

## Cancer Risks in Solid Organ Transplant Recipients: Results from a Comprehensive Analysis of 72 Cohort Studies

Zhenyu Huo<sup>a,b,#</sup>, Caichen Li<sup>a,#</sup>, Xin Xu<sup>c,#</sup>, Fan Ge<sup>a,d,#</sup>, Runchen Wang<sup>a,b</sup>, Yaokai Wen<sup>a,b</sup>, Haoxin Peng<sup>a,b</sup>, Xiangrong Wu<sup>a,b</sup>, Hengrui Liang<sup>a</sup>, Guilin Peng<sup>a,c</sup>, Run Li<sup>a,c</sup>, Danxia Huang<sup>a,c</sup>, Ying Chen<sup>a,c</sup>, Ran Zhong<sup>a</sup>, Bo Cheng<sup>a</sup>, Shan Xiong<sup>a\*</sup>, Weiyi Lin<sup>d</sup>, Jianxing He<sup>b,a\*</sup>, and Wenhua Liang<sup>b,a\*</sup>

<sup>a</sup>Department of Thoracic Surgery and Oncology, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; <sup>b</sup>Nanshan School, Guangzhou Medical University, Guangzhou, China; <sup>c</sup>Department of Transplantation, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; <sup>d</sup>First Clinical School, Guangzhou Medical University, Guangzhou, China

### ABSTRACT

Understanding the cancer risks in different transplant recipients helps early detection, evaluation, and treatment of post-transplant malignancies. Therefore, we performed a meta-analysis to determine the cancer risks at multiple sites for solid organ transplant recipients and their associations with tumor mutation burden (TMB), which reflects the immunogenicity. A comprehensive search of PubMed, Web of Science, EMBASE, Medline, and Cochrane Library was conducted. Random effects models were used to calculate the standardized incidence ratios (SIRs) versus the general population and determine the risks of different cancers. Linear regression (LR) was used to analyze the association between the SIRs and TMBs. Finally, seventy-two articles met our criteria, involving 2,105,122 solid organ transplant recipients. Compared with the general population, solid organ transplant recipients displayed a 2.68-fold cancer risk (SIR 2.68; 2.48–2.89;  $P < .001$ ), renal transplant recipients displayed a 2.56-fold cancer risk (SIR 2.56; 2.31–2.84;  $P < .001$ ), liver transplant recipients displayed a 2.45-fold cancer risk (SIR 2.45; 2.22–2.70;  $P < .001$ ), heart and/or lung transplant recipients displayed a 3.72-fold cancer risk (SIR 3.72; 3.04–4.54;  $P < .001$ ). The correlation coefficients between SIRs and TMBs were 0.68, 0.64, 0.59, 0.79 in solid organ recipients, renal recipients, liver recipients, heart and/or lung recipients, respectively. In conclusion, our study demonstrated that solid organ transplant recipients displayed a higher risk of some site-specific cancers, providing individualized guidance for clinicians to early detect, evaluate, and treat cancer among solid organ transplantation recipients. In addition, the increased cancer risk of solid organ transplant recipients is associated with TMB, suggesting that iatrogenic immunosuppression may contribute to the increased cancer risk in transplant recipients. (PROSPERO ID CRD42020160409).

### ARTICLE HISTORY

Received 11 September 2020  
Revised 4 November 2020  
Accepted 6 November 2020

### KEYWORDS

Solid organ transplantation;  
Tumor mutational burden;  
Cancer risk

## Introduction


Solid organ transplantation is a life-saving option for patients with some end-stage diseases. In recent decades, the overall survival of solid organ transplant recipients has been remarkably improved with the use of immunosuppressive drugs.<sup>1,2</sup> Nevertheless, cancer risk among solid organ transplant recipients is 2- to 5-fold higher compared with the general population.<sup>3</sup> Though great efficacy in the prolongation of survival in solid organ transplant recipients has been demonstrated, post-transplant immunosuppression therapy is considered to be an important inducement of de novo malignancies after solid organ transplantation.<sup>4–6</sup>

Large population-based cohort studies can systematically evaluate cancer incidence in solid organ transplant recipients.<sup>7,8</sup> However, the cancer risk might vary by region, population and transplantation category (such as lung or renal transplantation).

Previous systematic analyses were limited to renal transplant patients, and relevant study on the field of liver, heart, or lung transplantation has not been reported yet.


TMB is defined as the total number of somatic gene coding errors, base substitution, gene insertion or deletion errors detected in every million bases using sequencing technology.<sup>9</sup> The diversity of TMB and cancer type reflects the different immunogenicity, which is closely related to the ability of the immune system to recognize tumors cells. To some extent, TMB may be associated with post-transplant site-specific cancer risks, but their causality is unclear.

Understanding the cancer risk profile in different solid organ transplant recipients helps early detection, evaluation and treatment of post-transplant malignancies. The aim of our study is to determine whether cancer risks in the post-transplant population would increase, to compare the associations among

**CONTACT** Jianxing He  [drjianxing.he@gmail.com](mailto:drjianxing.he@gmail.com); Wenhua Liang  [liangwh1987@163.com](mailto:liangwh1987@163.com)  Department of Thoracic Surgery and Oncology, the First Affiliated Hospital of Guangzhou Medical University; China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease. No. 151, Yanjiang Rd, Guangzhou 510120, Guangdong Province, China.

#Huo ZY, Li CC, Xu X, Ge F are joint first authors.

\*He JX, Liang WH are joint corresponding authors.

 Supplemental data for this article can be accessed on the [publisher's website](#)

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recipients with different characteristics, and to explore the potential association between TMBs and the corresponding SIRs of post-transplant malignancies to better understand the role of immune system in solid organ transplant recipients, by a comprehensive analysis.

