Original Article

Risk of *de novo* esophageal cancer in liver transplant recipients: systematic review and meta-analysis

Shaoya Li, Shutian Zhang, Xiujing Sun

Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center for Digestive Diseases, Beijing Digestive Disease Center, Faculty of Gastroenterology of Capital Medical University, Beijing Key Laboratory for Precancerous Lesion of Digestive Diseases, Beijing, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: X Sun; (III) Provision of study materials or patients: S Zhang, X Sun; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xiujing Sun, MD. Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center for Digestive Diseases, Beijing Digestive Disease Center, Faculty of Gastroenterology of Capital Medical University, Beijing Key Laboratory for Precancerous Lesion of Digestive Diseases, 95 Yong'an Road, Tianqiao Street, Xicheng District, Beijing 100050, China. Email: sunxiujing@ccmu.edu.cn.

Background: *De novo* malignancy is the leading cause of death in liver transplant recipients. Numerous studies consistently show a significantly increased risk of esophageal cancer after liver transplantation. Therefore, this study aims to investigate the incidence and risk factors associated with *de novo* esophageal cancer post-liver transplantation.

Methods: PubMed, Embase, Medline and Cochrane Library were systematically searched. Screening, quality assessment, and data extraction were completed. The search was completed in November 2023. Standardized incidence rates (SIRs) were used to measure the risk of esophageal cancer among liver transplant recipients, along with corresponding 95% confidence intervals (CI). A random effects model was employed for comprehensive analysis, and results were presented using a forest plot. Sensitivity analysis was undertaken by systematically excluding individual studies one by one, while potential publication bias was assessed using funnel plots and Egger's test. Additionally, subgroup analyses were also performed to explore sources of heterogeneity.

Results: Out of 1,037 articles collected, only twelve met the inclusion criteria after rigorous screening. Statistical analysis showed a significantly increased risk of esophageal cancer following liver transplantation compared to the general population (SIR =6.75, 95% CI: 4.35–10.46).

Conclusions: The risk of esophageal cancer significantly increases after liver transplantation, so regular gastrointestinal endoscopy is necessary after the procedure.

Keywords: Liver transplantation; *de novo* cancer; esophageal cancer; morbidity risk; standardized incidence rates (SIRs)

Submitted Jan 23, 2024. Accepted for publication May 05, 2024. Published online Jun 27, 2024.
doi: 10.21037/jgo-24-66
View this article at: https://dx.doi.org/10.21037/jgo-24-66

Introduction

Liver transplantation is considered the preferred treatment for end-stage liver failure or disorders (1). Currently, there has been a continuous increase in the number of liver transplants worldwide, with a record of 9,234 liver transplants performed in the United States in 2021 (2). With advancements in liver transplantation surgical techniques and postoperative care, long-term survival rates for transplant patients are progressively improving. In the United States and Northern Europe, patient survival

rates at one and five years after transplantation have surpassed 90% and 80%, respectively (3,4). Malignant tumors following liver transplantation have emerged as the primary cause of patient mortality (5,6). Studies indicate that the incidence of malignant tumors after liver transplantation ranges from 11.5–22.3% at ten years (7-9), and increases to 31.5–34.7% at fifteen years (9,10), which represents a risk approximately 1.8–2.2 times higher than age- and sex-matched individuals within the general population (11-14).

Esophageal cancer is relatively uncommon among malignancies occurring after liver transplantation, but it exhibits a higher prevalence in East Asia. It often presents at an advanced stage with a poor prognosis upon detection. An Italian national cohort study revealed a significantly increased risk (23.4-fold) of *de novo* esophageal cancer following liver transplantation compared to the general population (15). Nevertheless, some studies suggest that this risk may not be significantly higher than that observed among non-transplant individuals (16,17). The current literature lacks a comprehensive systematic review on the risk of esophageal cancer recurrence following liver transplantation. Therefore, the objective of this meta-analysis is to determine these risks through comprehensive strategies including systematic literature searches and rigorous study evaluation processes in order to derive robust conclusions. We present this article in accordance with the PRISMA reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-66/rc).

