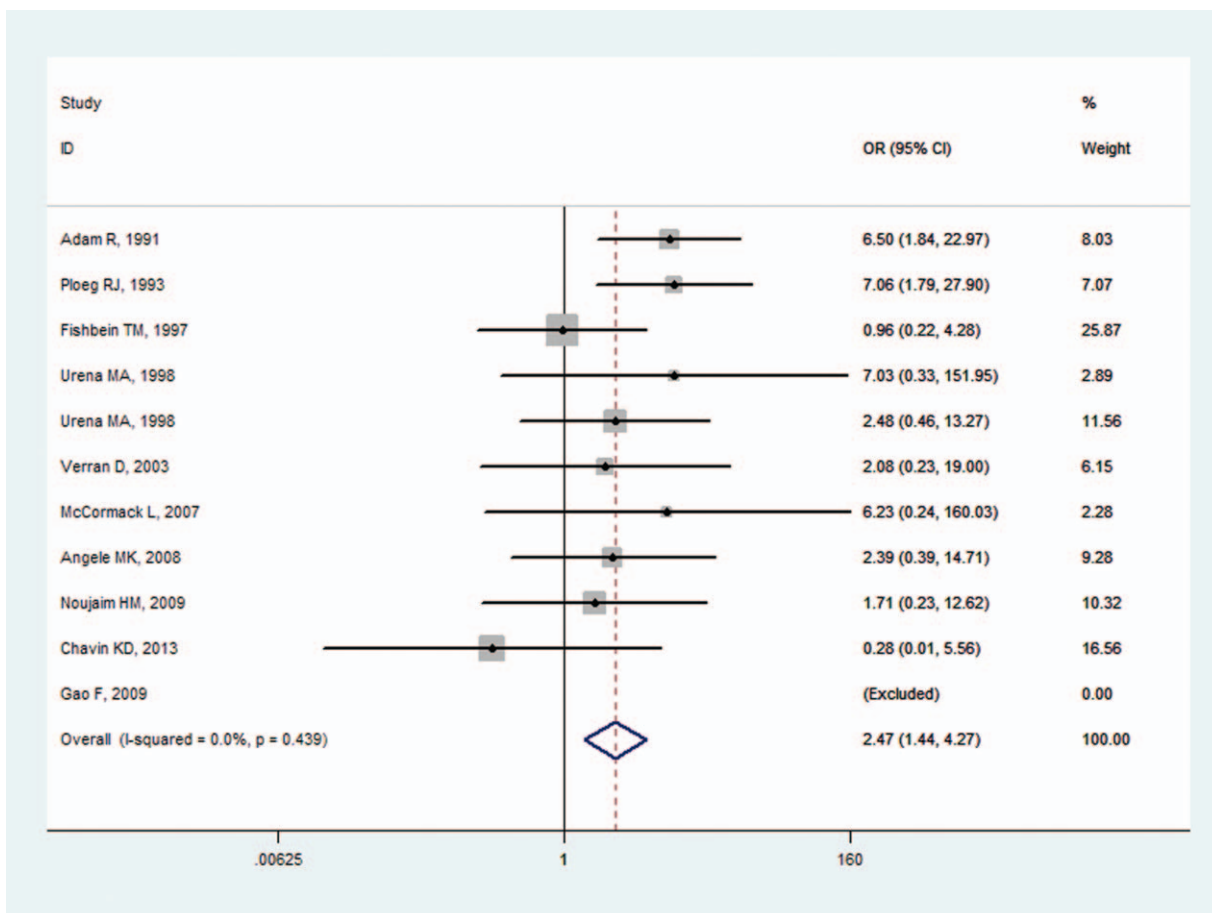


Figure 2. The incidence of PNF was significantly higher in the observation group than in the control group.

