Original Article

Effects of solid organ transplantation on the risk of developing thyroid cancer: a systematic review and meta-analysis

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Background: Solid organ transplantation (SOT), which is the best remedy for end-stage organ failure, is accompanied by the risk of developing a postoperative malignant tumor. To date, assessments of the changes in the increased risk of thyroid cancer (TC) after SOT remain controversial. This study sought to reevaluate the risk of TC after SOT based on the latest literature. Our findings could improve the early diagnosis of tumors and the overall prognosis of patients after SOT.

Methods: A computerized search of four major English-language databases (i.e., PubMed, EMBASE, Cochrane Library, and Web of Science) was performed to retrieve cohort studies on the risk of developing TC after SOT. The standardized incidence ratio (SIR) was used as the pooled-effect size and expressed as the 95% confidence interval (CI).

Results: In total, 20 cohort studies, comprising 362,079 patients who underwent SOT, were included in the meta-analysis. We found that the patients all had an increased risk of developing TC after the transplantation of different solid organs, including the kidney, heart, lung, and liver ($P<0.05$), and patients had the highest risk of developing TC after kidney transplantation (SIR =5.28, 95% CI: 4.03–6.92, $P<0.01$).

Conclusions: Patients have an increased risk of developing TC after SOT. Aggressive and regular tumor screenings after SOT for early detection and timely treatment may improve patient prognosis.

Keywords: Solid organ transplantation (SOT); thyroid cancer (TC); meta-analysis

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Introduction

Solid organ transplantation (SOT) is the best treatment for patients with end-stage organ failure. Numerous studies have suggested that malignancies develop after SOT in about 5% of patients (1), and the incidence of malignant tumors after SOT is 2–4 times that of the normal population (2-5). In adults undergoing SOT, the most common postoperative tumors include non-melanoma skin cancer with post-transplant lymphoproliferative disorders (6,7). New postoperative tumors may affect the long-term quality of life of such patients. Recently, there has been an upward trend in the risk of thyroid cancer (TC) worldwide (8). The question of whether there is an increased risk of developing TC after SOT remains controversial. Previous study has reported that the risk of

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developing postoperative TC does not differ significantly to that of the general population (9); however, other studies have found that the risk of patients developing TC after SOT during the clinical follow-up period is significantly higher (2,10). A previous meta-analysis indicated that patients have an increased risk of developing TC after renal transplantation (11); 11 additional cohort studies concerning the incidence of thyroid cancer after various type of SOT were included in this meta-analysis. Conflicting results of previous studies evaluating the risk of TC after SOT may be derived from differences in baseline of patients enrolled in various studies, such as patient origin region, preoperative disease status, and whether immunosuppressive therapy was received after surgery. In addition, new research results in related fields are constantly emerging, so it is urgent to use meta-analysis to comprehensively evaluate the risk of TC in patients with different organ transplantation. This study gathered the latest meta-analytic evidence of evidence-based medicine to evaluate the risk of patients developing TC after SOT. Based on the results of this meta-analysis, we believe that patients undergoing SOT need necessary early screening for TC and timely intervention or treatment when needed to improve the overall life quality of patients after SOT. We present the following article in accordance with the MOOSE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-137/rc).

Methods

Literature search

We performed a search of the four major English-language databases; that is, PubMed, EMBASE, Cochrane Library, and Web of Science. The search process was performed independently by two investigators and crosschecked. The search period started on Sep 25, 1995 and ended on Sep 25, 2020. The search terms included: (solid organ transplantation) and (thyroid neoplasms or thyroid carcinoma or thyroid cancer). Boolean logic was used to perform the preliminary literature retrieval in the databases.

Inclusion and exclusion criteria

To be eligible for inclusion in the meta-analysis, the studies had to meet the following inclusion criteria: (I) our target research population include patients undergoing SOT; (II) examine interventions in which the research objects were targeted organs, including the kidney, liver, heart, and lung (multiple transplants of different organs, such as a single pancreas, small intestine, and islet cell transplants, were also included), and examine postoperative screenings for cancer, such as TC. All included TC patients were diagnosed in strict accordance with the World Health Organization's diagnostic criteria; (III) be a cohort study; (IV) the experimental group was assigned to patients who had received SOT; (V) include the following outcome measures: the risk of developing TC after liver, kidney, heart, lung, or other transplant, the risk of developing different cancers, primarily thyroid, liver, lung, stomach or pancreas cancer, renal cell carcinoma, colorectal, oral or pharyngeal cancer, non-melanoma skin cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, or bladder, breast, cervical, ovarian, prostate or testicular cancer, after undergoing SOT; and (VI) be published in the English language. Our inclusion criteria were formulated in accordance with PICOS principles.