Highlight box

Key findings

- The risk of esophageal cancer is significantly increased following liver transplantation compared to the general population.

What is known and what is new?

- The risk of developing new cancer following liver transplantation is significantly elevated. However, the question regarding whether there is an increased susceptibility to esophageal cancer remains a subject of controversy.
- This study conducted a meta-analysis to ascertain the risk of esophageal cancer and examined the associated risk factors.

What is the implication, and what should change now?

- Screening for early cancer and implementing close follow-up after liver transplantation are of paramount importance.

Methods

The present study was also conducted in accordance with the guidelines outlined by Cochrane handbook of systematic reviews (18). The review was not registered.

Search strategy

We conducted a comprehensive search of the PubMed, Embase, Web of Science, and Cochrane Library databases from inception to 1 November 2023 with the following search terms: (liver transplant OR liver graft OR hepatic transplant OR hepatic graft) AND (esophageal OR esophagus) AND (cancer OR carcinoma OR neoplasm OR tumor). Additionally, we performed an extensive review of relevant references to ensure the completeness and accuracy of our findings.

Inclusion and exclusion criteria

The selected studies had to meet the following inclusion criteria: (I) study type: published cohort studies on *de novo* cancers after liver transplantation, which could be prospective or retrospective in nature. Language was limited to English. (II) Subjects: patients who underwent liver transplantation without any restrictions based on race, nationality, age, gender, etiology of liver transplantation, surgical method and type of liver transplantation. (III) The control group consisted of individuals from the general population. (IV) The outcome measure was the occurrence of esophageal cancer after liver transplantation, including both esophageal adenocarcinoma and esophageal squamous cell carcinoma confirmed through pathological reports. (V) Information regarding the incidence or number of new cases of esophageal cancer and the total study population were provided. (VI) Standardized incidence ratios (relative risks), along with their corresponding 95% confidence intervals (CIs), were calculated.

The following exclusion criteria were applied to exclude studies: (I) studies that involved subjects undergoing organ transplantations other than liver transplantation, such as kidney transplantation, heart transplantation, or lung transplantation. (II) Studies with insufficient data extraction and no provided 95% CI in the articles. (III) Duplicate publications. (IV) Studies with unavailable full text and unresponsive authors. (V) Studies with small

sample sizes. (VI) Studies that did not clearly specify whether malignancies were new or metastatic, nor explicitly mentioned cancers by anatomical site (e.g., gastrointestinal malignancies without specifying esophageal cancer). (VII) Case reports, case series, reviews letters, editorials, congress abstracts or book chapters were excluded from the analysis.

The eligible data underwent a meta-analysis using the STATA software, following established academic practices. In cases where multiple papers provided data for a specific cohort, priority was given to the most recently published reference.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies was employed to conduct a comprehensive evaluation of study quality. The analysis was independently conducted by two physicians (S.L. and X.S.), with any discrepancies resolved through consensus reached via discussion.

Data extraction

The titles, abstracts, and full texts of all studies were independently reviewed by two reviewers (S.L. and X.S.), based on the inclusion and exclusion criteria. Following completion of the screening process, a literature check was conducted, and opinions were discussed or sought from a third party simultaneously to determine final inclusion in the study. The literature screening software utilized in this study was EndNote X8. Concurrently, the two researchers independently extracted and organized the data using Excel. The extracted data encompassed: (I) basic information including the first author, publication year, study area, sample size, number of study centers; (II) cohort information including esophageal cancer cases, total sample size, sex distribution, age, range, follow-up time, time period, smoking history prevalence rate among participants, distribution of drinking history among participants, hepatitis B virus (HBV) infection in participants, hepatitis C virus (HCV) infection in participants, and indications for liver transplantation. If the results of a particular study were reported in insufficient detail, we contacted the authors to obtain the relevant data.

Outcomes of interest

Primary outcomes of interest included the standardized incidence rate (SIR) and 95% CI for *de novo* esophageal cancer following liver transplantation, in comparison to the general population. Notably, a minority of studies utilized the RR value, which is conceptually similar to our SIR, thus enabling a direct comparison.