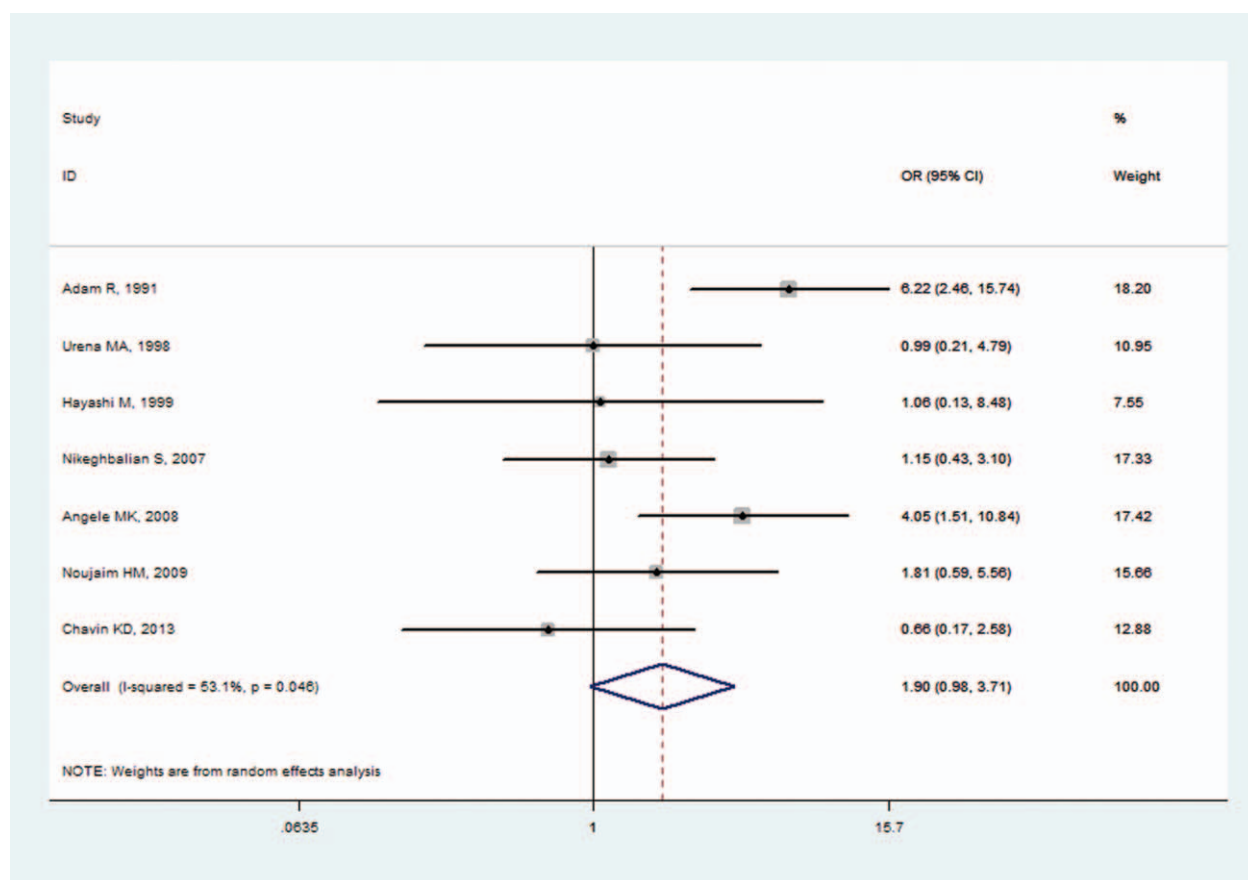


Figure 3. There were a trend of increase in the 1-month patient mortality in the observation group compared with the control group.

patients in the observation group developed PNF, and 2.82% (50/1770) of patients developed PNF in the control group. The incidence of PNF was significantly higher in the observation group than in the control group (OR: 2.47, 95% CI: 1.44–4.27; Fig. 2).

3.3. Short-term outcome

Ten studies reported the short-term patient mortality (≤ 4 months). Among these, 7 reported that the short-term mortality was not different between the control group and the observation group. The remaining 3 studies reported an increase in short-term mortality in the observation group in comparison to the control group. Seven studies reported 1-month patient mortality, and 4 studies reported 1-month graft mortality. The pooled analysis showed that 1-month patient mortality was 7.49% (89/1189) in the control group and 15.16% (37/244) in the observation group. A trend of increase in the 1-month patient mortality was noticed in the observation group compared with the control group (OR: 1.90, 95% CI: 0.98–3.71; Fig. 3). This result indicated that those patients who received moderately or severely steatotic donor livers are trend to have higher short-term mortality.