Articles were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) involved animal experiments; (II) included patients in whom the SOT failed; (III) included patients already diagnosed with cancer, such as TC, before transplantation; (IV) examined an unrelated research topic; (V) had incomplete data; and/or (VI) the article was edited material, a case report, conference abstract, meta-analysis, or review; (VII) literature that is not publicly published or whose authors cannot be contacted.

The reasons for the possible risk of bias based on the inclusion and exclusion criteria formulated in this study are as follows: (I) all the studies we included were cohort studies, lacking high-quality randomized controlled trials; (II) the underlying disease status of relevant patients in the included study before SOT, whether immunotherapy was selected after transplantation, and even different immunotherapy chosen were the possible reasons causing bias in this paper.

Data extraction

The literature statistics and results were extracted independently by two investigators at two research institutes. The process included an independent search and a reading of the full text, after the elimination of duplicate reports and unrelated literature. The articles were selected based on the above inclusion and exclusion criteria. Relevant information from the included articles was extracted, including details of the author, publication year, country, study methods, sample size, age, gender,

follow-up time, type of transplanted organs, and outcome measures. If the two researchers disagreed on an issue, they first attempted to resolve the issue via discussion, and if an agreement could not be reached, a third-party was asked to intervene.

Quality assessment

The quality of the cohort-study articles was evaluated by the 2 investigators using the Newcastle Ottawa scale, for which a total score of 10 points can be achieved, and for which a score of 1–4 indicates low quality and a score of 5–10 indicates high quality.

Publication bias assessment

Begg's test was used to quantitatively evaluate the publication bias of the meta-analysis to reduce the subjectivity of the evaluation.

Statistical analysis

Stata 15.1 software was used for the statistical analysis. The numerical data are presented as the pooled-effect size with the 95% confidence interval (CI) using the standardized incidence ratio (SIR). The I^2 test was used to assess the heterogeneity among the studies; a fixed-effects model was used if the heterogeneity was small (I^2<50%), and a random-effects model was used if the heterogeneity was large (I^2≥50%). Sensitivity analyses were performed for all outcome measures. A P value <0.05 was considered statistically significant calculated using two-sided test.

Results

Literature search results

A total of 617 articles were retrieved after searching the English databases. After eliminating 189 duplicate records, 428 articles remained for screening, of which 49 were included after a careful reading of the titles, abstracts and full texts, strictly following the exclusion criteria listed above. Ultimately, 20 cohort studies (comprising 362,079 patients undergoing SOT) were included in the meta-analysis after rigorous screening (4,12-30). A PRISMA flow diagram of our literature search is shown in *Figure 1*. The included studies were evaluated for quality, and 4 were classified as low quality and 16 as high quality. The specifics of the included studies are set out in *Table 1*.

Meta-analysis results

Risk of TC after the transplantation of different organs

Kidney transplantation

Of the articles, 15 reported on the risk of developing TC after renal transplantation (4,12,13,16-21,23,26-30). As the heterogeneity among the studies was large (I^2=76.1%), the random-effects model was used for the pooled analysis, and the specific results are shown in *Figure 2*. The meta-analysis showed that the risk of developing TC increased after renal transplantation (SIR =5.28, 95% CI: 4.03–6.92, P<0.01).

Heart transplantation

Of the articles, 2 reported on the risk of developing TC after heart transplantation (16,22). As the heterogeneity among the studies was large (I^2=63.6%), the random-effects model was used for the pooled analysis, and the specific results are shown in *Figure 3*. The meta-analysis showed that the risk of developing TC increased after heart transplantation (SIR =3.55, 95% CI: 1.21–10.41, P=0.021).