Statistical analysis

The SIR and its corresponding 95% CI were utilized to estimate the relative risk of patients with esophageal cancer after liver transplantation in comparison to the general population. The extracted observations were log-transformed. The findings from individual studies as well as the combined results were presented using forest plot. SIR was defined as the ratio between the actual number of esophageal cancer cases and the expected number, while its 95% CI was calculated assuming a Poisson distribution for the actual case numbers. Heterogeneity among studies was assessed using both I^2 statistic (%) and Cochran's Q test. The degree of heterogeneity was evaluated based on I^2 statistic, where mild heterogeneity ranged from 0 to 25%, moderate heterogeneity ranged from 25% to 75%, and significant heterogeneity ranged from 75% to 100%. In Cochran's Q test, a P value ≥0.10 indicated substantial heterogeneity, whereas a P value <0.10 suggested minor heterogeneity. For large heterogeneity (P<0.10 or I^2>50%), random-effects model (Der-Simonian and Laird method) as well as fixed-effects model (Mantel-Haenszel method) were employed for small heterogeneity (I^2≤50%, P≥0.10). Furthermore, univariate sensitivity analyses were conducted by stepwise exclusion of each study data to assess their influence on pooled SIR estimates. Publication bias was assessed through funnel plot analysis and Egger's test. Subgroup analysis was used to explore the sources of heterogeneity. Subgroup analyses were performed based on region, follow-up time, sample size, use of immunosuppressive agents, study type, inclusion criteria, and number of study centers. P values are derived from two-tailed tests. Statistical analyses were carried out using STATA software.

Results

Eligible studies and study characteristics

The initial search identified a total of 1,038 articles. After the screening process, twelve articles were included, encompassing a study population of 28,530 patients and a

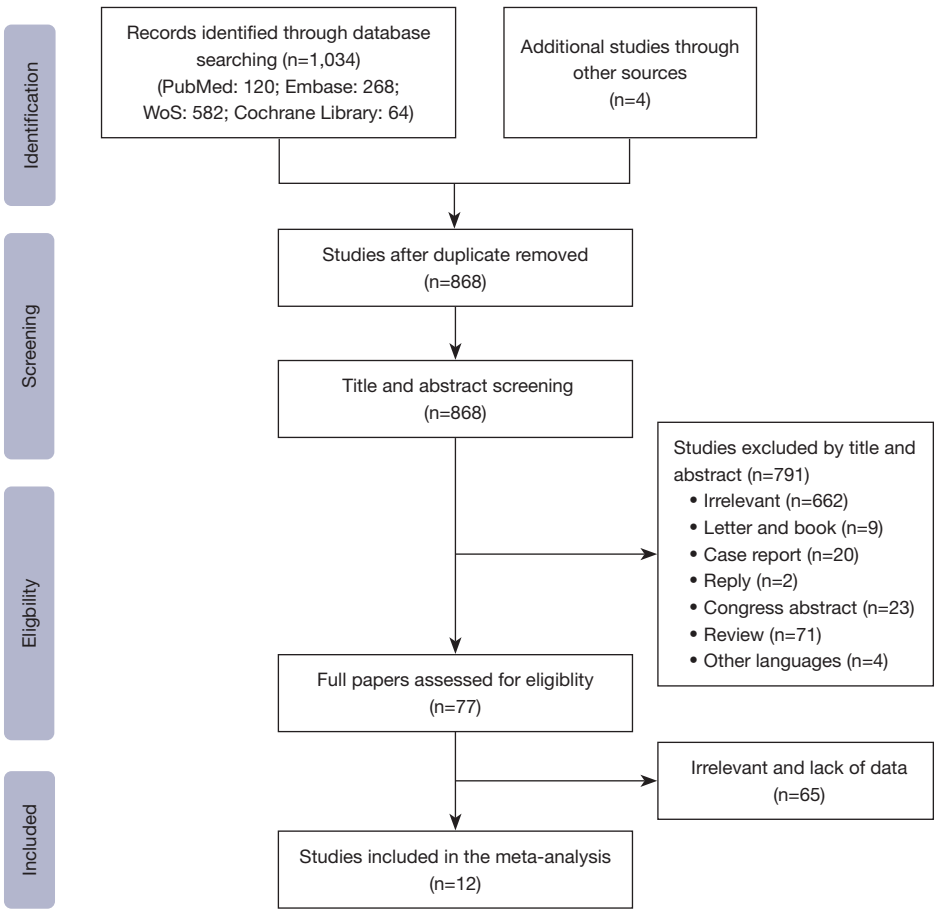

Figure 1 Flow diagram of studies included in the systematic review.