3.4. Long-term outcome

Eleven studies reported the long-term mortality (≥ 1 year). Among these, 10 reported that the long-term mortality was not different between the observation group and the control group.

The remaining one study reported an increase in long-term mortality in the observation group in comparison to the control group. Ten studies reported 1-year patient mortality, and the pooled mortality was 17.57% (292/1662) in the control group and 26.30% (91/346) in the observation group. Six studies reported 1-year graft mortality, and the pooled mortality was 24.50% (256/1045) in the control group and 36.13% (86/238) in the observation group. There were no statistical differences both 1-year patient mortality (OR: 1.52, 95% CI: 0.85–2.73; Fig. 4) and 1-year graft mortality (OR: 1.33, 95% CI: 0.45–3.91; Fig. 5). These results suggested that the 1-year mortality was relatively less influenced by the use of moderately and severely steatotic donor livers.

4. Discussion

To provide a more objective basis to clinical recommendations and to determine the safety of the use of moderately and severely steatotic donor livers for liver transplantation, we conducted a systematic literature review. Our results showed that the use of moderately and severely steatotic livers for liver transplantation is associated with a significant increase in incidence of PNF, a trend of increase in 1-month patient mortality, whereas the 1-year patient and graft mortality was relatively less influenced.

Hepatic steatosis is an important risk factor for liver surgery and transplantation due to an increased susceptibility to ischemia/reperfusion injury.^[5,48] The mechanisms for the increased susceptibility are associated with impaired hepatic

