Original Article

Liver transplantation improves erectile function in patients with end-stage liver disease: a systematic review and meta-analysis

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Background: Liver transplantation (LT) has been recognized as the most effective therapy for end-stage liver disease (ESLD). However, the question of whether LT can improve erectile function in patients with ESLD remains controversial. Therefore, we conducted this meta-analysis to evaluate the association between LT and erectile dysfunction (ED).

Methods: According to the PRISMA guidelines, studies were included after conducting searches in four databases from March 2024 onwards. These databases included PubMed, Cochrane Library, Web of Science, and Embase. The primary outcome of interest was to compare the International Index of Erectile Function (IIEF) scores between patients after and before LT. Standardized mean differences (SMDs) and their corresponding 95% confidence intervals (CIs) were utilized to assess the relationship between LT and ED.

Results: The results showed that the LT group had higher IIEF-5 domain scores for erectile function compared to the control group (SMD =–0.31, 95% CI: –0.53 to –0.09), P=0.007). No heterogeneity or publication bias was detected in the results. Additionally, the IIEF-15 domain score was also found to be improved after LT. Specifically, the LT group had higher domain scores for erectile function (SMD =–0.77, 95% CI: –1.07 to –0.48, P<0.001), orgasmic function (SMD =–0.82, 95% CI: –1.12 to –0.52, P<0.001), sexual desire (SMD =–0.89, 95% CI: –1.19 to –0.59, P<0.001), intercourse satisfaction (SMD =–0.92, 95% CI: –1.22 to –0.62, P<0.001), and overall satisfaction (SMD =–0.87, 95% CI: –1.17 to –0.57, P<0.001).

Conclusions: It is suggested by our meta-analysis that LT may contribute to improvements in erectile function among men with ESLD. This improvement may be related to the remarkable improvement in endocrine hormone disorders observed after LT. However, future studies with better designs and larger sample sizes are still needed to confirm our conclusions. Additionally, attention to erectile function before and after surgery in patients with liver failure is crucial.

Keywords: Liver transplantation (LT); erectile dysfunction (ED); meta-analysis

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Introduction

Erectile dysfunction (ED), previously known as impotence, is characterized by the inability to achieve or maintain an erection firm enough for vaginal penetration and sexual satisfaction (1). This condition represents a significant health issue, often underestimated and underdiagnosed in contemporary society due to patient embarrassment and a lack of awareness among doctors about its widespread prevalence and adverse effects on quality of life (2). The impact of ED extends beyond physical symptoms,

progressively inducing anxiety, depression, and a loss of self-esteem, thereby significantly deteriorating the quality of life (3). Moreover, ED adversely affects the sexual well-being of both patients and their partners, correlating strongly and negatively with the frequency of intercourse and the health of sexual relationships (4). On a global scale, the incidence of ED is expected to increase dramatically, with projections suggesting that the number affected will reach 322 million by 2025, marking a 111% rise since 1995 (5). This trend highlights the urgent need for increased recognition and treatment of this distressing condition.

Sexual dysfunction in chronic liver disease primarily stems from physiological abnormalities in the hypothalamic-pituitary-gonadal axis and underlying liver pathology (6). Patients with end-stage liver disease (ESLD) frequently suffer from various types of hypogonadism, such as testicular atrophy, gynecomastia, reduced libido, altered hair distribution, and hormonal imbalances. These issues often coincide with reduced levels of free and total testosterone, decreased basal secretion of gonadotropins, hyperestrogenemia, and hyperprolactinemia, all of which can contribute to the development of ED (7). Liver transplantation (LT) is considered the most effective treatment for ESLD and has been increasingly adopted as transplantation technology advances. This has led to a significant rise in the number of liver transplants performed annually and a notable increase in the survival time of recipients. Consequently, there is growing attention on improving the quality of life for liver transplant recipients, with a particular focus on erectile function. In theory, LT helps restore liver function, and consequently, sexual function should also theoretically improve.

However, current researches do not uniformly support the aforementioned hypothesis. Chien *et al.* discovered that male patients exhibited recovery in erectile function six months after undergoing LT (8). On the contrary, Sorrell *et al.* found that although sexual activity in male patients improved after LT, there was no significant improvement in their sexual function scores (9). However, the small sample sizes in these studies diminish the reliability of the results. These shortcomings highlight the necessity of conducting a meta-analysis, which synthesizes multiple studies to increase sample sizes and enhance the reliability of results.