cumulative follow-up duration of 16,614.44 person-years. The relative risk was employed to evaluate the incidence of cancer in Liero's and Carenco's [2015] studies, which aligned with the definition of SIR used in this study; thus, it was also incorporated. The research areas covered Italy, Northern Europe, France, Japan, Spain, Austria and Taiwan. *Figure 1* presents the PRISMA flow chart illustrating the selection process.

The basic information regarding the twelve included studies and study populations is presented in *Tables 1*,*2*. Among the twelve studies, data from multiple medical centers obtained through national or regional registries were utilized in five studies, demonstrating robust representation. Conversely, five studies relied solely on data from a single center, resulting in relatively limited representation. The remaining two studies encompassed data collected from multiple centers and exhibited comprehensive representativeness. The lowest risk was observed in Taiwan (SIR =1, 95% CI: 0.27–3.65), while the highest risk was identified in Italy (SIR =23.4, 95% CI: 8.72–62.78). The results of the literature quality evaluation indicated a NOS score ≥6, demonstrating high-quality literature that met the inclusion criteria. The mean or median duration of follow-up for all studies was approximately five years. The follow-up period spanned from 1970 to 2014. Due to incomplete data collection in some studies regarding patients' smoking, alcohol consumption, HBV, and HCV infection, the dataset lacked comprehensiveness.

Pooled estimates

A random-effects meta-analysis of twelve independent cohort follow-up studies revealed a SIR of esophageal cancer in liver transplant recipients as 6.75 (95% CI: 4.35–10.46) (*Figure 2*). The analysis demonstrated significant heterogeneity among the studies, with an I^2 value of

Table 1 Summary of the basic information of the included literature

Study	Region	Research center	Number of centers	Follow-up time (years)	Patient-years (years)	Number of esophageal cancers	Number of LT incident cases
Yeh [2020]	Taiwan	Multiple	– (all medical centers)	4.2 (2.7)	9,197	2	2,127
Tamborello [2018]	Italy	Multiple	9	5.4 (2.4–10.0)	18,642	8	2,832
Sérée [2018]	France	Multiple	24	6.1 (4.3)	75,708	52	11,226
Piselli [2015]	Italy	Multiple	9	Median: 4.6	16,350	9	2,770
Nordin [2017]	Nordic	Multiple	– (all medical centers)	6.6 (6.2)	28,999	2	4,246
Lee [2016]	Taiwan	Single	1	Median: <4.3	5,879.44	3	1,748
Kurnitz [2012]	Sweden	Multiple	– (national)	5 [0–21]	7,450	1	1,221
Kaneko [2013]	Japan	Single	1	7.5 (3.4)	NA	1	360
Herrero [2011]	Spain	Single	1	Mean: 7.5	2,533	3	339
Incensed [2009]	Austria	Single	1	4.1 [0–24]	NA	5	779
Carencro [2015]	France	Single	1	Median: 7.8	NA	4	465
Baccarin [2010]	Italy	Multiple	2	6.9 (4.0–9.7)	2,856	5	417

Values of follow-up time are presented as median (IQR), median [range] or mean (SD). LT, liver transplantation; NA, not available; IQR, interquartile range.