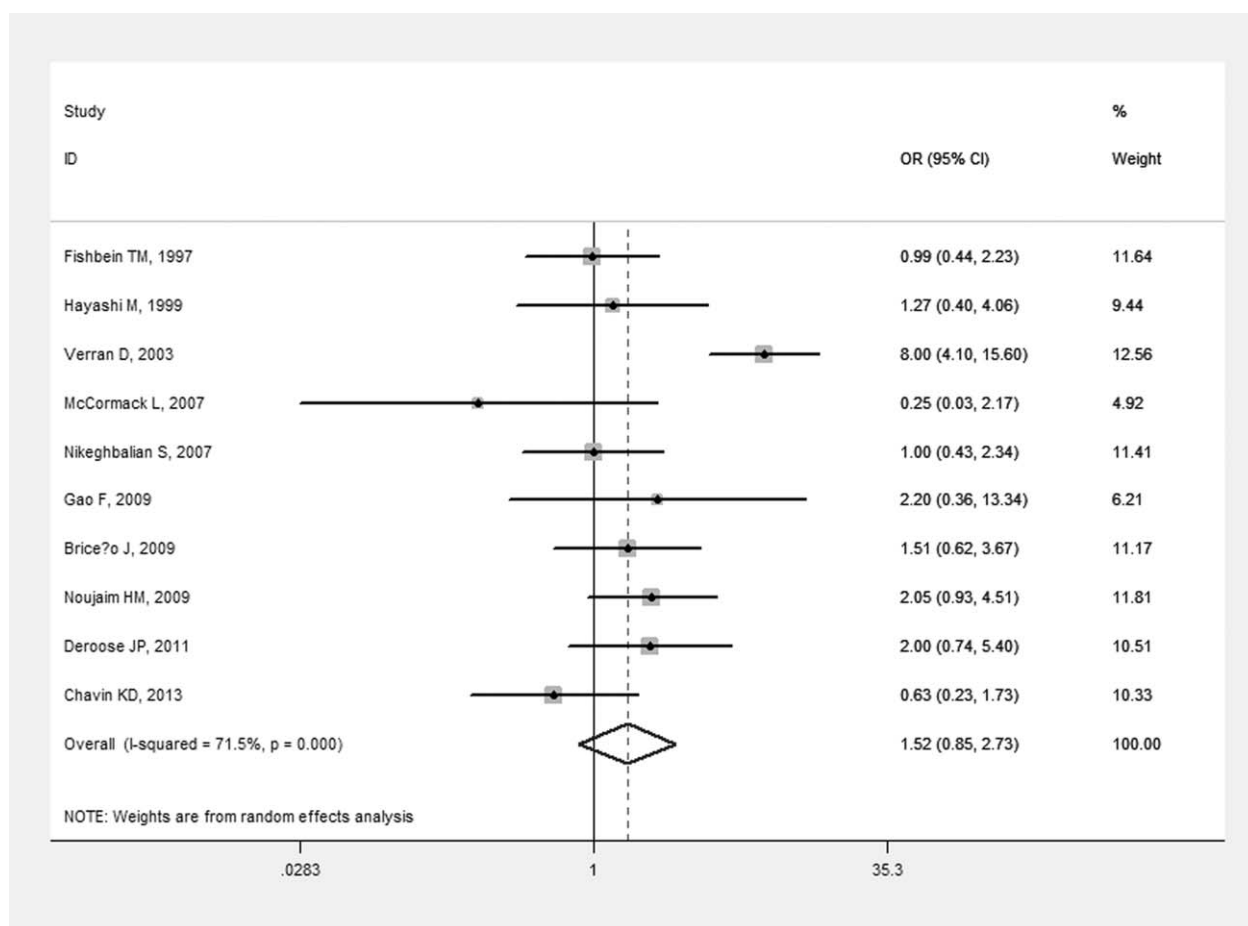


Figure 4. There were no statistical differences of 1-year patient mortality.

microcirculation, increased mitochondrial oxidative injury,^[49–51] as well as increased neutrophil aggregation and imbalance of cytokine release.^[6]

Therapeutic approaches to extend the use of steatotic donor livers for liver transplantation are currently under intensive investigation. Ischemic preconditioning could reduce the xanthine accumulation and percentage of xanthine oxidase observed in steatotic liver grafts during cold ischemia and protect against liver and lung damage following transplantation.^[52] Some pharmacological strategies aimed to modulate hepatic microcirculation, oxidative stress, and inflammatory response have also been shown to be effective at protecting steatotic donor livers against ischemia-reperfusion injury.^[53–55] However, the majority of these studies are still at an experimental stage, and whether these approaches are suitable for clinical application needs further investigation.

Despite less favorable outcomes compared with nonsteatotic donor livers, steatotic donor livers remain the most common type of marginal donor livers that have been introduced during the last 2 decades due to the shortage of donor organs.^[56] Moderately and severely steatotic donor livers may be used for recipients in relatively good clinical condition but with an acute need for liver transplantation. A major reason is that healthier recipients could better tolerate poor initial graft function or major postoperative complications.

The outcome of the use of moderately and severely steatotic donor livers remains unclear. Our pooled analysis showed that

the incidence of PNF for the subjects who received moderately and severely steatotic donor livers were more than 2 times higher than that in control group (5.75% vs 2.82%). The 1-month patient mortality also tends to be higher in the observation group than that in control group (15.16% vs 7.49%; OR: 1.90, 95% CI: 0.98–3.71). However, the 1-year patient and graft mortality was less influenced by the use of moderately and severely steatotic donor livers. The pooled patient mortality only increased 11.14% from 1 month to 1 year in the observation group, and the corresponding increase was 10.08% in the control group. This indicated that the disadvantages of the use of moderately and severely steatotic donor livers mainly occurred in the short term after transplantation. This may be partially explained by the observation that the grade of steatosis dramatically decreases after the transplantation.^[33,34] This encouraging observation further supports the use of moderately and severely steatotic donors for liver transplantation.