Therefore, we conducted the present systematic review and meta-analysis of the existing literature to assess the impact of LT on erectile function in patients with ESLD. To the best of our knowledge, this is the first meta-analysis to offer comprehensive insights into the effects of LT on erectile function. This article is written in accordance with the PRISMA reporting checklist (10) (available at https://tau.amegroups.com/article/view/10.21037/tau-24-185/rc).

Highlight box

Key findings

- Liver transplantation may contribute to improvements in erectile function among men with end-stage liver disease (ESLD).

What is known and what is new?

- Chronic liver disease results in abnormal hormone secretion, progressively leading to male erectile dysfunction.
- We compared erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction between the liver transplantation group and the control group, revealing superior outcomes in the liver transplantation group.

What is the implication, and what should change now?

- It is worth recognizing that patients with ESLD could experience improvements in erectile function through liver transplantation.

Methods

This meta-analysis involved reviewing data from existing studies, negating the need for additional ethical approval from our institution.

Data sources and search strategy

An extensive search of four databases—PubMed, Cochrane Library, Web of Science, and Embase—was conducted by two authors (Y.M., Y.L.) from inception through March 2024 to identify studies reporting the effects of LT on erectile function. The systematic literature search was conducted using Medical Subject Headings (MeSH) terms, free words, and keywords. The Search terms included: ((((((Penile Erection[MeSH]) OR (Sexual Behavior[MeSH])) OR (Erectile Dysfunction[MeSH])) OR (sexual function)) OR (erectile function)) AND ((((((((((End Stage Liver Disease[MeSH]) OR (Chronic Hepatic Failure[MeSH])) OR (end-stage liver disease)) OR (liver disease, end stage)) OR (liver disease, end-stage)) OR (disease, end stage liver)) OR (liver failure, end stage)) OR (end stage liver failure)) OR (liver failure, end-stage)) OR (esld))) AND (((Liver Transplantation[MeSH]) OR (liver grafting)) OR (Hepatic Transplantation)). We adjusted the retrieval strategy according to the requirements of different databases. Additionally, we manually searched the reference lists of all

eligible articles to retrieve any additional studies.

Selection and exclusion criteria

The following criteria were used to determine inclusion in the review: (I) studies assessing the relationship between erectile function and LT, with no limitation on study design; (II) use of the International Index of Erectile Function (IIEF) or IIEF-15 questionnaires to assess erectile function; (III) presence of age-matched control groups or patients before LT; (IV) availability of sufficient data to calculate weighted mean differences (WMDs) with 95% confidence intervals (CIs) or odds ratios (ORs). On the contrary, our meta-analysis excluded studies if (I) studies conducted on animals; (II) studies lacking control groups; (III) studies with insufficient data; (IV) studies categorized as case reports, reviews, letters, or comments.

Evidence quality assessment

Two reviewers (X.F., R.X.) independently assessed the included studies' quality using the Newcastle-Ottawa Scale (11). The Newcastle-Ottawa Scale incorporates three methodological components: (I) selection: assessing whether the definition of cases is distinct, if the cases are representative, if controls are appropriately chosen, and if the definition of controls is clear; (II) comparability: evaluating whether the main factors are comparable between cases and controls, as well as whether additional factors are comparable; (III) outcome: determining if the exposure is confirmed, if the method of confirmation for both controls and cases is consistent, and if the nonresponse rate of the case group matches that of the control group. Each affirmative answer was assigned 1 point, while a negative answer received 0 points. The scores for all questions were totaled to determine the overall quality assessment. Research with a score of >5 was considered high-quality. In cases where two reviewers provided different opinions, a third reviewer was introduced and ultimately made the final decision on the scoring.

Data extraction

All identified documents were independently screened and assessed for eligibility by two authors (Y.M., Y.L.). Any discrepancies were resolved through consensus with another author (X.F.). Initially, studies that did not meet the predefined selection criteria were excluded. Subsequently, the abstract or full text of the remaining studies was reviewed to further refine the selection. Finally, all eligible studies underwent a thorough re-examination to determine inclusion in this meta-analysis.