Table 2 Summary of the cohort information of the included literature

Study	Age (years)	Male	Smoking	Drinking	HCV	HBV	Time period	Matching variables in SIR calculation
Yeh [2020]	45.5±18.0	1,523 (71.6)	NA	NA	498 (23.4)	1,212 (57.0)	1997 to 2011	Age, sex, and year
Tamborello [2018]	53 [46–59]	2,113 (74.6)	841 (29.7)	776 (27.4)	1,420 (50.1)	1,192 (42.1)	1985 to 2014	Age, sex, area of residence and calendar period
Sérée [2018]	50.1 [40.3–57.4]	7,325 (65.3)	NA	NA	NA	NA	1993 to 2012	Age, sex, and calendar period
Piselli [2015]	Median 53.5	2,069 (74.7)	796 (28.7)	746 (26.9)	1,379 (49.8)	1,165 (42.1)	1990 to 2010	Age, sex, and region, calendar period
Nordin [2017]	49±20	2,390 (56)	NA	NA	NA	NA	1982 to 2013	Age, sex, calendar time and country
Lee [2016]	NA	1,139 (65.16)	NA	NA	NA	NA	2001 to 2012	Age, sex, calendar time
Kurnitz [2012]	47 [35–57]	695 (57)	NA	NA	NA	NA	1970 to 2008	Age, sex, calendar time
Kaneko [2013]	NA	NA	NA	NA	NA	NA	NA	Age and sex
Herrero [2011]	Mean 55.9	263 (77.6)	135 (39.7)	132 (39.0)	105 (31.0)	129 (38.0)	1990 to 2009	Age and sex
Incensed [2009]	53.0 [15.1–76.4]	544 (69.9)	NA	NA	NA	NA	1982 to 2007	Age, sex and calendar year
Carencro [2015]	50.4±10.2	346 (74.4)	60.30%	0.701	NA	NA	1991 to 2008	Age and sex
Baccarin [2010]	51.9 [44.4–57.4]	289 (69.3)	NA	NA	NA	NA	1991 to 2005	Age and sex

Values are presented as mean ± standard deviation, n (%), or median [interquartile range] unless otherwise indicated. HCV, hepatitis C virus; HBV, hepatitis B virus; SIR, standardized incidence rate; NA, not available.

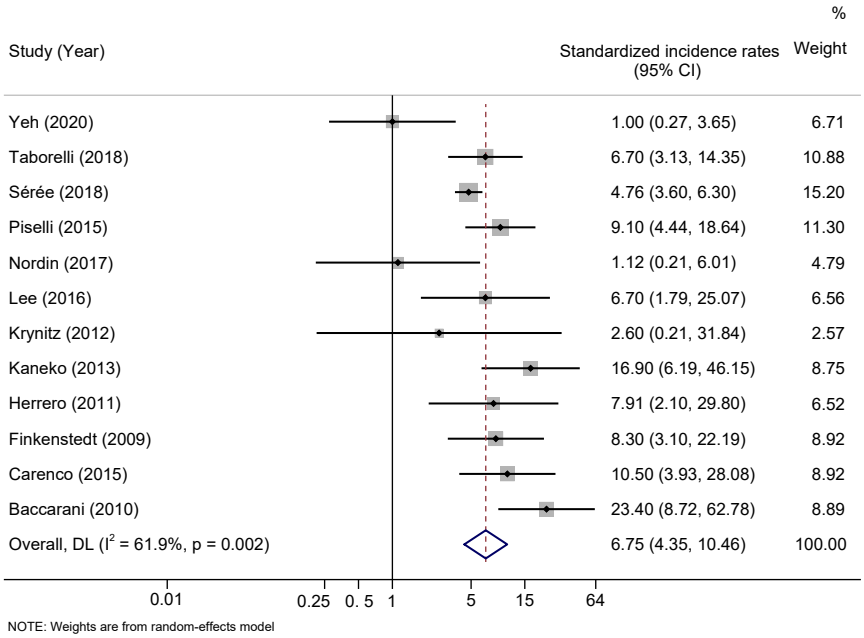

Figure 2 The forest plot depicts meta-analysis of the SIR and 95% CI for *de novo* esophageal cancer after liver transplantation. SIR, standardized incidence ratio; CI, confidence interval.