## Methods

### Search strategy and selection criteria

Cochrane Library (Issue 12, 2019), PubMed (update to January 2020), Web of Science (update to January 2020), EMBASE (from 1980 to January 2020), and Medline (from 1949 to January 2020) databases were searched to identify relevant studies. The following keywords and their MeSH terms were used: solid organ transplantation, lung transplantation, kidney transplantation, and liver transplantation, combined with cancer risk or cancer incidence. We also searched the references from relevant articles. The authors were contacted for supplemental data when important information was missing. We evaluated all searched results according to the PRISMA statement.<sup>10</sup> The protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO ID CRD42020160409).

Studies were included in our analysis if they met the following criteria: (1) population-based cohort studies on solid recipients, (2) included at least one type of site-specific organ transplantation (3) reported at least one site-specific cancer risk in solid organ transplant recipients. (4) published or accepted in English that could be retrieved from the network databases mentioned above as of January 2020. Studies were excluded for the following reasons: (1) sampling of non-solid organ transplantations, (2) SIRs and 95% CIs could not be obtained or estimated from the article, (3) studies that could not be retrieved from the network databases mentioned above, (4) lack of available data with appropriate statistics.

### Data extraction and quality assessment

Three authors (Z.H., F.G., R.W.) extracted the necessary data independently and any disagreements were resolved after discussion by three investigators. The clinical characteristics and demographics of patients, first author's name, year of publication, country, type of transplant, mean or median age, sample size, and duration of follow-up were recorded. The number of solid organ transplant cases, number of all cancers, SIRs of all cancers after solid organ transplantation, survival and other adverse events were extracted as outcome data.

In 2017, Chalmers et al.<sup>9</sup> measured the distribution of TMB across a diverse cohort study of 100,000 cancer cases through a targeted CGP assay, and validated the association between TMB and somatic alterations in over 100 tumor types. Relevant Median TMBs of malignancies were extracted from the study of Chalmers et al. (*see Additional file 3: Table S1: Summary of TMB properties by disease*).<sup>9</sup> If there were no available Median TMB value given a certain malignancy, its TMB value is calculated by averaging the TMBs of its subtypes mentioned in this study (leukemia, non-Hodgkin's lymphoma, the cancer of pancreas, ovary, small intestine, brain and central nervous system, colorectum, skin and lung). The extracted Median

TMB values and their natural logarithm forms were listed in Supplementary Table S1 and Supplementary Table S2.

The methodological quality of the selected studies was evaluated using criteria by the Newcastle Ottawa Scale (NOS) (Supplementary Table S3), which includes selection (4 items), comparability (1 item), and outcome (3 items).<sup>11</sup> Any disagreement was resolved by consensus.

### Statistical analysis

We examined the cancer risks in solid organ transplant (all solid organs, kidney, liver, heart and/or lung) recipients based on the SIRs and their 95% CIs published in each study. A random-effects model was adopted to synthesize SIRs and 95% CIs for solid organ transplant recipients versus the general population.<sup>12,13</sup> The synthesized SIRs were classified into eight modules by anatomical site or histology: overall cancer, digestive system, integumentary system, reproductive and urinary organs, respiratory system, hematological malignancies, head and neck cancers, and other malignancies. A heat map was generated to better observe the site-specific cancer risks' spectrum of different transplantation types. We used the Cochran's Q test and the I<sup>2</sup> statistic to examine the heterogeneity across studies;<sup>14</sup> significant statistical heterogeneity was considered when an I<sup>2</sup> statistic >50%.<sup>14</sup> Additionally, to explore potential associations among the included studies with different characteristics, a subgroup analysis was conducted according to the region (Europe, Asia, North America, Oceania) and age (<40 years, between 40 and 50 years, > 50 years). Sensitivity analysis was conducted by consecutive exclusion of each study. The Begg's test<sup>15</sup> and Egger's test<sup>16</sup> were performed to analyze the publication biases statistically.

In addition, we used LR method to analyze the association and calculated the correlation coefficients between TMBs and pooled SIRs of site-specific malignancies. Because both TMBs and SIRs were not normally distributed, we took the natural logarithm of each to perform the analyses. Statistical analyses and linear regression were conducted using the STATA 15.0 software (STATA Corp, College Station, TX, USA). GraphPad Prism 7<sup>®</sup> (GraphPad Software, Inc., La Jolla, USA) was used to generate the heat map. All the P-values were 2-tailed; statistical significance was set as P-value <0.05.

### Role of the Funding Source

The funders had no role in the study design, data collection, data synthesis and analysis, writing of the manuscript, or the decision to submit the article for publication.

## Results

### Systematic search and study characteristics

A total of 10,514 studies were identified through the database search and were screened on title and abstract. The full-texts of 217 articles were examined and 72 of them<sup>7,8,17-75</sup> met the inclusion criteria of the analyses.

All 72 studies were prospective cohort studies. Supplementary Table S3 provides details of the included studies, which involved

a total of 2,105,122 solid organ transplant recipients and reported 45 types of site-specific cancer. Of them, 52 studies<sup>7,8,17–62,75</sup> provided SIRs of multiple cancers of solid organ transplantations (11 for multiple organs,<sup>7,8,17–25</sup> 19 for kidney,<sup>26–44</sup> 16 for liver,<sup>45–55,75</sup> 7 for heart and/or lung<sup>60–62,76–79</sup>). The other 20 studies<sup>63–74,80–87</sup> provided SIRs of several or single cancer risks of solid organ transplantations (Figure 1).

### Cancer risks in solid organ transplant recipients

Compared with the general population, solid organ transplant recipients displayed a 2.68-fold cancer risk (SIR 2.68; 2.48–2.89;  $P < .001$ ). Among them, renal transplant recipients displayed a 2.56-fold cancer risk (SIR 2.56; 2.31–2.84;  $P < .001$ ), liver transplant recipients displayed a 2.45-fold cancer risk (SIR 2.45; 2.22–2.70;  $P < .001$ ), heart and/or lung transplant recipients displayed a 3.72-fold cancer risk (SIR 3.72; 3.04–4.54;  $P < .001$ ). SIRs of each site-specific malignancy were listed in Table 1. Comparison of common site-specific cancer risks from different transplant categories became more intuitionistic by generating a heat map (Figure 2).