After completing the final selection of literature, we used a standardized data extraction form aligned with PRISMA guidelines to extract the following data: first author's name, publication year, country, race, study design, sample size, number of participants in the control and experimental groups, erectile function assessment tool, follow-up duration post-surgery, ensuring both thoroughness and uniformity.

Statistical analysis

In our meta-analysis, the primary outcome of interest was to compare the IIEF scores between patients after and before LT. The second outcome of interest was to compare the sub-scores of the IIEF-15 in ESLD patients before and after LT. The summary effect sizes were calculated as the Standardized mean differences (SMDs) and their corresponding 95% CIs, considering that both primary and secondary outcomes are continuous variables. Data analysis was conducted using Stata software (version 16.0; Stata Corporation, College Station, TX, USA) and Open Meta-Analyst (completely open-source, funded by AHRQ, grant number: R01HS018574). When the P value of the Z test is less than 0.05, the combined result is considered statistically significant. When pooling the research data comprehensively, the Q test or I^2 value was calculated to assess heterogeneity. The choice between a fixed-effect model or random-effects model was made based on the level of heterogeneity observed. If the I^2 value is less than 50% or the P value is greater than 0.05, indicating no significant heterogeneity among studies, a fixed-effect model was employed. However, if the I^2 value is 50% or higher or the P value is 0.05 or lower, suggesting high heterogeneity, a random-effects model was utilized. In cases of heterogeneity, sensitivity analysis was conducted to identify its source, where each study was systematically excluded one at a time to assess the single study's impact on the summary results. However, due to the limited number of included studies, we were unable to further perform subgroup analyses to explore potential sources of heterogeneity. The Begg's test was utilized to assess publication bias, with bias considered to exist when the P value was less than 0.05.