Lung transplantation

Of the articles, 2 reported on the risk of developing TC after lung transplantation (16,17). As there was no heterogeneity among the studies (I^2=0.0%), the fixed-effects model was used for the pooled analysis, and the specific results are shown in *Figure 4*. The meta-analysis showed that the risk of developing TC increased after lung transplantation (SIR =2.73, 95% CI: 1.60–4.68, P<0.001).

Liver transplantation

Of the articles, 3 reported on the risk of developing TC after liver transplantation (15-17). As the heterogeneity among the studies was large (I^2=73.7%), a random-effects model was used for the pooled analysis, and the specific results are shown in *Figure 5*. The meta-analysis showed that the risk of developing TC increased after liver transplantation (SIR =2.49, 95% CI: 1.27–4.85, P=0.008).

Risk of different cancers after SOT

This study found that patients had an increased risk of developing several tumors after SOT, including solid tumors (SIR =3.45, 95% CI: 2.58–4.60, P<0.001), TC (SIR =4.95, 95% CI: 3.80–6.46, P<0.001), hepatocellular carcinoma (SIR =3.23, 95% CI: 1.69–6.16, P<0.001), lung cancer (SIR =1.79, 95% CI: 1.45–2.20, P<0.001), gastric cancer (SIR =2.22, 95% CI: 1.88–2.61, P<0.001), pancreatic cancer (SIR =1.74, 95% CI: 1.34–2.25, P<0.001), renal cancer (SIR =7.59, 95% CI: 5.38–10.17, P<0.001), oral and pharyngeal cancer (SIR =3.64, 95% CI: 3.10–4.24, P<0.001), non-melanoma skin cancer (SIR =10.01, 95% CI: 3.82–26.23, P<0.001), Hodgkin's lymphoma (SIR =4.13, 95% CI: 1.72–

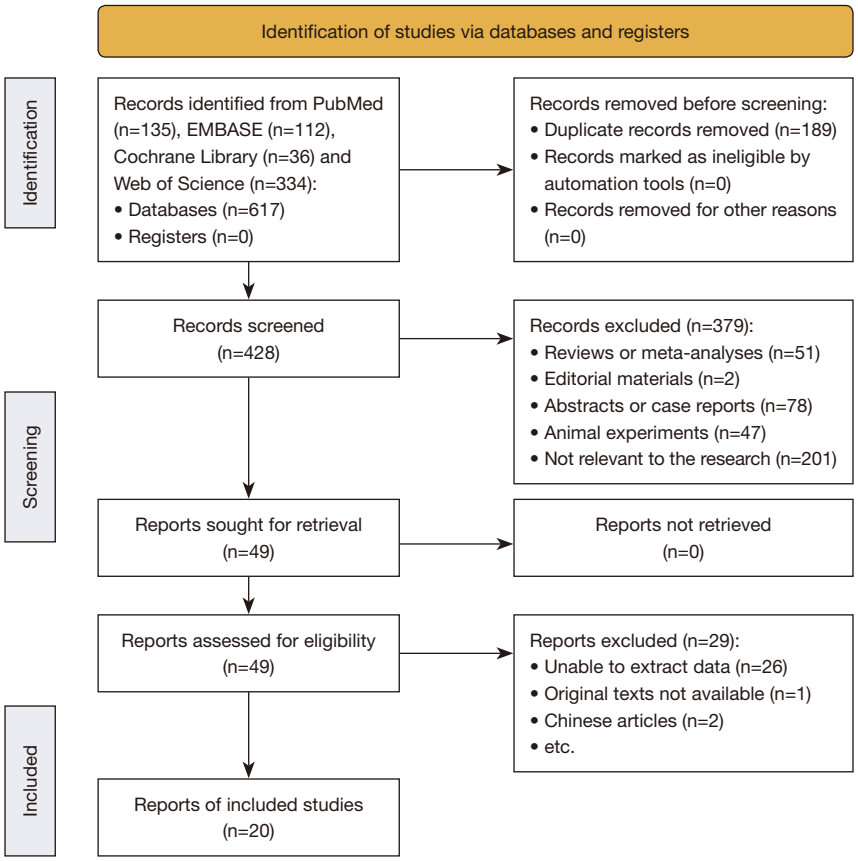

Figure 1 Search flow diagram of literature included in meta-analysis.