### Associations between TMB and cancer incidence

In solid organ transplant recipients, we observed a significant correlation between TMBs and SIRs ( $P < .001$ ). The correlation coefficients between SIRs and TMBs were 0.68, 0.64, 0.59, 0.79 in solid organ transplant recipients, renal recipients, liver recipients

and heart and/or lung recipients, respectively, suggesting that the corresponding 46%, 41%, 35%, and 63% of the differences in SIRs across cancer types might be explained by the TMBs (Figure 3).

### Sensitivity analysis

The results of sensitivity analyses were listed in Supplementary Figure S1–S4. It indicated that the omission of any single study did not result in a significant difference in the pooled results, even though there was inevitably a mild amount of overlapping of the included population. The variable findings may be attributed to the limited included cohorts.

### Subgroup analyses

The forest plots of subgroup analyses were presented in Supplementary Figure S5. We conducted the subgroup analyses by region (Europe, Asia, North America, Oceania) and age (<40 years, between 40 and 50, > 50 years). First, we found that the overall cancer risk did not show significant differences in different regions. (SIR 2.45; 2.22–2.70;  $P < .001$ ) Second, we noticed that solid organ transplant recipients over 50 had a 3-fold cancer risk (SIR 3.01; 2.41–3.75;  $P < .001$ ) while solid organ transplant recipients between 40 and 50 and under 40 had a 2.6-fold risk (SIR 2.61; 3.04–4.54;  $P < .001$ ) and a 2-fold risk (SIR 2.00; 1.63–2.47;  $P < .001$ ), respectively.

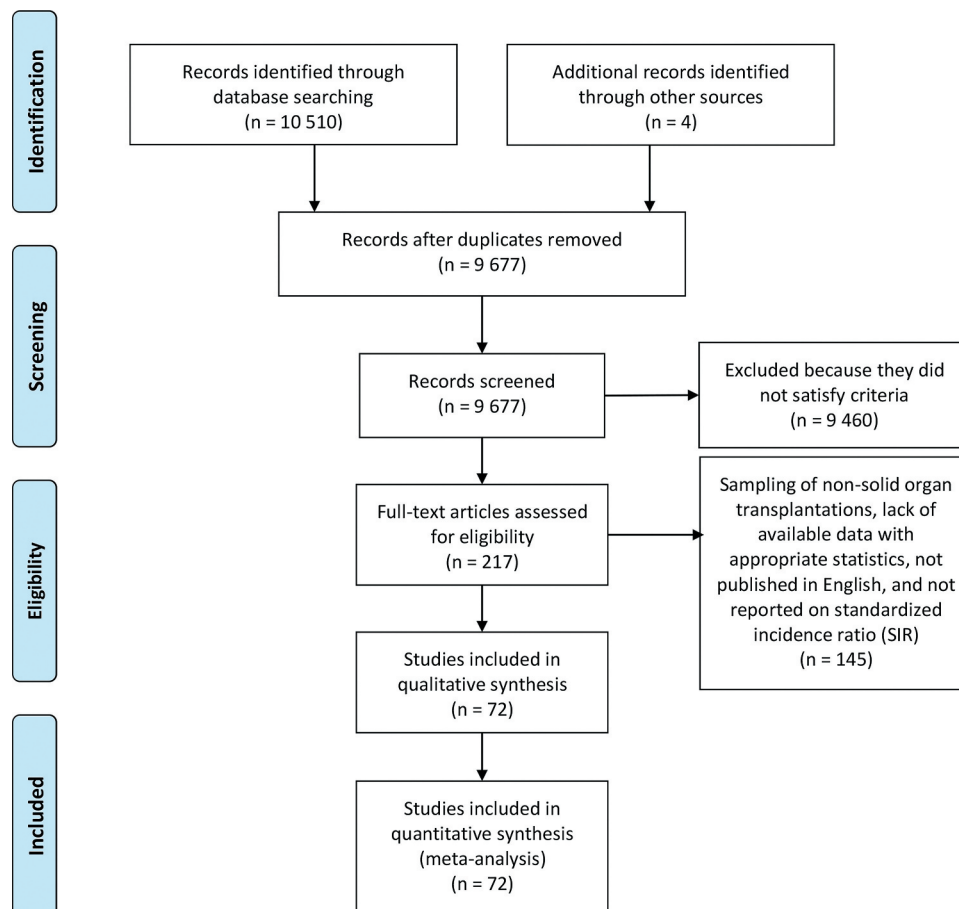
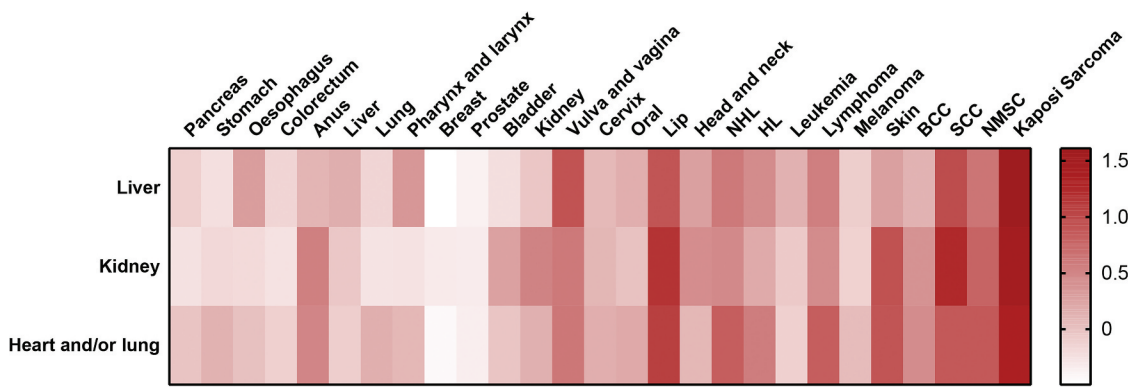


Figure 1. PRISMA diagram of study selection.