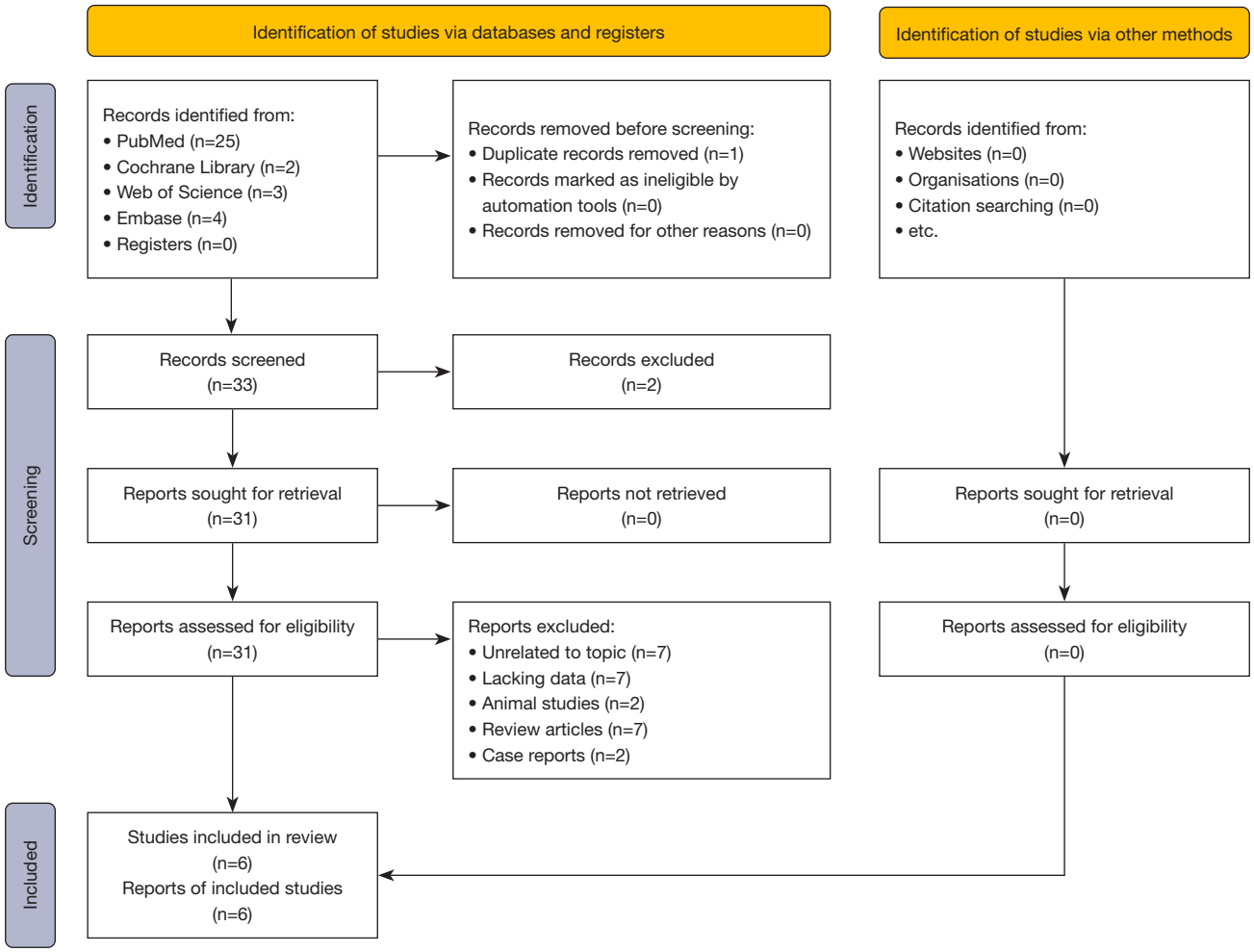

Figure 1 Flowchart of literature screening and selection.

Results

Characteristics of included studies

We retrieved a total of 34 possibly related studies from the databases PubMed, Cochrane Library, Web of Science, and Embase. After removing 1 duplicate record, the titles and abstracts of 33 records were screened to determine their eligibility. Subsequently, 2 articles were excluded based on their lack of relevance to the topic, as determined by reading the abstracts and titles. We proceeded to review the full text of the remaining 31 articles. Subsequently, 25 studies were excluded for the following reasons: 7 were unrelated to LT or ED, 7 lacked sufficient data for synthesis, 2 were animal tests, 7 were review articles, and 2 were case reports. Among the 7 studies that lacked sufficient data for synthesis, three focused on erectile function in cirrhosis patients but did not provide post-transplantation data; two investigated the use of tadalafil for treating ED in cirrhosis patients; and two only assessed survival and quality of life post-transplantation without evaluating erectile function. Ultimately, our meta-analysis included 6 studies (8,12-16). The study selection process for relevant literature is shown in *Figure 1*. Erectile function of patients with ESLD was compared in five out of the six prospective studies before and after LT. The remaining study was a cross-sectional study that compared liver transplant recipients with age-matched patients suffering from ESLD. The characteristics of the included studies can be found in *Table 1*, while *Table 2* displays the quality assessment of the included studies, independently assessed by two authors using the Newcastle-Ottawa Scale (NOS). The NOS component applied to cohort, cross-sectional, and case-control studies aimed for

Table 1 Characteristics of included studies

Study	Country	Ethnicity	Study design	Sample size*	ED evaluation tool	Follow-up period (months)
Coelho *et al.*, 2003 (12)	Spain	Caucasian	Prospective study	25/25	IIEF-15	≥6
Wang *et al.*, 2013 (16)	China	Asian	Cross-sectional study	57/60	IIEF-5	≥3
Chien *et al.*, 2015 (8)	China	Asian	Prospective study	58/58	IIEF-5	6–7
Chiang *et al.*, 2018 (14)	China	Asian	Prospective study	41/41	IIEF-5	≥6
Chan *et al.*, 2019 (13)	China	Asian	Prospective study	28/28	IIEF-5	≥6
Karabulut *et al.*, 2021 (15)	Turkey	Caucasian	Prospective study	39/39	IIEF-15	6

*, number of participants followed up/total number of participants. ED, erectile dysfunction; IIEF-15, International Index of Erectile Function-15.