9.91, P=0.001), non-Hodgkin's lymphoma (SIR =10.01, 95% CI: 3.82–26.23, P<0.001), bladder cancer (SIR =2.38, 95% CI: 2.09–2.71, P<0.001), cervical cancer (SIR =2.60, 95% CI: 1.75–3.88, P<0.001), ovarian cancer (SIR =1.80, 95% CI: 1.29–2.51, P=0.001), and testicular cancer (SIR =2.37, 95% CI: 1.14–4.94, P=0.021). Among these, non-melanoma skin cancer, non-Hodgkin's lymphoma, and renal cell carcinoma had the highest risk, followed by TC and Hodgkin's lymphoma.

Publication bias

There was no evidence of significant publication bias based on the results of the Begg's test; thus, the included studies could be considered to have no significant publication bias.

Discussion

It has been more than half a century since SOT technology was developed clinically for the treatment of end-stage organ failure. Due to improved surgical techniques, the introduction of the concept of rapid perioperative rehabilitation, and the application of novel immunosuppressive agents, the postoperative mortality of patients undergoing SOT has decreased significantly. However, the occurrence of postoperative tumors remains a vital risk factor affecting the quality of life of SOT patients. The question of whether there is an increased risk of developing TC after SOT remains controversial (2,9,10). Thus, we sought to explore the potential risk of TC after SOT to provide a theoretical basis for postoperative tumor screenings to improve patients' long-term quality of life.

Research has shown that patients in the United States endure an evident increased risk of developing TC after SOT, including the most common papillary TC in terms of pathological classifications, such patients have been reported to be more than twice as likely as the general population to develop TC after SOT (2), which is consistent with the conclusions drawn in this study. The risks of developing TC after different types of organ transplantation were analyzed

Table 1 Characteristics of included studies

First author	Year	Country	Recipients of transplantation (n)	Renal transplantation (n)	Liver transplantation (n)	Heart transplantation (n)	Lung transplantation (n)	Pancreas transplantation (n)	Intestinal transplantation (n)	Other transplantation (n)	Literature quality
Lengwiler (12)	2019	Switzerland	2,758	1,557	557	208	278	–	–	158	6
Heo (13)	2018	South Korea	1,343	1,343	–	–	–	–	–	–	8
Yanik (14)	2017	America	17,958	7,822	5,713	3,735		9	162	517	5
Oweira (15)	2017	Switzerland	9,302	–	9,302	–	–	–	–	–	4
Kitahara (16)	2017	America	248,136	144,276	54,105	24,154	10,837	–	–	14,764	7
Hortlund (17)	2017	Sweden	12,420	9,427	1,754	894	584	292	–	–	8
		Denmark	6,794	4,428	609	506	471	–	–	–	
Schrem (18)	2016	Germany	1,655	1,655	–	–	–	–	–	–	5
Kim (19)	2014	South Korea	2,365	2,365	–	–	–	–	–	–	4
Hibberd (20)	2013	Australia	5,970	6,626	–	–	–	–	–	–	6
Wisgerhof (21)	2011	Netherlands	1,906	1,906	–	–	–	–	–	–	5
Kellerman (22)	2009	America	851	–	–	851	–	–	–	–	7
Mäkitie (23)	2008	Finland	3,440	3,440	–	–	–	–	–	–	4
Végso (24)	2007	Hungary	2,535	2,852	–	–	–	–	–	–	8
Adami (25)	2003	Sweden	5,931	5,004	394	236	117	26	–	154	6
Hoshida (26)	1997	Japan	1,744	1,744	–	–	–	–	–	–	5
Birkeland (27)	2000	Denmark	1,821	1,821	–	–	–	–	–	–	7
Kyllönen (28)	2000	Finland	2,890	3,440	–	–	–	–	–	–	5
Pond (29)	2005	Australia	10,689	10,689	–	–	–	–	–	–	3
Vajdic (30)	2006	Australia	10,180	10,180	–	–	–	–	–	–	6
Villeneuve (4)	2007	Canada	11,391	11,391	–	–	–	–	–	–	7

in this study, and the risk of developing TC was the highest in patients after renal transplantation, which suggests that after SOT, patients' should undergo regular postoperative tumor screenings, especially after renal transplantation.