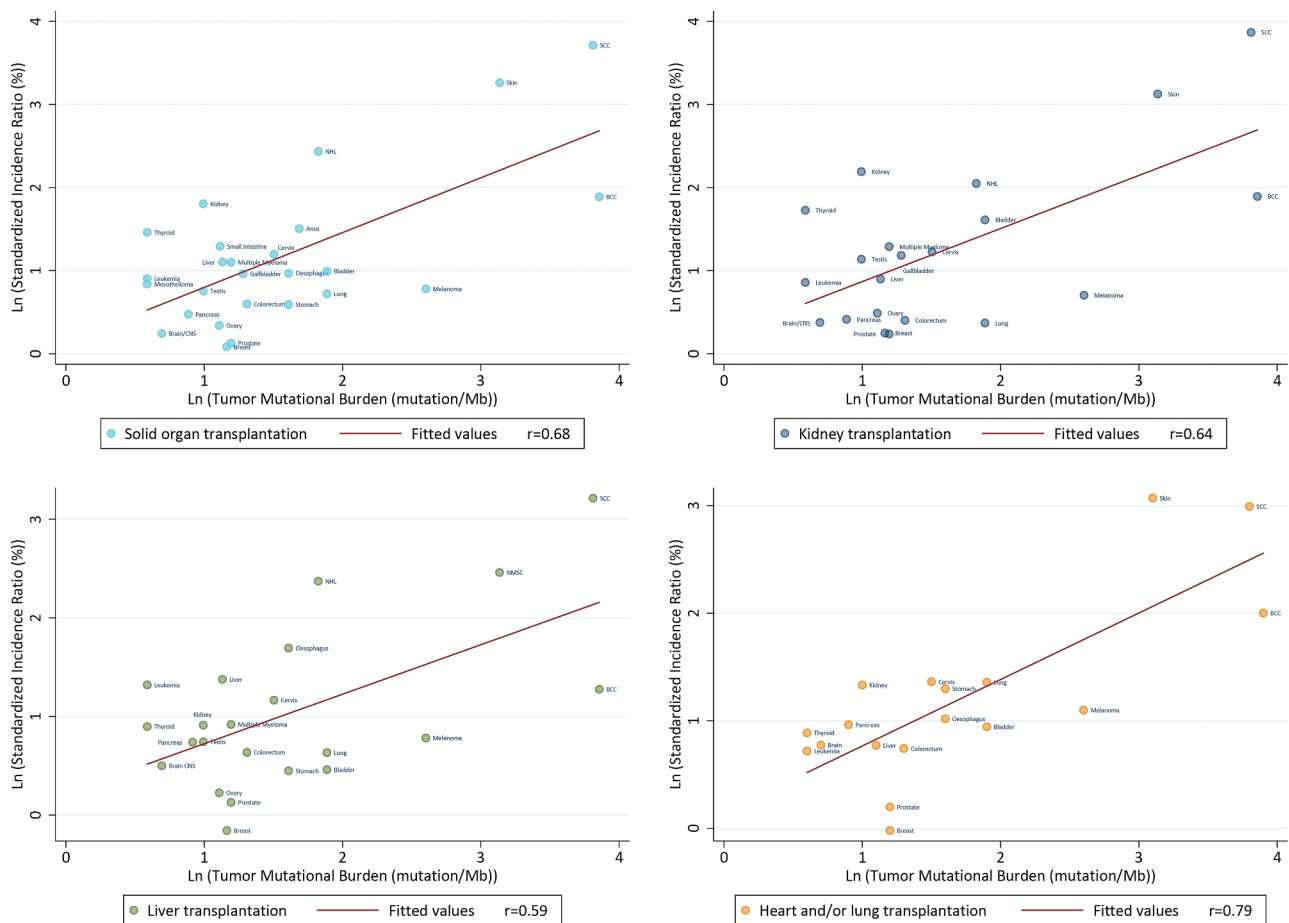
**Table 1.** SIRs of all-cancer and cancer types by anatomical site or histology among solid organ transplant recipients.