Due to the limited available data, there are some limitations in this study. The first is that we did not clarify whether the outcome differed between the use of microvascular and macrovascular steatotic donor livers. As macrovascular and microvascular steatosis may respond differently to ischemia-reperfusion injury,^[57,58] it would be of interest to compare the outcome of the use both types of steatotic donor livers. Another limitation is that we did not analyze the potential heterogeneity due to the relatively small sample size of the studies enrolled. We grouped all of the patients irrespective of their age, gender, etiology for liver

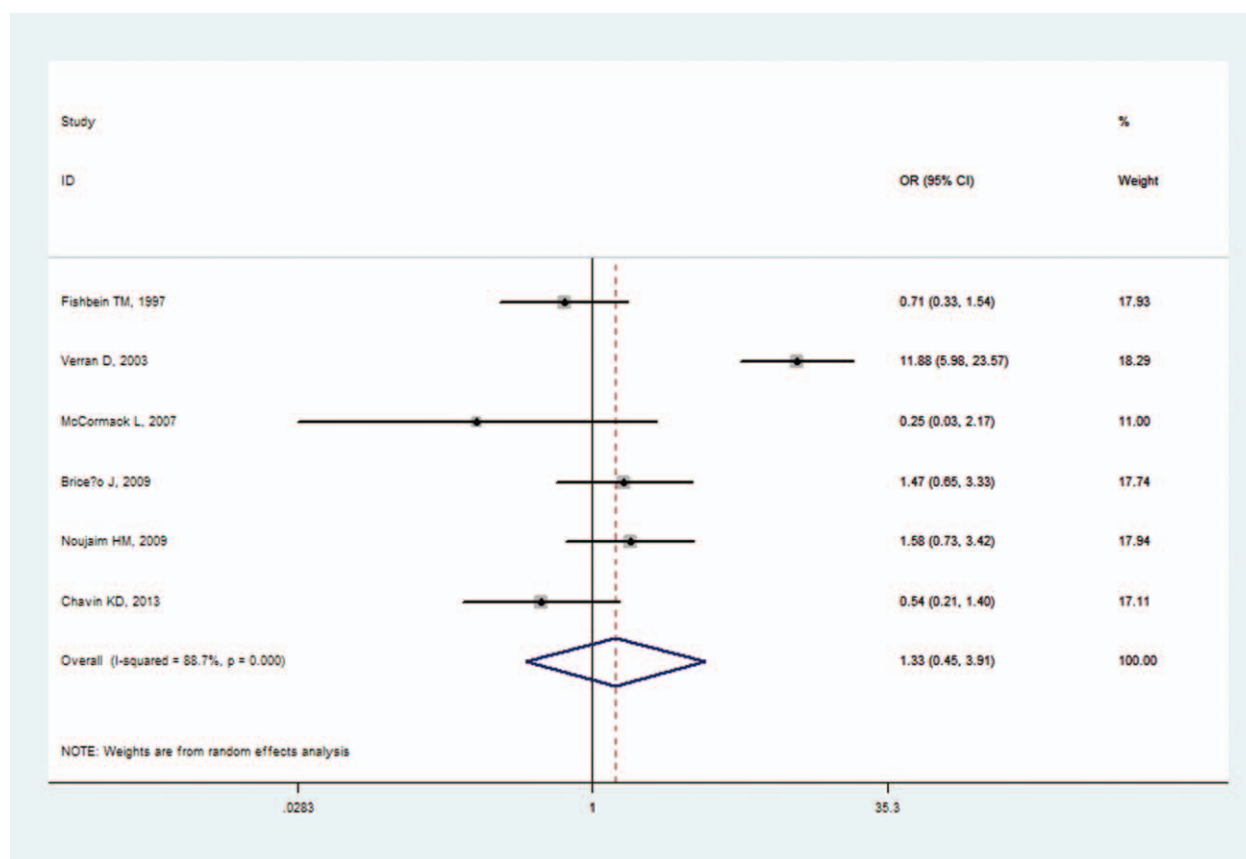


Figure 5. There were no statistical differences of 1-year graft mortality.

transplantation, cold storage time, etc. The pooled analysis of all of the cases provided a clearer general picture of the outcomes in a relatively large sample of the use of marked steatotic donor livers.

In conclusion, our systematic review showed that the use of moderately and severely steatotic donor livers for liver transplantation is associated with an increased incidence of PNF and a trend of increase in 1-month patient mortality, but the long-term outcome was relatively less influenced. Moderately and severely steatotic donor livers may also be suitable for use, with caution, to expand the pool of donor organs.

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