At the end stage of renal failure, carcinogens may accumulate in the human body due to impaired deoxyribonucleic acid repair, decreased antioxidant capacity, and decreased renal excretion, thereby affecting the occurrence and development of TC (31). Renal function decline and chronic kidney disease can contribute to the development of thyroid dysfunction, goiters, and thyroid nodules, which have been shown to be associated with

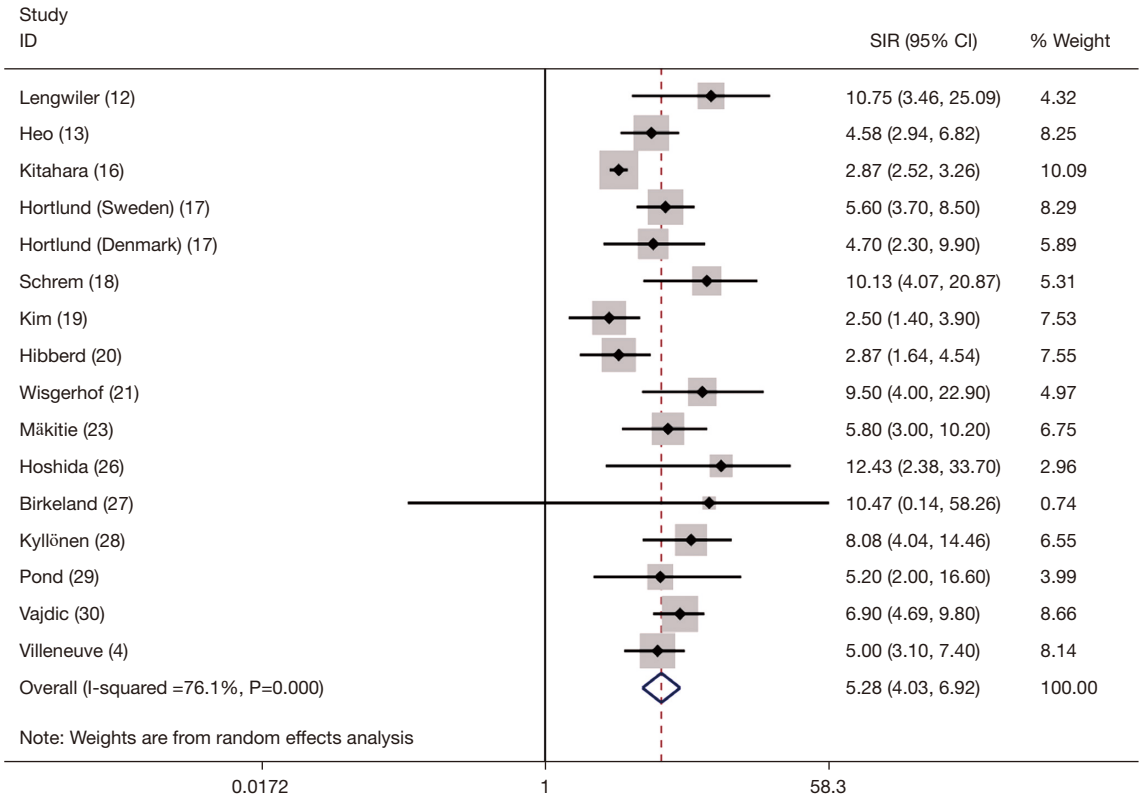

Figure 2 Risk of developing TC after renal transplantation. TC, thyroid cancer; SIR, standardized incidence ratio; CI, confidence interval.