| Site                                   | All organ |                          |                  | Kidney    |                          |                  | Liver     |                          |                  | Heart and/or lung |                          |                  |
|--|-----------|--------------------------|------------------|-----------|--------------------------|------------------|-----------|--------------------------|------------------|-------------------|--------------------------|------------------|
|  | N         | SIR (95% CI)             | P value          | N         | SIR (95% CI)             | P value          | N         | SIR (95% CI)             | P value          | N                 | SIR (95% CI)             | P value          |
| <b>Overall cancer</b>                  | <b>56</b> | <b>2.68 (2.48, 2.89)</b> | <b>&lt;0.001</b> | <b>28</b> | <b>2.56 (2.31, 2.84)</b> | <b>&lt;0.001</b> | <b>24</b> | <b>2.45 (2.22, 2.70)</b> | <b>&lt;0.001</b> | <b>18</b>         | <b>3.72 (3.04, 4.54)</b> | <b>&lt;0.001</b> |
| All squamous cell carcinomas           | 13        | 40.97 (25.09, 66.90)     | <0.001           | 6         | 47.83 (26.05, 87.82)     | <0.001           | 4         | 24.87 (13.43, 46.05)     | <0.001           | 11                | 19.92 (7.83, 50.64)      | <0.001           |
| <b>Digestive system</b>                |           |                          |                  |           |                          |                  |           |                          |                  |                   |                          |                  |
| Oesophagus                             | 25        | 2.64 (1.97, 3.52)        | <0.001           | 9         | 1.72 (1.32, 2.24)        | <0.001           | 9         | 5.44 (3.11, 9.51)        | <0.001           | 4                 | 2.77 (1.29, 5.93)        | 0.009            |
| Liver                                  | 34        | 3.02 (2.30, 3.96)        | <0.001           | 18        | 2.46 (1.67, 3.60)        | <0.001           | 9         | 3.96 (1.45, 10.84)       | 0.007            | 12                | 2.16 (1.14, 4.13)        | 0.01             |
| Colorectum                             | 53        | 1.82 (1.59, 2.09)        | <0.001           | 23        | 1.49 (1.19, 1.88)        | 0.001            | 20        | 1.89 (1.59, 2.24)        | <0.001           | 15                | 2.10 (1.40, 3.15)        | <0.001           |
| Bile duct                              | 4         | 3.15 (1.67, 5.92)        | <0.001           | -         | -                        | -                | 3         | 4.18 (2.68, 6.52)        | <0.001           | -                 | -                        | -                |
| Anus                                   | 12        | 4.50 (2.55, 7.96)        | <0.001           | 2         | 9.40 (6.50, 13.60)       | <0.001           | 4         | 3.43 (1.22, 9.66)        | 0.019            | 2                 | 8.49 (2.63, 27.39)       | <0.001           |
| Salivary glands                        | 12        | 7.13 (4.43, 11.47)       | <0.001           | -         | -                        | -                | 3         | 13.62 (4.46, 41.58)      | 0.776            | 4                 | 12.53 (1.99, 78.85)      | 0.007            |
| Small intestine                        | 6         | 3.65 (2.19, 6.07)        | <0.001           | -         | -                        | -                | -         | -                        | -                | -                 | -                        | -                |
| Stomach                                | 36        | 1.81 (1.61, 2.03)        | <0.001           | 15        | 1.76 (1.52, 2.04)        | <0.001           | 12        | 1.57 (1.17, 2.10)        | 0.722            | 5                 | 3.66 (1.58, 8.48)        | 0.03             |
| Gallbladder                            | 7         | 2.62 (1.87, 3.67)        | <0.001           | 4         | 3.27 (1.92, 5.55)        | <0.001           | -         | -                        | -                | -                 | -                        | -                |
| Pancreas                               | 30        | 1.61 (1.43, 1.80)        | <0.001           | 12        | 1.51 (1.17, 1.95)        | 0.001            | 9         | 2.10 (1.50, 2.94)        | 0.392            | 2                 | 2.62 (0.91, 7.55)        | 0.075            |
| <b>Integumentary system</b>            |           |                          |                  |           |                          |                  |           |                          |                  |                   |                          |                  |
| All skin cancer                        | 10        | 26.09 (13.61, 50.03)     | <0.001           | 4         | 22.78 (7.69, 67.48)      | <0.001           | 4         | 5.12 (3.97, 6.62)        | <0.001           | 4                 | 21.53 (6.49, 71.39)      | <0.001           |
| Melanoma                               | 38        | 2.18 (1.88, 2.53)        | <0.001           | 18        | 2.02 (1.58, 2.58)        | <0.001           | 10        | 2.18 (1.20, 3.98)        | 0.011            | 7                 | 3.00 (2.22, 4.06)        | <0.001           |
| Basal cell carcinoma                   | 7         | 6.60 (5.71, 7.64)        | <0.001           | 4         | 6.63 (5.55, 7.93)        | <0.001           | 4         | 3.58 (2.79, 4.59)        | <0.001           | 6                 | 7.40 (5.60, 9.78)        | <0.001           |
| Non-melanoma skin cancer               | 22        | 12.53 (9.15, 17.17)      | <0.001           | 12        | 16.10 (10.28, 25.22)     | <0.001           | 8         | 11.70 (6.65, 20.60)      | <0.001           | 10                | 20.01 (11.55, 34.65)     | <0.001           |
| <b>Reproductive and Urinary Organs</b> |           |                          |                  |           |                          |                  |           |                          |                  |                   |                          |                  |
| Kidney                                 | 46        | 6.08 (5.00, 7.40)        | <0.001           | 27        | 8.95 (7.20, 11.13)       | <0.001           | 15        | 2.49 (1.88, 3.29)        | <0.001           | 8                 | 0.98 (0.68, 1.41)        | <0.001           |
| Bladder                                | 39        | 2.70 (1.83, 3.99)        | <0.001           | 19        | 5.01 (2.47, 10.14)       | <0.001           | 11        | 1.59 (1.01, 2.48)        | 0.044            | 8                 | 2.57 (1.77, 3.72)        | <0.001           |
| Breast                                 | 48        | 1.09 (0.97, 1.21)        | 0.136            | 21        | 1.28 (1.08, 1.53)        | 0.005            | 17        | 0.85 (0.72, 1.01)        | 0.064            | 8                 | 0.98 (0.68, 1.41)        | 0.89             |
| Cervix                                 | 28        | 3.31 (2.10, 5.22)        | <0.001           | 11        | 3.41 (1.61, 7.18)        | 0.001            | 9         | 3.20 (1.56, 6.56)        | 0.001            | 6                 | 3.91 (1.41, 10.80)       | 0.009            |
| Penis                                  | 6         | 8.47 (3.76, 19.05)       | <0.001           | -         | -                        | -                | 2         | 6.58 (1.56, 27.67)       | 0.01             | -                 | -                        | -                |
| Prostate                               | 38        | 1.14 (1.00, 1.29)        | 0.042            | 18        | 1.27 (1.02, 1.58)        | <0.001           | 11        | 1.14 (0.69, 1.87)        | 0.61             | 9                 | 1.22 (1.00, 1.49)        | 0.034            |
