Journal of Cancer Research and Clinical Oncology (2018) 144:543–550
https://doi.org/10.1007/s00432-018-2590-z

ORIGINAL ARTICLE – CANCER RESEARCH

Risk for cancer in living kidney donors and recipients

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Received: 11 December 2017 / Accepted: 17 January 2018 / Published online: 22 January 2018

Abstract

Objective Malignancy following renal transplantation remains inconsistent with the reported safety of kidney donation during the long-term follow-up.

Methods We conducted searches of the published literature which included healthy participants, recipients, living kidney donors (LKDs), and the availability of outcome data for malignancy. Eight from 938 potentially relevant studies were analyzed by means of fixed-effects model or random-effects model, as appropriately.

Results In 48,950 participants, the follow-up range was 18 months to 20 years, and the mean age of the subjects was approximately 41 years. The incidence rate with 95% confidence interval (CI) for malignancy after kidney transplantation was 0.03 (0.01–0.05) in recipients and 0.03 (0.1–0.07) in LKDs, giving a pooled incidence rate of 0.03 (95% CI 0.02–0.04). LKDs contrasted nondonors by the overall odds ratio and 95% CI for total cancer of 2.80 (2.69–2.92).

Conclusions Kidney transplantation was associated with an increased risk of cancer during a long-term follow-up. Long-term risk for cancer in LKDs and kidney recipients should be monitored.

Keywords Kidney transplantation · Cancer · Living kidney donors · Recipients · Long-term outcomes

Introduction

A person has only one working kidney because of birth defect, surgical removal of a kidney, kidney transplantation and kidney donation. As the organ shortage increases, inherently the demand for donor kidneys continues to rise, while living kidney donation is essential for expanding the donor pool (Segev et al. 2010). It is necessary to considered extended criteria for living kidney donors (LKDs). Yet, living kidney donation in young donors seems to be dangerous as the outcome is comparable to old donors (up to 70 years of age) (Robitaille et al. 1985). Analogously, obese donors have comparable outcome to lean donors, in short- and mid-term follow-up. Some literature has proved the safety of donation of hypertensive donors (Boudville et al. 2006; Lewington et al. 2002). And, vascular multiplicity poses no direct danger to the donors, albeit caution is advised. Even women of childbearing age and minors can be safely included as living donors. Recently, more attention is being paid to the long-term outcomes of recipients and donors in the domains of metabolic function, risk of chronic renal disease, and health-related quality of life (Li et al. 2016).

In the United States, 40% of kidney transplants have been derived from living donors (Schold et al. 2014). Previous studies have suggested that LKDs maintain long-term renal function and experience no increase in cardiovascular or all-cause mortality (Schold et al. 2013). These minimal long-term health consequences after donation are limited due to the non-comprehensive design, such as inadequate control, insufficient follow-up period, and simplistic outcomes (Robitaille et al. 1985; Schold et al. 2013). As we reported previously, uninephrectomized rats

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-018-2590-z) contains supplementary material, which is available to authorized users.

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progressively developed renal impairments accompanied by metabolic disorders (Sui et al. 2007), fat redistribution (Zhao et al. 2008), lipid partitioning (Zhao et al. 2011), renin–angiotensin system (RAS) activation (Sui et al. 2010; Yang et al. 2009b, 2016), and remnant kidney cancer (Sui et al. 2009; Yang et al. 2009b). Similarly, albuminuria, proteinuria, end-stage renal disease, and death might be the major concerns of LKDs after 5 years and onward (Li et al. 2016).

Renal function plays an important role in immune response, especially for the development of T cells which is dependent on thymus. A long-term immune dysfunction in LKDs would lead to one of the significant severe outcomes, cancer. The wide participation of healthy persons as kidney donors calls for awareness of cancer risk associated with donation which may have a long latency period (Spital 2015). Most strikingly, both LKDs and kidney recipients with some degree of immunity dysfunction face a similarly increased risk of incident cancer (Kasiske et al. 2004; Lentine et al. 2012), although these two groups of persons are biologically completely different. Based on this initial finding, we pooled these extracted effects sizes using meta-analytical techniques. Thus, the primary question of this study is whether kidney transplantation increases the risk of cancer over a long-term follow-up in LKDs or recipients.

Methods

We use the preferred reporting items for systematic reviews and meta-analyses statement as guide in this study.