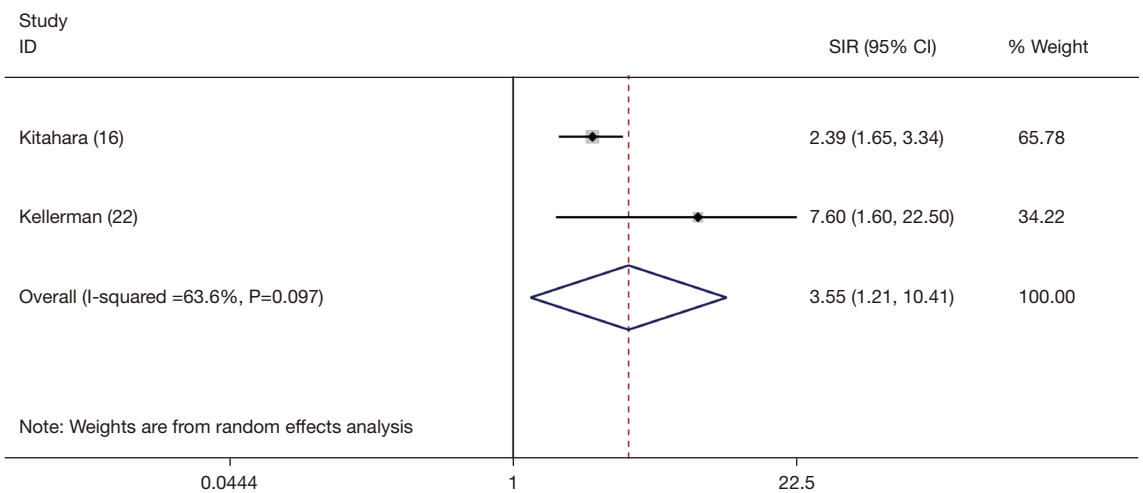

Figure 3 Risk of developing TC after heart transplantation. TC, thyroid cancer; SIR, standardized incidence ratio; CI, confidence interval.

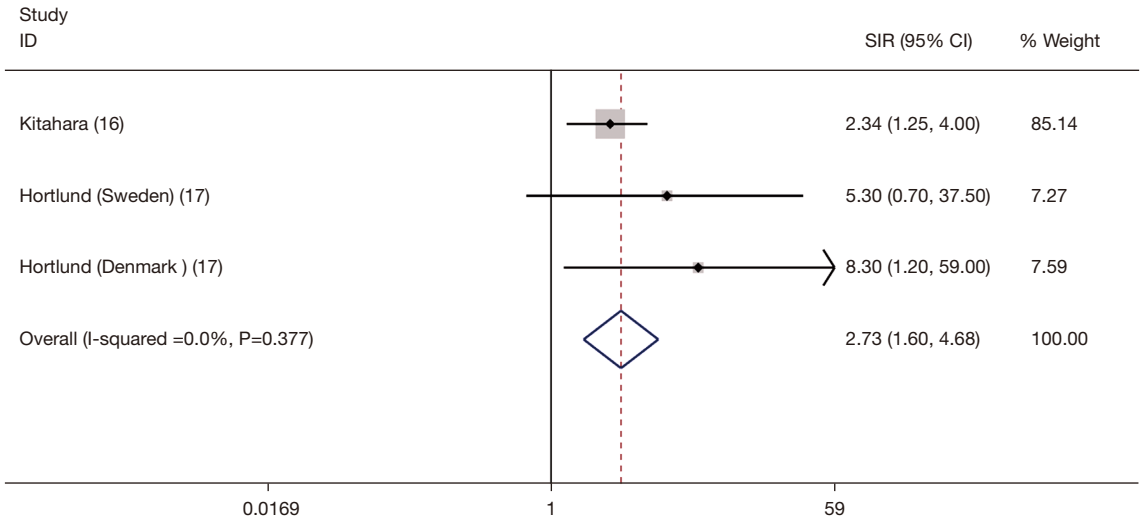

Figure 4 Risk of developing TC after lung transplantation. TC, thyroid cancer; SIR, standardized incidence ratio; CI, confidence interval.