| Vulva and vagina                       | 10        | 14.36 (8.90, 23.15)      | <0.001           | 2         | 10.87 (4.82, 24.53)      | <0.001           | 3         | 22.08 (10.34, 47.15)     | <0.001           | 5                 | 11.16 (4.14, 30.08)      | <0.001           |
| Uterus corpus                          | 17        | 1.17 (0.92, 1.48)        | 0.191            | 9         | 1.17 (0.87, 1.57)        | 0.291            | 3         | 1.09 (0.63, 1.88)        | 0.759            | -                 | -                        | -                |
| Ovary                                  | 18        | 1.40 (1.18, 1.67)        | <0.001           | 8         | 1.63 (1.30, 2.04)        | <0.001           | 4         | 1.25 (0.66, 2.37)        | 0.488            | -                 | -                        | -                |
| Testis                                 | 10        | 2.13 (1.66, 2.73)        | <0.001           | 3         | 3.12 (1.62, 5.99)        | 0.001            | 2         | 2.10 (0.31, 14.18)       | 0.446            | 2                 | 5.03 (0.75, 33.56)       | 0.095            |
| <b>Respiratory system</b>              |           |                          |                  |           |                          |                  |           |                          |                  |                   |                          |                  |
| Lung                                   | 49        | 2.06 (1.77, 2.39)        | <0.001           | 21        | 1.45 (1.23, 1.70)        | <0.001           | 18        | 1.88 (1.60, 2.22)        | <0.001           | 17                | 3.89 (3.00, 5.06)        | <0.001           |
| Mesothelioma                           | 6         | 2.31 (1.11, 4.81)        | 0.025            | 2         | 4.98 (2.14, 11.58)       | <0.001           | -         | -                        | -                | -                 | -                        | -                |
| <b>Hematological malignancies</b>      |           |                          |                  |           |                          |                  |           |                          |                  |                   |                          |                  |
| Leukemia                               | 26        | 2.47 (1.74, 3.50)        | <0.001           | 12        | 2.36 (1.41, 3.94)        | 0.001            | 12        | 3.74 (2.13, 6.59)        | <0.001           | 5                 | 2.05 (1.08, 3.92)        | 0.029            |
| Multiple Myeloma                       | 19        | 3.01 (2.29, 3.95)        | <0.001           | 5         | 3.63 (1.91, 6.90)        | <0.001           | 4         | 2.51 (0.91, 6.88)        | <0.001           | -                 | -                        | -                |
| Lymphoma                               | 12        | 9.13 (7.12, 11.70)       | <0.001           | 6         | 7.53 (5.19, 10.92)       | <0.001           | 5         | 9.60 (7.06, 13.04)       | 0.075            | 4                 | 17.95 (15.33, 21.02)     | <0.001           |
| Non-Hodgkin's lymphoma                 | 41        | 11.41 (9.74, 13.36)      | <0.001           | 20        | 7.76 (6.39, 9.43)        | <0.001           | 19        | 10.72 (9.09, 12.64)      | <0.001           | 14                | 18.16 (12.17, 27.09)     | <0.001           |
| Hodgkin's lymphoma                     | 25        | 4.50 (3.33, 6.08)        | <0.001           | 8         | 4.3 (2.85, 6.49)         | <0.001           | 10        | 7.55 (4.94, 11.54)       | <0.001           | 9                 | 9.96 (4.84, 20.49)       | <0.001           |
| <b>Head and Neck Cancers</b>           |           |                          |                  |           |                          |                  |           |                          |                  |                   |                          |                  |
| Head and neck                          | 9         | 6.83 (3.51, 13.32)       | <0.001           | 5         | 7.27 (4.29, 12.34)       | <0.001           | 6         | 5.19 (4.30, 6.27)        | <0.001           | 4                 | 3.30 (1.06, 10.28)       | 0.04             |
| Thyroid                                | 32        | 4.31 (3.30, 5.62)        | <0.001           | 21        | 5.62 (4.12, 7.67)        | <0.001           | 9         | 2.45 (1.37, 4.41)        | 0.003            | 4                 | 2.43 (0.84, 6.98)        | 0.1              |
| Oral cavity                            | 35        | 3.60 (2.79, 4.64)        | <0.001           | 13        | 2.70 (1.71, 4.28)        | <0.001           | 12        | 3.93 (2.51, 6.17)        | <0.001           | 10                | 4.32 (2.31, 8.06)        | <0.001           |
| Lip                                    | 22        | 34.69 (26.82, 44.86)     | <0.001           | 13        | 39.13 (30.79, 49.73)     | <0.001           | 8         | 21.54 (12.71, 36.48)     | <0.001           | 11                | 32.27 (18.25, 76.11)     | <0.001           |
| Eye                                    | 5         | 2.86 (1.67, 4.90)        | <0.001           | -         | -                        | -                | 2         | 3.03 (0.46, 20.09)       | 0.251            | -                 | -                        | -                |
| Nose                                   | 5         | 7.072 (3.881, 12.887)    | <0.001           | -         | -                        | -                | 2         | 14.37 (3.33, 60.82)      | <0.001           | -                 | -                        | -                |
| Nasopharyngeal carcinoma               | 3         | 0.80 (0.46, 1.39)        | 0.433            | -         | -                        | -                | 2         | 1.96 (0.67, 5.71)        | 0.219            | -                 | -                        | -                |
| Pharynx                                | 23        | 2.36 (1.55, 3.60)        | <0.001           | 9         | 1.46 (0.96, 2.22)        | 0.08             | 4         | 6.15 (4.09, 9.24)        | <0.001           | 4                 | 3.34 (1.51, 7.40)        | 0.003            |
| <b>Other Malignancies</b>              |           |                          |                  |           |                          |                  |           |                          |                  |                   |                          |                  |
| Kaposi sarcoma                         | 22        | 73.55 (54.06, 100.06)    | <0.001           | 11        | 80.69 (50.07, 130.02)    | <0.001           | 7         | 108.83 (59.31, 199.71)   | <0.001           | 6                 | 58.55 (19.96, 171.79)    | <0.001           |
| Brain and CNS                          | 23        | 1.27 (1.01, 1.61)        | 0.043            | 8         | 1.46 (0.80, 2.65)        | 0.218            | 7         | 1.65 (0.97, 2.80)        | 0.064            | 5                 | 2.17 (1.10, 4.27)        | 0.026            |
| Soft tissues                           | 12        | 3.03 (2.31, 3.98)        | <0.001           | 3         | 3.10 (1.53, 6.30)        | 0.002            | 3         | 3.15 (0.80, 12.48)       | 0.102            | 4                 | 6.82 (2.95, 15.73)       | <0.001           |
| Bones and joints                       | 3         | 2.23 (1.35, 3.68)        | 0.002            | -         | -                        | -                | -         | -                        | -                | -                 | -                        | -                |
| Adrenal gland                          | 2         | 27.40 (6.53, 114.96)     | <0.001           | -         | -                        | -                | -         | -                        | -                | -                 | -                        | -                |