Literature search

Three reviewers systematically compiled citations and searched English databases including PubMed, Cochrane Library, MEDLINE, EMBASE, and the U.S. Organ Procurement and Transplantation Network; Chinese databases including Wangfang database, Chinese National Knowledge Infrastructure; and Japan science and technology information aggregator electronic from 1955 through May 2016. The strategies included the terms "living kidney donation", "living kidney transplantation", "renal transplantation", and "unilateral nephrectomy" were used in various combinations with "cancer", "mortality", "incidence", "malignancy", "tumor", "neoplasm", and "carcinoma". We also conducted manual search of the bibliographies and reference lists to identify relevant studies. Countries worldwide were involved in this study, including America, Spain, Norway, Korea, Danmark, Poland, Canada, Japan, Swiss, Pakistan, and China.

Study selection

All published articles were meeting the following eligibility criteria (Li et al. 2016): (a) comparisons were conducted between donation/transplantation and controls or before and after donation/transplantation; (b) available data were cancer outcomes including incidence and mortality of malignancies, or they could be calculated by disclosed sufficient data; (c) for the recipients and LKDs, duration of follow-up was accrued from the date of uninephrectomy, and non-donors were accrued from the enrollment into the study; (d) if there were multiple articles, we cited the most representative one with the largest number of participants and longest duration of follow-up; (e) all relative literatures were in Chinese or English, and published in their entirety. After systematical training, pairs of reviewers independently evaluated the eligibility of all English language and non-English language publications. A third reviewer resolved disagreements.

The following literatures were excluded: studies that did not investigate the development of cancer as end point outcomes, outcomes were unclear; non-clinical nature, duplications, and non-original reports including reviews, editorials, letters, and commentaries.

Data abstraction

Four reviewers independently abstracted the following data from all eligible studies: description of study design, general characteristics of participants, cancer outcomes, measurement of various outcomes. We conducted comparison between LKDs and non-donors to avoid the age-related risk for development of cancer in this study. The primary outcomes included incidence and mortality of cancer.

Validity assessment

In this study, we chose the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) to assess the quality of the included studies for the purpose of validity, feasibility and reliability, like our previous report (Kim et al. 2013). A total of six sections composed the assessment system, including selection of individuals, consideration of confounding variables, blinding of outcome assessments, measurements of outcomes, handling of incomplete outcome data and selective reporting of outcomes.

Statistical analysis

Summarized mean or odds ratio estimates were calculated by the fixed-effect or random-effect models with generalized least-squares estimation. Q test was used to ensure whether

between-study heterogeneity was present and a 2-tailed *P* value less than 0.1 was considered statistically significant. The I^2 statistic was used to examine the magnitude of heterogeneity among the literatures. $I^2 > 75\%$ indicates high heterogeneity and random-effects model is appropriate, otherwise fixed-effects model was selected.

Publication bias was evaluated through visual inspection of funnel plot. Egger regression tests the symmetry of funnel plot and a 2-tailed *P* value less than 0.05 indicates the presence of publication bias. All analyses were conducted using Review Manager 5 software package (version 5.1; The Nordic Cochrane Center, Copenhagen Denmark), Microsoft Excel 2010 (Microsoft Corporation., Washington), and Stata 11.0SE statistical software package (StataCorp, College Station, TX). Results were graphed in SigmaPlot 12.0 software package (Systat Software International., Chicago).