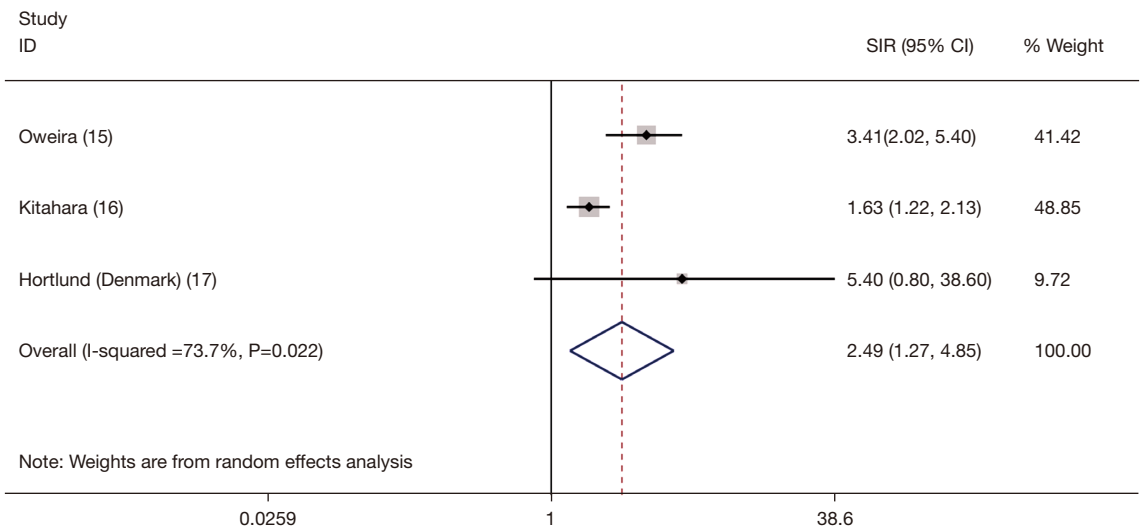

Figure 5 Risk of developing TC after liver transplantation. TC, thyroid cancer; SIR, standardized incidence ratio; CI, confidence interval.

TC (16). End-stage renal disease and prolonged dialysis may also be responsible for an increased risk of TC after renal transplantation (30,32,33).

At present, studies have shown that the mechanism by which patients develop tumors after SOT may be related to their immunosuppressive status. The long-term suppression of the immune system in the postoperative period may impair immune surveillance, resulting in an inability to promptly recognize and clear newly developed malignant tumor cells, thereby increasing the risk of tumorigenesis (34), which may also account for the increased risk of TC after SOT.

Previous studies have shown that the occurrence of TC is associated with multiple viral infections, such as Epstein-Barr virus (35), human parvovirus B19 (36), and hepatitis C virus (37). Immunocompromised patients have a higher probability of acquiring oncogenic viruses, and thus an increased risk of developing TC after SOT. Additionally, the toxicity of immunosuppressants themselves also has carcinogenic effects. Some researchers have found a clear

correlation between the level of postoperative cyclosporine and goiters in patients undergoing renal transplantation, and have confirmed that high doses of immunosuppressive agents may increase the risk of developing TC (38). Most patients clinically need to be on poly-immunosuppressive regimens after undergoing SOT to suppress immunity, and the use of polytherapy may further increase the risk of TC.

The results of the present study also revealed that patients undergoing SOT had the highest risk of developing cancers including non-melanoma skin cancer, non-Hodgkin's lymphoma, renal cell carcinoma, followed by TC and Hodgkin's lymphoma. These findings are consistent with previous findings (39). Among the common malignant tumors in China, the incidence of lung cancer ranks first, followed by esophagus, gastric and liver cancer (25). The results of this meta-analysis suggest that patients undergoing SOT may have a predilection site for the tumor that is distinguishable from that in the general population. Thus, such patients should be regularly screened for particular tumors, such as non-melanoma skin cancer and non-Hodgkin's lymphoma, and common malignancies should be focused on during the postoperative follow-up period.

The present meta-analysis had a number of limitations. The included studies did not report on immunosuppressive regimens after SOT; thus, this indicator could not be analyzed. The included studies were all cohort studies, which may have had residual confounding factors. The follow-up time of each study, pre-transplant disease status, and postoperative immunotherapy regimens all influence the risk of cancer, which may also be the source of the large heterogeneity in this study; thus, high-quality randomized controlled trials need to be conducted to validate our results. In addition, all the databases we searched were in English, and no databases in other languages were searched, which may limit the number and breadth of included studies.

Conclusions

Patients have an increased risk of developing TC after SOT, and have the highest risk of developing TC after renal transplantation. The development of TC after SOT may affect the long-term quality of life of patients. Thus, for patients undergoing SOT, postoperative tumor screenings for early detection and timely treatment may be effective measures for improving patient prognosis.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-137/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-137/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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