An SIR > 1 suggests that the cancer risk is higher than that of the ordinary population. SIR = Standardized incidence ratio; CI = confidence interval  
N refers to the total number of SIR values of corresponding site-specific cancers after solid organ transplantation



**Figure 2.** Heat map of the comparison of common cancer risks. Each SIR value was treated as follows: (1) all-cancer risk of solid organ transplantation was taken as reference (ref = 1); (2) natural logarithm was taken. Each SIR value was treated as follows: (1) all-cancer risk of solid organ transplantation was taken as reference (ref = 1); (2) natural logarithm was taken. HL: Hodgkin's lymphoma; NHL: Non-Hodgkin's lymphoma.



**Figure 3.** Correlation between TMB and SIR in solid organ transplant recipients. Data on the x and y axis are shown on a logarithmic scale.

## Publication bias

Significant heterogeneity was observed in the pooled analyses. With the limited information, we were unable to detect any source leading to substantial heterogeneity. Furthermore, the Egger's and Begg's test results showed no evidence of significant publication bias for all cancers analyzed in solid organ transplant recipients, renal transplant recipients, liver transplant recipients and heart and/or lung transplant recipients (Supplementary Table S4).

## Discussion

This study showed a risk spectrum of overall cancer and site-specific cancers in solid organ transplant recipients compared with the general population. Subgroup analyses showed that age could contribute to the elevated overall post-transplant cancer risk. When stratified by region, the overall post-transplant cancer risk did not show a significant difference. When it comes to the correlation between the cancer risk and TMBs, the

correlation coefficient was 0.68, suggesting that the increased incidence of cancer was associated with immunosuppression.

Several mechanisms could explain the increased cancer risk in solid organ transplant recipients. Both viral and non-viral factors are involved in the progression of post-transplant malignancies. Infections with the hepatitis C and hepatitis B virus are considered risk factors for liver cancer, while EBV infection may be associated with an increased risk of non-Hodgkin's lymphoma.<sup>88,89</sup> HPV infection may be related to squamous cell carcinoma.<sup>5</sup> However, compared with people with HIV or AIDS, solid organ transplant recipients demonstrated higher HPV-related cancer risks, while EBV-related cancer risks were lower than HIV-infected.<sup>5</sup> The difference between the above two immune deficiencies remains to be explored. These infectious factors support our findings of the elevated site-specific cancer risks.

Long-term use of post-transplant immunosuppressive therapy is related to the increased incidence of cancer. Immunosuppression therapy is possibly related to the direct damage of cells and cell repair systems.<sup>90,91</sup> Generally, the immunosuppressive drugs act by depleting T lymphocytes, leading to the decreased acute rejection rates, which results in the increased graft survival.<sup>92</sup> In the meantime, they also have the ability to reduce immune surveillance, which facilitates the survival and proliferation of atypic cells.<sup>93</sup> In addition, the significant elevation of skin-related malignancies (e.g. BCC and SCC) and cervical cancer in transplant recipients may be related to the increased susceptibility to human papillomavirus.<sup>94</sup> Compared with 11% to 32% in normal skin, up to 90% of SCCs in solid organ transplant recipients contain human papillomavirus DNA.<sup>95</sup> Immunosuppressive drugs have also shown the possibility to increase the risk of ultraviolet-related carcinogenic effects.<sup>96,97</sup>

Among solid organ transplant recipients, heart and/or lung transplant recipients were found to have the highest lung cancer risk. The risk factors include post-transplant chronic immunosuppression and previous smoking status.<sup>98</sup> Meanwhile, due to the etiologic factors of end-stage pulmonary diseases such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, these patients are at increased lung cancer risk compared with the general population. Also, the native lung disease or undetected cancerous cells in the donor's lung predispose to an increased incidence of lung cancer in the allograft after transplantation.<sup>98–100</sup> Moreover, a higher intensity and a longer duration of immunosuppressive therapy in heart and/or lung transplant recipients contribute to the elevation of the risks, which results in a higher inhibitory effect on the immune system, leading to a further decline in its ability to monitor and clear pathogens and cancer cells, and ultimately an increase in lung cancer risk.<sup>8,101</sup>

We also found that liver cancer risk was most elevated in liver transplant recipients among solid organ transplant recipients. Liver cancer is the most common complication in end-stage liver disease patients, and liver transplantation can be an ideal therapy for patients with localized liver cancer.<sup>102</sup> Possible reasons to explain the elevated liver cancer risk include the relapse of infection of HBV and HCV, diabetes mellitus, and the delayed recognition of liver cancer in the donor liver.<sup>56</sup> Due to the significant organ specificity, we speculate the elevated liver cancer risk may also be related to the chronic rejection reaction after liver transplantation. Also, the incidence of ulcerative colitis after liver transplantation was

increased, which could result in the elevated colorectal cancer risk in post-liver transplant recipients.<sup>55, 103</sup>

Among solid organ transplant recipients, the kidney recipients were found to have the highest renal cancer risk. Guba *et al.*<sup>6</sup> found that some nephrotoxic effects or direct carcinogenic effects in immunosuppressive drugs may lead to a higher renal cancer risk. Some early post-transplant renal cancer cases were the results of malignant conversion from benign cysts developing in pre-transplant donor kidneys.<sup>104</sup> Another potential reason could be the aging donor population, some of whom may have unrecognized kidney cancer before transplantation, which could contribute to the facilitation of renal cancer.<sup>18</sup> These mechanisms support our finding of the elevated 9-fold renal cancer risk we found in renal transplant recipients. In summary, lung cancer risk, liver cancer risk and renal cancer risk were mostly elevated in heart and/or lung recipients, liver recipients and kidney recipients, respectively.