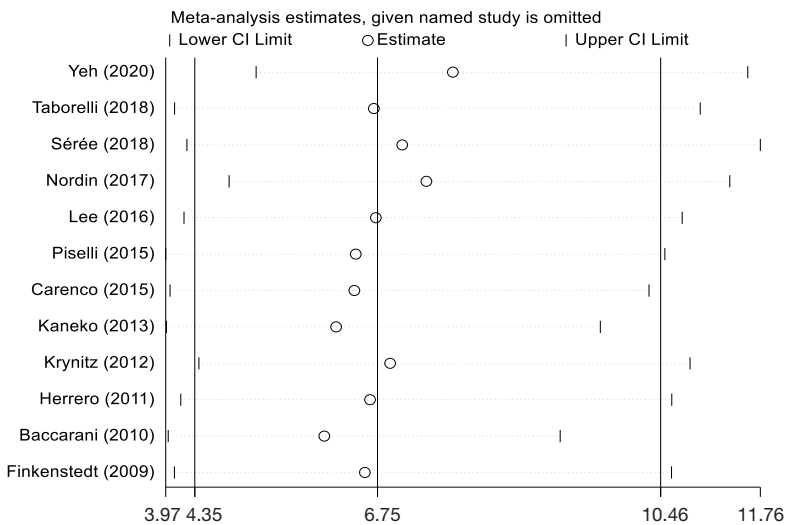

Figure 3 Sensitivity analysis was performed on the pooled SIR and 95% CI of esophageal cancer. SIR, standardized incidence ratio; CI, confidence interval.

61.9% and a P value of 0.002, leading to the adoption of a random effects model. Sensitivity analysis was conducted by excluding each study individually and combining the remaining studies (n-1) for meta-analysis. All 95% CI did not contain 1, suggesting that the results were statistically significant. The robustness of the initial meta-analysis results was confirmed (*Figure 3*). Publication bias was assessed using funnel plot analysis and Egger's test; although some asymmetry was observed in the funnel plot (*Figure 4*), no potential for publication bias was detected with a P value associated with esophageal cancer incidence in liver transplant recipients being reported as 0.607 (<0.05).

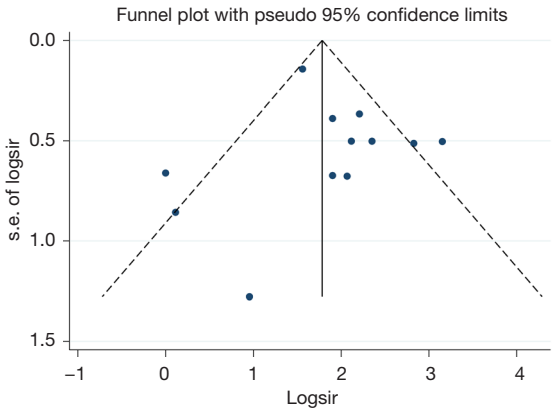

Figure 4 Funnel plot for evaluating publication bias.

The subgroup analyses were performed based on various factors including region, number of study centers, transplant population sample size, inclusion of children, pre-transplant tumor history, duration of follow-up, and availability of immunotherapy regimens. The results are presented in *Table 3*. It is evident that the inclusion or exclusion of children contributes to a reduction in heterogeneity, suggesting that this factor partially explains the source of heterogeneity.

There was no significant difference in the incidence of esophageal cancer across different regions, number of research centers, inclusion criteria based on liver cancer transplantation, and length of follow-up. However, the relative risk compared to the general population varied among regions, with Oceania exhibiting the highest relative risk (SIR =8.3, 95% CI: 3.10–22.19). When considering small sample sizes within the transplant population, a higher risk of esophageal cancer was observed compared to larger sample sizes, suggesting potential statistical bias. The presence of other tumors in patients included in the liver transplantation cohort did not increase the risk of new esophageal cancer; however, an increased risk was found in patients with liver cancer included in this cohort compared to those without liver cancer history, indicating that liver cancer may be a contributing factor for new esophageal cancers. Furthermore, longer follow-up periods were associated with a higher risk of developing new esophageal cancers (SIR =7.91, 95% CI: 2.1–29.80), as anticipated.