Table 2 Quality assessment for all the included studies

First author, year	Selection				Comparability		Outcome			Score
	Case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Main factor	Additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	
Coelho *et al.*, 2003 (12)	★	★	★	★	★	–	★	★	—	7/9
Wang *et al.*, 2013 (16)	★	★	★	★	★	★	–	★	—	7/9
Chien *et al.*, 2015 (8)	★	★	★	★	★	★	–	★	—	7/9
Chiang *et al.*, 2018 (14)	★	★	–	★	★	–	★	★	—	6/9
Chan *et al.*, 2019 (13)	★	★	★	★	★	★	★	★	—	8/9
Karabulut *et al.*, 2021 (15)	★	–	★	★	★	–	–	★	—	5/9

"★" indicates "fulfilled" or "yes".

evaluation. The total score of the included studies ranged from 5 to 8, indicating excellent quality across all adopted studies. This enhances the reliability of our meta-analysis and provides more robust evidence.

Erectile function domain score of the IIEF-5 between patients after LT and patients before LT

The SMD and 95% CI was calculated to compare the level of IIEF-5 between patients after LT and patients before LT. Four studies, comprising 187 patients after LT and 184 patients before LT, compared the erectile function domain score of the IIEF-5 between patients after and before LT. The results indicated that the score of the IIEF-5 in patients after LT was higher than that in patients before LT (SMD =–0.31, 95% CI: –0.53 to –0.09, P=0.007), with no significant heterogeneity observed (I^2=42.3%, P=0.16). The result is displayed in *Figure 2*. The stability and reliability of the IIEF-5 results were evaluated by conducting a sensitivity analysis, as demonstrated in *Figure 3*. Due to the limited number of studies included in the present meta-analysis, publication bias assessment was not conducted by our group.

The subdomains scores of IIEF-15

We utilized the IIEF-15 to conduct a meta-analysis of two studies to determine if LT has an influence on other aspects of sexual function. As shown in *Figure 4*, the IIEF-EF score of the LT group was significantly higher than that of the control group (SMD =–0.77, 95% CI: –1.07 to –0.48, P<0.001), with no substantial heterogeneity

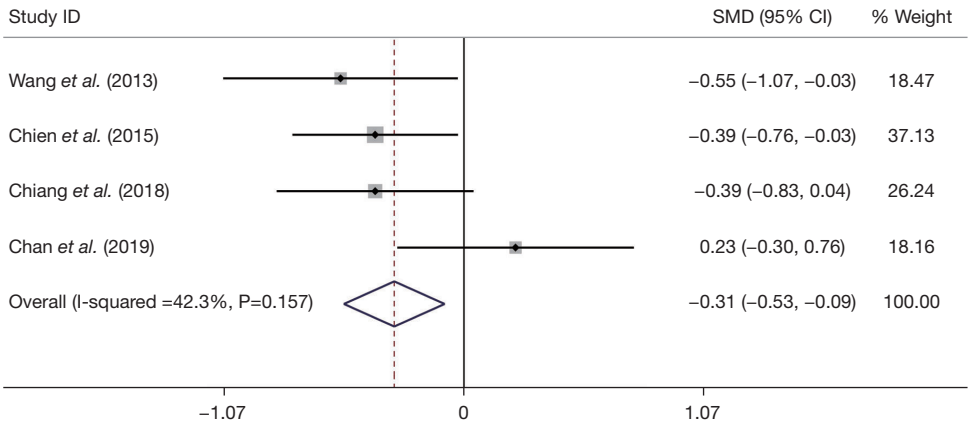

Figure 2 Forest plot of erectile function domain score performed on the four studies used IIEF-5 comparing pre- and post-transplanted patients. IIEF-5, International Index of Erectile Function-5; SMD, standard mean difference; CI, confidence interval.

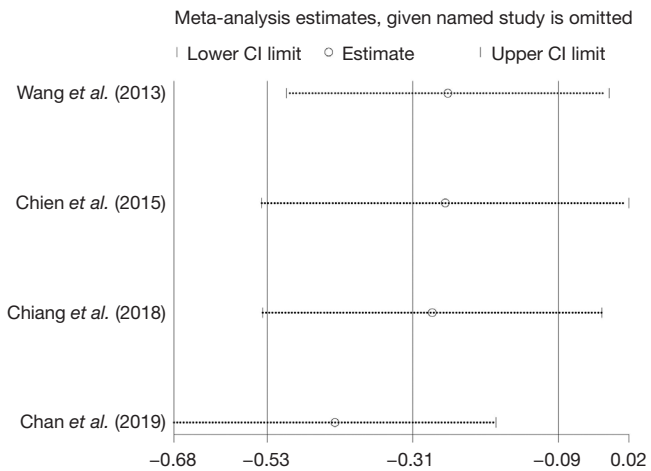

Figure 3 Sensitivity analysis of the selected studies for score of IIEF-5 between pre- and post-transplanted patients. IIEF-5, International Index of Erectile Function-5; CI, confidence interval.