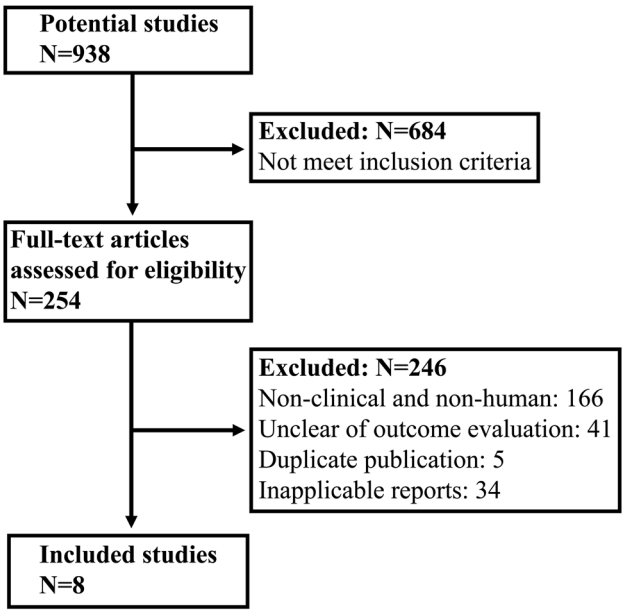

Fig. 1 Flow chart of study selection process

Results

Preparation and description of studies

A total of eight full-text articles (Birkeland and Storm 2002; Chu et al. 2012; Kasiske et al. 2004; Lentine et al. 2012; Nafar et al. 2005; Park et al. 2000; Schold et al. 2014; Veroux et al. 2004) with 48,950 participants derived from 938 potential studies in six countries were eligible in this study (Fig. 1). The eight articles were published between 2002 and 2014. Table 1 shows the essential information of these eight studies. Most studies were conducted in America (37.5%). Five studies reported the frequency of being lost to follow-up with an average rate of 5.5% in selected participants. Three articles conducted the comparison between donors and controls, and five showed outcomes between post-donation and pre-donation. Of the eight studies, six provided classification and only two calculated the incidence of each type of cancer.

Methodological quality and bias of studies

According to the results of RoBANS, there is no distinct risk of bias in this meta analysis. For all studies included, the overall risk of bias analysis showed low-risk vs. high-risk of bias for selection of participants (87.5% vs. 0), confounding variables (62.5% vs. 0), measurement of exposure (50.0% vs. 0), blinding of outcome assessments (75.0% vs. 0), incomplete outcome data (100.0% vs. 0), and selective reporting (100.0% vs. 0), as shown in Fig. 2. No significant

Table 1 Characteristics of the included eight clinical trials of living kidney transplantation

References	Location	Lost to follow-up, %	Donors, *n*	Women, %	Age at donation (years)	Duration of follow-up	Period of donation
Birkeland et al. (2002)	Copenhagen, Denmark	NR	626	NR	NR	NR	1969–1996
Chu et al. (2012)	Hong Kong, China	27.4	149	56.0	33.9 ± 9.7	160.39 ± 87.96 M	1980–2009
Kasiske et al. (2004)	Minneapolis, America	NR	35,765	40.0	NR	NR	1995–2001
Lentine et al. (2012)	Missouri, America	0	4650	54.0	37.2 ± 10.0	7.7 Y	1987–2007
Nafar et al. (2005)	Tehran, Iran	0	2117	NR	43.5 ± 12.1	81.1 ± 61 M	1984–2004
Park et al., (2000)	Seoul, Korea	NR	1130	37.9	NR	5.1 ± 3.9 Y	1969–1999
Schold et al. (2014)	Cleveland, America	0	4524	61.0	41.1 ± 11.5	NR	2005–2010
Veroux et al. (2004)	Catania, Italy	0	138	NR	NR	18.1 M	2000–2003

Data are shown as mean ± standard deviation

NR not report, *D* days, *M*, months; Y, years

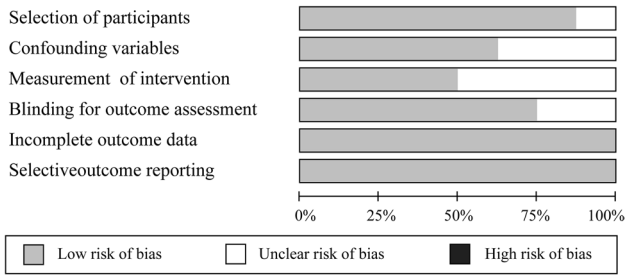

Fig. 2 Risk of bias graph of all included quasi-randomized trials

biases existed in the analyses shown by funnel plots (Fig. 3, $P = 0.070$) and egger regression test ($P > 0.050$).

Increased risk of cancer after kidney transplantation

Six studies involved the observed incidence of cancer in 4803 recipients and LKDs over 6.7 years of follow-up (Fig. 4), and the pooled overall rate was 0.03 (95% CI 0.02–0.04; $P < 0.001$) by random effects model ($I^2 = 83.2\%$). Furthermore, the estimated incidence rates of cancer were almost the same as recipients (0.03; 95% CI 0.01–0.05; $P < 0.001$) and LKDs (0.03; 95% CI 0.1–0.07; $P = 0.001$). Two studies assessed the risk for cancer in 9102 LKDs and recipients compared with 3319 controls from 1987 to 2007 (Fig. 5). One study detected the occurrence of cancer after kidney transplantation by comparing rates of cancer in first-time kidney transplant recipients with rates in the general US population (Kasiske et al. 2004). Another study carried out this comparison in prior LKDs and age- and sex-matched non-donor controls, and both cohorts were from the same database, the US Organ Procurement and Transplantation Network (Lentine et al. 2012). An increased risk for all