TMB is a promising biomarker for predicting the response to immune checkpoint inhibitors (ICIs) of tumors.<sup>9,105</sup> In a clinical trial, TMB was more remarkably associated with response rate than the expression of PD-L1 by immunohistochemistry.<sup>106</sup> In 2017, Mark Yarchoan *et al.*<sup>105</sup> plotted the objective response rate for anti-PD-1/PD-L1 therapy against the corresponding median TMB values across multiple cancer types, which highlighted the strong relationship between TMB and the activity of anti-PD-1 treatments across site-specific cancers. To some extent, TMB reflects the immunogenicity of the tumor. The higher the TMB of a specific cancer is, the more kinds of abnormal proteins it produces. These proteins are recognized as antigens, leading to a higher possibility of being recognized by the immune system, which makes them the targets of activated immune cells.<sup>9</sup> Therefore, when the immune system is normal, malignancies with a high TMB are less likely to grow. Immunosuppressive drugs would lower immune surveillance of the immune system, leading to increased survival of high-TMB malignancies, which may eventually lead to an increase of overall and site-specific cancer incidence. In this study, linear regression was used to analyze the association between TMBs and corresponding cancer incidences. **Figure 2** shows that the occurrence of cancers in multiple sites is possibly immunosuppression-related. Heart and/or lung transplantation has the highest correlation coefficients ( $r = 0.79$ ), which may be related to a higher intensity and a longer duration of immunosuppressive therapy.<sup>8,101</sup> In comparison, renal transplantation and liver transplantation had relatively lower correlation coefficients ( $r = 0.64$  and  $0.59$ , respectively), which could be attributed to the lower intensity and shorter duration of immunosuppressive therapy.<sup>17</sup> In conclusion, the high correlation between the cancers' SIRs and their TMBs in solid organ transplantation supported that iatrogenic immunosuppression-generated site-specific cancer risk was elevated in transplant recipients.

Three strengths of our study should be highlighted. First, to our knowledge, this is the first and the most comprehensive quantitative summary estimating the cancer risks after multiple types of solid organ transplantation, and exploring the relationship between the corresponding SIRs and their TMBs. Second, previous meta-analyses were limited to a specific organ, specific malignancy, single region, or small sample size. Our study initially collected large-sample data and assessed the cancer risks of solid organ transplantation from various areas of the world. The collected global data and our findings could provide clinicians and researchers with ideas to prevent and treat cancer

in solid organ transplant recipients. Third, this is also the first study to associate TMBs with site-specific cancer risks, which could provide a way to explore the cancer risk of solid organ transplantation at the perspective of immunology.

We acknowledge some limitations in regards to our comprehensive analysis. First, significant heterogeneity between studies was observed, which may be due to the following reasons: (1) various transplant types were included in one overall analysis (2) differences between oncological characteristics of included malignancies (3) no detailed information on the smoking status,<sup>107</sup> body mass index,<sup>108</sup> alcohol use<sup>109</sup> and immunosuppressive drugs<sup>110</sup> were available to perform an adjustment for these potential confounders; (4) although all studies used the general population as references, the matching criteria for studies in different countries may be different. Second, as there were no pre-transplant disease data for solid organ transplant recipients, we could not rule out their effects on solid organ transplant recipients' cancer risk. Third, due to the inclusion of research publications, publication bias is inevitable.

## Conclusion

This comprehensive analysis showed that solid organ transplant recipients displayed a higher cancer risk, and different malignancies presented different risks. Such associations provided guidance for clinicians to prevent specific types of post-transplant malignancies. In addition, the increased cancer risk of solid organ transplant recipients is significantly associated with TMB, suggesting that iatrogenic immunosuppression may lead to an increased cancer risk in transplant recipients.

## Author contributions

HZY, GF, XX and WRC designed this study. LCC, CB, LJF and XS searched the literature. HZY, GF and WRC extracted data. HZY, CY, LHR, LWY, PHX and WXR analysed data. HZY and GF wrote the first draft of the manuscript. LCC, HDX, LR and ZR revised the primary version and performed English editing. LWH and HJX revised the final version of the manuscript. All authors contributed to revisions of the manuscript. HZY is the guarantor. All authors approved the final manuscript

## Acknowledgments

The authors thank Ms. Lindsey Hamblin for helping to edit the manuscript.

## Abbreviations

|        |  |
|--------|--|
| BCC    | Basal Cell Carcinoma   |
| CGP    | Comprehensive Genomic Profiling                                    |
| CI     | Confidence Interval  |
| EBV    | Epstein-Barr virus   |
| HPV    | Human papillomavirus   |
| LR     | Linear Regression  |
| MeSH   | Medical Subject Headings   |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analysis |
| SCC    | Squamous Cell Carcinoma  |
| SIR    | Standardized Incidence Ratio                                       |
| TMB    | Tumor Mutational Burden  |

## Conflict of interest

All the authors declare no conflicts of interest.

## Ethical statement

This study was approved by the ethics committee of The First Affiliated Hospital of Guangzhou Medical University. Considering that the study was a retrospective analysis, informed consent of all patients was waived by the ethics committee.

## Highlights

We summarized the spectrum of overall and site-specific cancer risks in patients with different types of solid organ transplantation, and showed the relationship between TMB and risks of post-transplant cancers.

## Funding

This study was supported by the National Natural Science Foundation of China (Grant No.81871893) and Key Project of Guangzhou Scientific Research Project (Grant No.201804020030) provide and maintain database

## ORCID

Zhenyu Huo  <http://orcid.org/0000-0002-9841-5081>  
 Fan Ge  <http://orcid.org/0000-0002-6599-8807>  
 Jianxing He  <http://orcid.org/0000-0003-1737-8192>  
 Wenhua Liang  <http://orcid.org/0000-0002-1391-8238>

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