observed (I^2=0.0%, P=0.90). Additionally, the IIEF-OF score improved after LT (SMD =−0.82, 95% CI: −1.12 to −0.52, P<0.001), with no substantial heterogeneity (I^2=0.0%, P=0.74). The IIEF-SD score was lower in the control group than in the LT group (SMD =−0.89, 95% CI: −1.19 to −0.59, P<0.001), with no substantial heterogeneity (I^2=0.0%, P=0.46). Similarly, the IIEF-IS score was higher in the LT group than in the control group (SMD =−0.92, 95% CI: −1.22 to −0.62, P<0.001), with no substantial heterogeneity (I^2=0.0%, P=0.48). The IIEF-OS score also improved after LT (SMD =−0.87, 95% CI: −1.17 to −0.57, P<0.001), with no substantial heterogeneity (I^2=0.0%, P=0.54). The results are presented in *Figure 4A-4E*. For these analyses, due to the limited number of included studies, further sensitivity analysis and publication bias analysis could not be conducted. Additionally, subgroup analysis was not feasible due to the constraints imposed by the limited number of included studies.

Discussion

There are still several limitations in our study that should be considered when interpreting the results. First, the relatively small sample size of each study limits the ability of our meta-analysis to provide higher-quality clinical evidence. Second, the limited number of published studies makes it difficult to trace the origin of heterogeneity through subgroup analysis. Furthermore, due to the lack of available literature, conducting meta-regression was also challenging. Third, since most of the studies we selected are observational, causality cannot be definitively proven, and potential confounding factors may be difficult to dismiss. Despite these limitations, our meta-analysis provides valuable insights into the changes in erectile function before and after LT. Our study demonstrates that LT can improve erectile function in patients with ESLD. Addressing erectile function in patients with ESLD and those who undergo LT is of significant importance for enhancing sexual quality of life and overall quality of life.

With the increasing prevalence of ESLD, approximately 11,000 patients with ESLD are listed for LT annually in the United States, while the number of LTs performed annually ranges from 6,000 to 7,000 (17). LT is considered