Discussion

We searched as many articles as possible, included and evaluated them normatively, and the results were robust without publication bias. The findings revealed that liver transplant patients face a significantly elevated risk of developing esophageal cancer compared to the general population, with a SIR of 6.75 (95% CI: 4.35–10.46).

Due to the relatively low incidence of *de novo* esophageal cancer after liver transplantation, there is currently a lack of systematic reviews focusing on this risk. To our knowledge, this meta-analysis represents the first endeavor to investigate the occurrence of *de novo* esophageal cancer subsequent to liver transplantation. Our article also has certain limitations. Firstly, all the included literatures are retrospective studies, and it is imperative to conduct more prospective studies in order to explore the incidence further. Secondly, due to insufficient statistical data from some studies, such as information regarding the regimen of immunosuppressive agents, conducting subgroup analysis to assess heterogeneity becomes unfeasible. Simultaneously, since a majority of the included studies primarily focus on northern Europe, it is essential to obtain data from additional regions and developing countries in order to enhance the representativeness of our findings.

Currently, the indications for liver transplantation vary across different regions. In the United States, alcohol-related liver disease and non-alcoholic steatohepatitis (NASH) are the two most prevalent transplant indications in patients without hepatocellular carcinoma (HCC). The incidence of viral hepatitis is declining, while NASH remains predominant among HCC patients (19). Viral hepatitis cirrhosis remains the primary indication for transplantation in China. In terms of *de novo* malignancies after liver transplantation, skin tumors and post-transplant lymphoproliferative disorders are more prevalent in Europe and North America (20,21). However, digestive tract tumors and head and neck tumors are the predominant types observed in East Asia (22).

In 1996, the first documented case of esophageal cancer was reported, presenting with multiple metastases to the liver and lungs (23). Prior to the transplantation procedure, the patient presented with a pre-existing condition called Barrett's esophagus. Within 9 months after transplantation, the Barrett's esophageal carcinoma rapidly progressed and transformed into poorly differentiated adenocarcinoma. This accelerated transition from a precancerous state to malignancy following transplantation highlights the substantial role of the precancerous state as a significant risk factor for tumor development (23). Subsequently, an increasing number of cases have been reported on the occurrence of esophageal cancer following

Table 3 Subgroup analysis

Subgroup	Heterogeneity			SIR	95% CI
	I^2 (%)	P (subgroup)	P (between group)		
Overall	61.90	0.002		6.75	4.35, 10.46
Region			0.88		
Asia	82.50	0.003		5	0.95, 26.33
Europe	58.60	0.02		7.06	4.34, 11.51
Oceania	0.00	<0.001		8.3	3.1, 22.19
Research center			0.10		
Multi-center	72.50	0.001		5.12	2.72, 9.67
Single center	0.00	0.80		10.03	6.16, 16.34
Number of transplantation patients			0.009		
>2,000	67.50	0.02		4.22	2.29, 7.76
≤2,000	0.00	0.51		11.33	7.36, 17.43
Liver cancer			0.07		
Excluded	72.10	0.003		1.66	1.41, 1.91
Included	35.30	0.17		2.08	1.69, 2.47
Other cancer history			0.03		
Included	68.2	0.008		1.8	1.56, 2.04
Excluded	0.00	0.78		2.08	1.57, 2.6
Not given	64.40	0.06		0.8	–0.01, 1.61
Children			0.001		
Excluded	37.30	0.16		2.12	1.73, 2.51
Included	45.00	0.12		1.54	1.29, 1.8
Not given	0.00	<0.001		3.15	2.17, 4.14
Follow-up time (mean/median)			0.36		
>5 years	68.90	0.004		7.91	4.42, 14.18
≤5 years	58.00	0.05		4.93	2.16, 11.24
Immunotherapy regimen			0.02		
Given	68.4	0.002		2.14	1.78, 2.51
Not given	0.00	0.77		1.61	1.35, 1.86

SIR, standardized incidence rate; CI, confidence interval.

liver transplantation. The risk of new esophageal cancer following liver transplantation has been consistently demonstrated to be significantly elevated compared to the general population in numerous studies. In a multicenter cohort study conducted in Italy in 2015, tracking 2,770 liver transplant patients from 1997 to 2010, researchers identified a total of 186 cases of post-transplant cancer, including nine instances of esophageal cancer. The findings revealed that the risk of developing cancer after liver transplantation is significantly higher compared to the general population, particularly among individuals who underwent transplants due to alcoholic liver disease (ALD). Notably, patients

undergoing transplantation for ALD exhibited an SIR more than ten times higher than expected when compared to the general population (24).