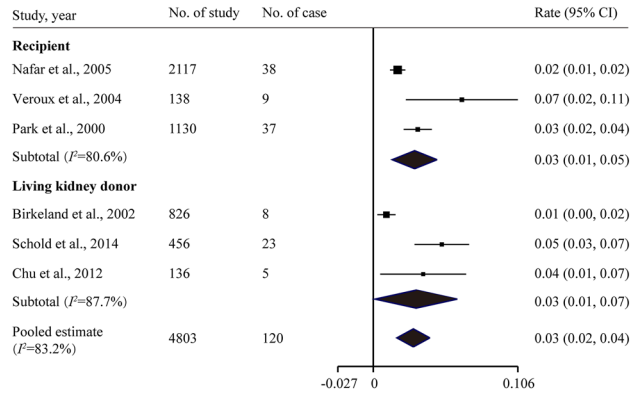

Fig. 4 Rate of cancer after donation

cancer after transplantation was detected, with an overall odds ratio (OR) 2.80 (95% CI 2.69–2.92) by random effects model ($I^2 = 99.0\%$). Especially, both recipients and LKDs showed a significant higher risk of melanoma than controls, with an overall OR 2.94 (95% CI 2.39, 3.61) by random effects model ($I^2 = 96.7\%$). The same results were found in skin cancer and non-skin cancer (Figure S1).

Discussion

The eight studies included in this analysis varied greatly in methodological rigor, follow-up period, and conclusions on whether living kidney transplantation increases risk of cancer. In this study, we mathematically pooled results from a subset of small inconclusive studies that conducted non-donors. Here we show that living kidney donation was associated with an increased risk of cancer in both LKDs

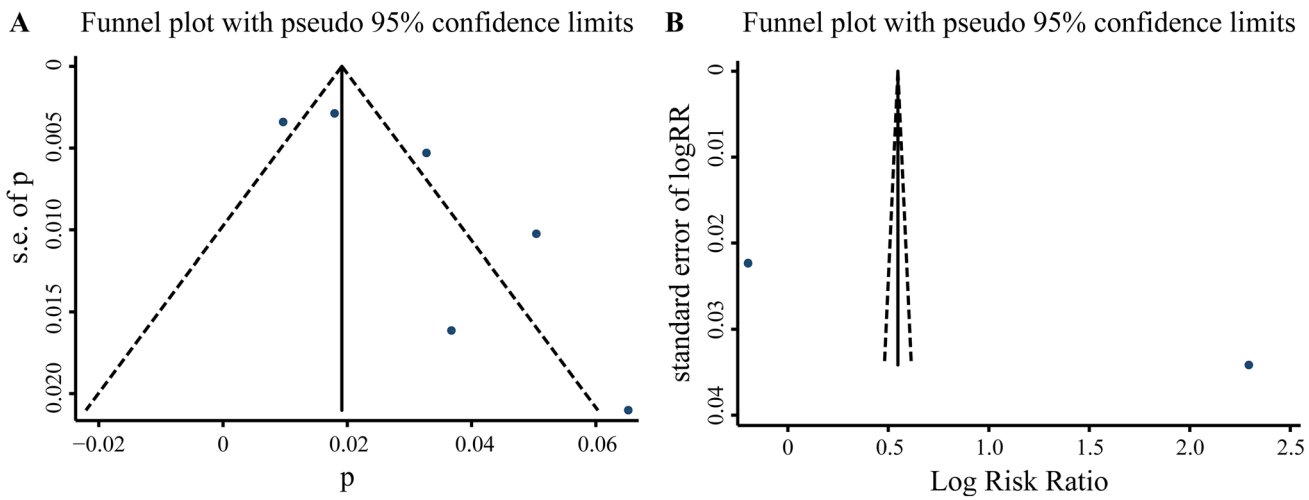

Fig. 3 Funnel plots for assessing publication bias. **a** Rate of malignancy, and **b** risk of all malignancy and melanoma