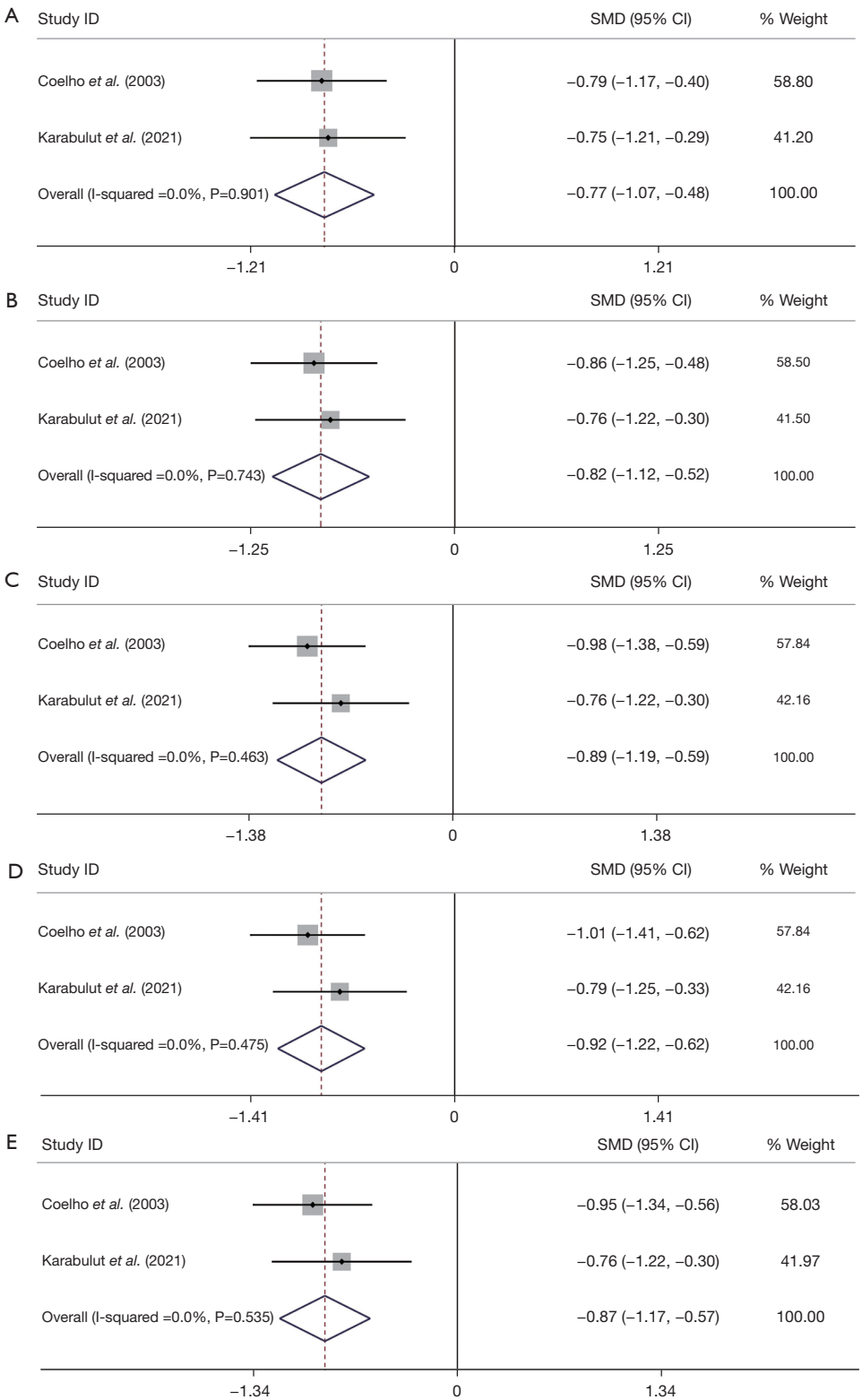

Figure 4 Subgroup analysis of EF domain score. Forest plot of IIEF-EF (A), IIEF-OF (B), IIEF-SD (C), IIEF-IS (D), and IIEF-OS (E). IIEF, International Index of Erectile Function; EF, erectile function; OF, orgasmic function; SD, sexual desire; IS, intercourse satisfaction; OS, overall satisfaction; SMD, standard mean difference; CI, confidence interval.

the standard curative therapy for patients with alcohol-related ESLD and for patients with advanced hepatocellular carcinoma (HCC). Advances in surgical techniques and medical treatments have led to improved long-term survival outcomes for patients requiring LT. However, patients with chronic diseases often prioritize quality of life over lifespan. The prevalence of ED in patients with ESLD is extremely high (9). Sexual function is an integral part of the life quality and is the main concern for men with ESLD and patients undergoing LT (12). ED has a profound and lasting impact on the quality of life of patients with ESLD, which warrants our attention. The pathogenesis of sexual dysfunction involves multiple factors, with ESLD being one of the many contributing reasons. Sexual dysfunction in patients with liver cirrhosis is primarily attributed to liver function impairment and disruption of the hypothalamic-pituitary-gonadal axis (13). The hypogonadism observed in patients with impaired liver function has been attributed to changes in the estrogen-androgen ratio, alterations in the hypothalamic-pituitary-gonadal axis, and disruptions in sex hormone transport (14). According to reports, patients with liver cirrhosis experience decreased libido, reduced testicular size, lower testosterone levels, and may even face infertility (15).