The incidence of esophageal cancer following liver transplantation is relatively low during the initial five-year period; however, it demonstrates a progressive increase over time. Several studies have identified a duration of transplantation exceeding two years as a significant risk factor for the development of esophageal cancer, with the cumulative risk increase showing deceleration after fifteen years (22).

The exact etiology of malignant tumors following liver transplantation remains uncertain; however, multiple factors may contribute to their occurrence. Of particular significance is the utilization of immunosuppressive agents, which not only impede immune cell functionality and undermine immune surveillance (25,26), but also possess direct carcinogenic properties. The stimulation of tumor growth can be attributed to the induction of transforming growth factor-β production by calcineurin inhibitors (CNI) (26). Furthermore, CNI can enhance tumorigenesis through upregulation of vascular endothelial growth factor, an angiogenic cytokine (27). Additionally, CNI has been demonstrated to activate the proto-oncogene Ras and promote cancer cell proliferation through activation of the Ras-RAF-MEK-ERK signaling pathway (28). CNI may enhance tumor progression by downregulating chemokine CXCR3-B and upregulating chemokine CXCR3-A (29). Moreover, it increases susceptibility to infection (30), leading to immune abnormalities caused by persistent viral infection (31), and facilitates the development of malignancies associated with viral infections (32).

The incidence of esophageal cancer following liver transplantation may be associated with a history of tobacco and alcohol consumption. A systematic meta-analysis reveals that both smoking and alcohol consumption increase the risk of esophageal cancer in the general population (33). Furthermore, increased alcohol intake is associated with a higher risk of all cancers, including those related to alcohol, while sustained cessation from smoking and reduced drinking are linked to a lower risk of all cancers (34). Notably, there exist ADH1B and/or ALDH2 risk alleles (35). Ethanol is metabolized to acetaldehyde via ADH1B and ALDH2, which is subsequently converted into the non-toxic acetate. However, when ADH1B and ALDH2 undergo mutations, enterotoxic acetaldehyde accumulates, leading to disruption of barrier function (36).

Several studies have reported a rapid progression of Barrett's esophagus to esophageal cancer following liver transplantation (37,38). However, the underlying mechanism remains unclear and may be associated with the use of immunosuppressants. A retrospective cohort study conducted in 2023 suggested that the utilization of immunosuppressive agents was a risk factor for the progression from Barrett's esophagus to esophageal cancer (39).

Furthermore, age-related factors also contribute to an increased risk of developing new cases of esophageal cancer (40). Gender also influences the risk of esophageal cancer. In a 2018 Italian cohort study, women exhibited a significantly higher risk of esophageal cancer (SIR =30.5; 95% CI: 3.7–110.1) compared to men (SIR =5.3; 95% CI: 2.0–11.6) (13). Similarly, a French national long-term cohort study published in the same year revealed that women had an elevated risk of developing new esophageal cancer following liver transplantation relative to men (11.93:4.17) (14).

Conclusions

The risk of *de novo* esophageal cancer is significantly increased following liver transplantation. Routine upper gastrointestinal examination is recommended for post-liver transplant patients to assess their condition.

Acknowledgments

The statistical data provided are valid and certified by Dr. Shanshan Wu, Associate Professor of Epidemiology and Health Statistics (Beijing Friendship Hospital, Capital Medical University).
Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-66/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-66/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-66/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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Cite this article as: Li S, Zhang S, Sun X. Risk of *de novo* esophageal cancer in liver transplant recipients: systematic review and meta-analysis. J Gastrointest Oncol 2024;15(3):851-861. doi: 10.21037/jgo-24-66