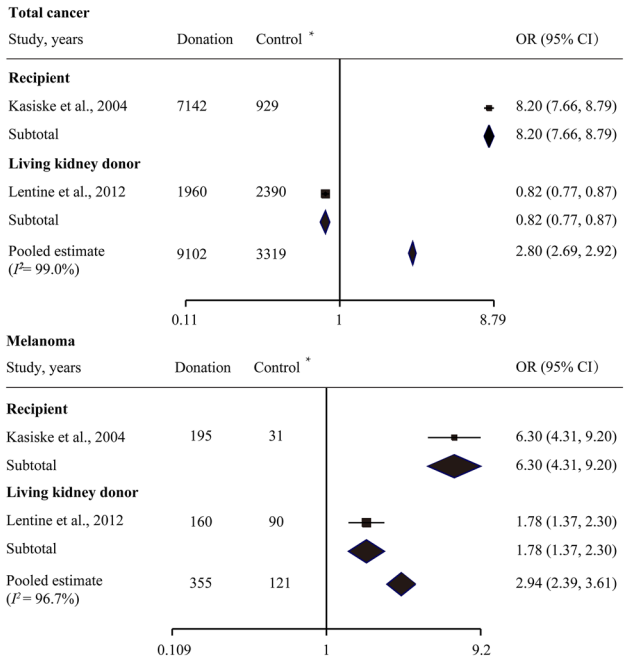

Fig. 5 Risk of all cancer and melanoma at least 5 years after donation (Rate per 100,000 person-years). *The control was defined as the general US population in Kasiske et al. (2004), and age- and sex-matched nondonor in Lentine et al. (2012). *OR*, odds radio

and recipients. However, these finding are based on limited access to trial results from publicly available source. Furthermore, some results are derived from a relatively small number of events, resulting in OR that could be affected by small changes in the classification of events, such as included types of cancer and sample size of each study.

Cancer in recipients

Although we did not have access to the adequate source data to construct a composite outcome that indicates the risk for various malignancies after donation, cancer is the one of the most common causes of death in renal transplant recipients (Howard et al. 2001). It is well-recognized that the development of post-transplant cancer is a complication of kidney transplantation mainly due to immunosuppressive therapy (Rostami et al. 2011). Immunotherapeutics that promote effector T cell responses have the potential to eliminate tumors when used in a therapeutic setting. There is growing evidence that long-term renal transplant survivors with immunotherapeutics are at an increased risk for cancer (Peddi et al. 1998). One study reported that organ transplant recipients are at high risk for post-transplant lymphoma (Opelz and Dohler 2004). Kidney transplantation increase risk for cancer of the genitourinary system by the odds ratio of 7.3 in males and 11.2 in females (Schmidt et al. 1995).

Compared with the general population, the rates for most malignancies are higher in patients after kidney transplantation. In the present study, recipient group showed the odds ratio of 6.3 for melanoma. Similar results emerged after comparing incidence of malignancies in patients on the waiting list and after kidney transplantation (Kasiske et al. 2004). Skin tumors, especially Kaposi's sarcoma and non-melanoma skin malignancies, were highly prevalent with up to 20-fold increase in recipients than the general population (Moray et al. 2004; Strauss and Thomas 2010; Yan et al. 2014). In observational studies, both kidney recipients and patients on the waiting list showed increased risk of the above-mentioned tumors.

Generally, the cumulative incidence of cancer in recipients increased noticeably in the second and third post-transplantation decades and the overall rates were currently raised with period after post-transplantation, from 1.8% at 5 years to 25.6% at 25 years (Arichi et al. 2008). A higher estimated incidence rate of cancer (3000 per 100,000) emerged in recipients in our study than the global estimated incidence rate of cancer for 182 per 100,000 reported in 2014 (Bernard 2014). Thus, transplant-related malignancies in the organ-recipient population have become a major contributor to morbidity and mortality in long-term studies of kidney transplantation. Most often develop de novo or recurrent cancer in the immunosuppressed recipients after transplantation (Mazuecos et al. 2009). Although the increased risk for cancer in kidney recipients has long been established, a similarly increased risk for cancer in LKDs is a surprisingly novel finding.