Orthotopic liver transplantation (OLT) has been demonstrated in numerous studies to restore the hypothalamic-pituitary-gonadal axis (16). Foresta *et al.* reported a decrease in the level of sex hormone binding protein in patients after OLT, accompanied by an increase in serum free testosterone levels (18). This finding could potentially explain the improvement in postoperative physical function (19). LT, aimed at restoring liver function, should theoretically improve sexual function (9). It is important to recognize that the significant effect of LT on ED has now been well demonstrated. Numerous studies have demonstrated that the erectile function of patients who have undergone LT can be improved to some extent (20). However, some scholars believe that the difference in erectile function between patients with ESLD undergoing LT is not significant (21). According to Sorrell *et al.* (2006), 32% of patients who did not experience sexual dysfunction before LT developed sexual dysfunction after the procedure (9).

The question of whether LT benefits erectile function in patients with ESLD remains controversial. Therefore, this meta-analysis is the first to analyze the difference in erectile function between patients before and after LT. Our results suggest that erectile function scores were higher in liver transplant recipients. In other words, receiving a LT may be beneficial for patients with ESLD in improving erectile function. Wang *et al.* found that the proportion of sexually active patients was higher, the overall IIEF-5 score was higher, and the incidence of ED was lower in the post-LT group compared to the pre-LT group, consistent with our meta-analysis (16). The research suggests that the erectile function of patients with ESLD could be improved by LT (22).

In Karabulut *et al.*'s study, the rate of severe ED was 60.5% before LT, which decreased to 28.9% after transplantation, and the subscale scores of IIEF in male patients increased significantly, indicating a recovery in the sexual life of male patients after transplantation (15). Wang *et al.* (2013) reported that 59.1% of the patients had severe ED before LT, while this rate decreased to 21.7% after transplantation (16). Chien *et al.* (2015) found that erectile function recovered within 6 months after LT (8). The findings from these studies are consistent with our results, underscoring the importance for clinicians to pay attention to erectile function in male patients with ESLD. Additionally, LT plays a significant role not only in improving liver function but also in enhancing erectile function, which can further enhance the overall quality of life for patients.

The IIEF-5 scale, a simplified version of the IIEF-15, possesses advantageous features for detecting the presence and severity of ED (23). In a study by van Kollenburg *et al.*, both the electronic versions of the IIEF-5 and IIEF-15 demonstrated prominent internal consistency and test-retest reliability (24). Clinical studies have confirmed that the IIEF-15 is a validated psychometric tool used to assess various aspects of sexual function (25-27). The IIEF domain score reflecting psychological aspects was found to significantly increase within the LT group. This suggests that LT may ameliorate the erectile function of patients suffering from ESLD.

In addition to ESLD, increasing evidence suggests that non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and chronic viral hepatitis also impact male erectile function (28). A survey study found that 24.6% to 85.0% of men experience varying degrees of ED. Potential mechanisms behind this include associated insulin resistance, decreased testosterone levels, and the use of medications such as interferons and diuretics. However, a nationwide survey from the Italian Society of Gastroenterology (SIGE) revealed that both gastroenterologists and patients have a low awareness of sexual function issues (29). This is reflected in the lack of knowledge among doctors, time constraints, and feelings of embarrassment. Patients also

generally expect gastroenterologists to address these issues. Therefore, more research should focus on the sexual function of these patients to identify more treatment options and improve quality of life.

Furthermore, potential sources of bias in our meta-analysis should be considered. Publication bias is a concern, as studies with positive results are more likely to be published, while those with negative or null results may be underreported. This can lead to an overestimation of the true effect. However, the limited number of eligible studies prevented us from performing a reliable assessment of publication bias. Selection bias is another potential issue, as the inclusion criteria for studies may have excluded relevant research, particularly those published in non-English languages. This can result in a skewed representation of available evidence. Additionally, the observational nature of most included studies introduces a risk of selection bias within the studies themselves, where patients included in the studies may not be representative of the broader population with liver disease. By acknowledging these potential biases, more comprehensive and high-quality studies in this area are needed in the future to confirm our results.

Conclusions

In conclusion, our meta-analysis suggests that LT may contribute to improvements in erectile function among patients with ESLD. This improvement may be attributed to the remarkable improvement in endocrine hormone disorders observed after LT. However, it is important to note that most of the published studies on this topic have been conducted with small sample sizes. Therefore, future research, particularly carefully designed cohort studies, especially those with large cohorts, are required to validate our findings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-185/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-185/coif). 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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