Risk of cancer for living kidney donors

Until now, de novo development of cancer in the solitary remnant kidney and elsewhere after donation remains controversial (Gupta et al. 2004). Here we show that, as compared with nondonors, donors were associated with a significant increase in the risk of melanoma. The different trends appeared in the risk of total cancer and melanoma for LKDs probably due to selected controls. In Fig. 5, recipients were compared with the general US population and LKDs vs. nondonors who passed selection criteria for living kidney transplantation. In fact, general population included a large proportion of individuals with chronic disease and other health-related conditions that might be associated with an increased risk of cancer. Therefore, the risk of cancer is more likely underestimated when LKDs are compared with the general populations. Of the donors, about 60% rated their physical and mental health higher than average for their age–gender peers in the USA general population (Ibrahim et al. 2009). That means the risk of total cancer and melanoma in LKDs were underestimated again. Thus, a higher estimated incidence rate of cancer for 3100 per 100,000

was found in LKDs than the global estimated incidence rate of cancer in 2014 (Bernard 2014). The mechanism for the apparent increase of cancer in LKDs associated with unilateral nephrectomy remains uncertain. One potential contributing factor may be attributed to the persistent activation of renin–angiotensin system, hemodynamic disturbance and fluid overload in the residual kidney (Stocks et al. 2012). LKDs might have impaired glomerular filtration rate in short-term after donation, followed by albuminuria and end-stage renal disease as long-term outcomes (Gossmann et al. 2005; Hew et al. 2014; Li et al. 2016). Previously, we have performed a series of studies using uninephrectomized rats to show uninephrectomy-induced renal carcinogenesis under metabolic disorders of insulin resistance and renal dysfunction (Sui et al. 2010, 2009, 2007; Yang et al. 2009b; Zhao et al. 2008, 2011). The uninephrectomy-induced renal carcinogenesis and metabolic disorders might be associated with cross-talks of persistent RAS activation with disturbed insulin-like growth factor-1 and adenosine 5′-monophosphate-activated protein kinase signaling pathways (Yang et al. 2016, 2017). Indeed, RAS blockade protects against cancer, renal failure and death in systemic review and meta-analysis (Shen et al. 2016a, b). Alternatively, albuminuria and proteinuria might increase the risk of cancer in LKDs and patients with type 2 diabetes. (Li et al. 2016; Yang et al. 2009a).

Our previous studies have found the important role of RAS and lipid metabolism in the development of cancer in uninephrectomized rats and type 2 diabetes patients usually accompanied by immune disorders (Yang et al. 2009a, b). It is well-established that adaptive immunity can restrain tumor growth, in particular, IFN-γ-secreting T cells. The induction of protective antitumor immunity is compromised by innate immunosuppressive mechanisms and regulatory cells that often dominate the tumor microenvironment (Butt and Mills 2014). However, immune escape and immune suppression are also evolved in tumor growth through the induction or recruitment of regulatory cells and the production of molecules that suppress antitumor effector T cell responses (Byrne et al. 2011). Presence of hypertension, obesity and inflammatory mediators increased over time after transplantation (Kasiske et al. 2015). These findings could provide further support for the similar cancer risks in both LKDs and kidney recipients as long as disorders of metabolic and immunologic homeostasis are concerned.

Better living donation

Monitoring the short- and long-term health of LKDs remains critically important to the continued success of living donation (Davis 2009; Schold et al. 2013; Srinivas and Poggio 2012). Further study of cancer after kidney donation and transplantation is warranted to ensure that evaluation, selection, and long-term follow-up outcomes support overall good health of the donors (Lentine et al. 2012). We must encourage financing studies that follow large diverse cohorts of LKDs over their entire lifetime to detect key characteristics that influence outcomes. As follow-up of LKDs in general is limited in scope, duration, completeness, definition of control groups, different surgical techniques (Lentine and Patel 2012), additional methods for quantifying risk of cancer among diverse LKDs are urgently needed.

Acknowledgements The authors thank all the participants for their contribution to this study. The authors also thank the eight authors of included studies that generously confirmed and provided information and performed additional analyses for this study. This work was supported by grants from the National Natural Science Foundation of China (81270934, 81471054) and the Natural Science Foundation of Guangxi (2016GXNSFBA380009).

Author contributions MW composed manuscript, checked results, and drew table and figures. HZ wrote the first draft of manuscript and performed statistical analyses. DZ and YCQ performed literature searching. YHP provided administrative help. YCW extracted information. HLZ designed the project and revised the manuscript.

Funding This study was funded by the National Natural Science Foundation of China (81270934, 81471054) and the Natural Science Foundation of Guangxi (2016GXNSFBA380009).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocols conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee Board of Guilin Medical University (GLMC20120308HL).

Informed consent Informed consent was obtained from all individual participants included in the study.

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