Renal Replacement Therapy

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Complications associated with kidney transplantation, causes of graft failure and mortality following kidney transplantation in patients with systemic lupus erythematosus: a meta-analysis

Xin Li[1†], Chun Xiang Cao[2†] and Jian Chen[3*]

Abstract

Introduction Despite improvement in the management of systemic lupus erythematosus (SLE) during the past two decades, 10–22% of patients with lupus nephritis (LN) will progress to end-stage renal disease (ESRD). Kidney transplantation is among the possible treatment for patients with SLE progressing to ESRD. However, the issue with kidney transplantation in patients with SLE is controversial. In this analysis, we aimed to compare the complications associated with kidney transplantation, causes of graft failure and causes of mortality following kidney transplantation in patients with SLE with ESRD.

Methods The sources of data included http://www.ClinicalTrials.gov, EMBASE, MEDLINE, Google Scholar, Web of Science and the Cochrane database. Revman software version 5.4 was used for the data analysis whereby risk ratio (RR) with 95% confidence intervals (CI) were used to represent data following analysis. In addition, the Q statistic test and the I^2 statistic test were used to assess heterogeneity. A random effect statistical model was used and a subgroup outcome with a *P*-value less than 0.05 was considered statistically significant.

Results A total number of 149,330 participants enrolled between the years 1968 and 2018 were included in this analysis with 7534 participants with SLE.

Results of this analysis showed that mortality (RR 1.07, 95% CI 0.89–1.29; $P=0.45$), graft failure (RR 1.22, 95% CI 0.99–1.55; $P=0.07$) and delayed graft function (RR 1.01, 95% CI 0.44–2.34; $P=0.98$) were not significantly higher in renal transplant patients with SLE versus a control group. When the causes of graft failure were analysed in renal transplant patients with SLE versus without SLE, acute graft rejection (RR 1.20, 95% CI 0.98–1.47; $P=0.07$), chronic graft rejection (RR 0.76, 95% CI 0.57–1.03; $P=0.08$), graft thrombosis (RR 1.47, 95% CI 0.83–2.63; $P=0.19$), recurrence of disease (RR 3.08, 95% CI 1.00–9.47; $P=0.05$) and chronic allograft nephropathy (RR 1.08, 95% CI 0.60–1.95; $P=0.80$) were also not significantly higher in patients with SLE. On the basis of the analysis, mortality from any cardiac cause (RR 0.82, 95% CI 0.67–1.01; $P=0.06$), sepsis (RR 1.19, 95% CI 0.93–1.53; $P=0.17$), malignancy (RR 0.79, 95% CI 0.51–1.24;

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P = 0.31) and cerebrovascular attack (RR 0.76, 95% CI 0.44–1.30; *P* = 0.31) were not significantly different in kidney transplantation patients with versus without SLE.

Conclusions Complications associated with kidney transplantation including mortality, graft failure and delayed graft function were not significantly higher in patients with SLE when compared with a control group. The causes of graft failure and mortality after kidney transplantation were also comparable in both groups. Therefore, kidney transplantation represents a promising treatment in patients with SLE with ESRD.

Keywords Kidney transplantation, Allograft failure, Mortality, Systemic lupus erythematosus, Lupus nephritis, Complications, End-stage renal disease

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting mostly women of child-bearing ages, with almost ten women patients for every man who has been affected by the disease [1]. The incidence of SLE has increased in recent years, with incidence ranging between 0.3 and 31.5 cases per 100,000 individuals yearly, and the global adjusted prevalence rates could reach or even exceed 50–100 per 100,000 adults [2]. Lupus nephritis (LN) [3] occurs when the kidneys are affected due to SLE, and scientific research has shown that LN is considered a major cause of morbidity in patients with SLE [4]. Despite improvement in the management of SLE during the past two decades, 10–22% of patients with LN will progress to end-stage renal disease (ESRD) [5]. Recently, kidney transplantation has become a promising possible treatment for patients with SLE progressing to ESRD [6].

During the past, a high mortality rate was observed among patients with SLE following the initiation of hemodialysis for ESRD [7]. Due to this reason and because of its association with a poor prognosis, SLE was once considered a contraindicated factor for renal transplantation [8, 9]. At that time, since there was a limited number of comparative studies with non-SLE participants, several studies attempted to characterise negative factors in patients with LN who opted for kidney transplantation as a treatment strategy. There was also a common belief that patients with SLE could present with a high flare-up of disease after kidney transplantation, and therefore kidney transplantation was not recommended for patients with SLE. However, later on, the Advisory Committee to the Renal Transplant Registry reported comparable outcomes among 56 patients with SLE who had undergone 60 renal transplantations at 36 institutions, and therefore kidney transplantation became an acceptable treatment strategy for patients with SLE with ESRD [10, 11].

Nevertheless, the issue with kidney transplantation in patients with SLE is still controversial. Findings of the European Renal Association (ERA) Registry showed that the prognosis of patients with SLE receiving kidney transplantation was worse when compared with patients without SLE [12]. However, a case–control study from a single centre showed that compared with matched cohorts, patients with SLE who underwent kidney transplantation were inferior and had satisfactory graft survival rate with similar mortality rates [13]. In a single Latin American transplant centre experience with Hispanic participants, the patients' survival, graft survival and incidence of graft rejection were similar compared with a control group [14]. In contrast, a retrospective analysis using data from the US Renal Data System (USRDS) and United Network for Organ Sharing (UNOS) databases showed renal transplantation in patients with SLE to be associated with worse allograft and survival rate when compared with a control group [15].

This controversial issue about kidney transplantation in patients with SLE has also been observed among different ethnicities. For example, a study showed a higher number of African patients with SLE to develop rejection and recurrence of SLE compared with Hispanic and Caucasian Americans following renal transplantation [16]. In addition, African Americans with SLE had higher prevalence for graft failure, which could explain a poor prognosis following kidney transplantation [16]. In contrast, a Korean study showed kidney transplantation to be associated with similar outcomes in patients with SLE versus without SLE [17].

Therefore, this controversial issue based on the complications associated with kidney transplantation in patients with SLE has yet to be solved. Such controversial issues might be solved through meta-analyses which combine together all published data from studies whether supporting or against kidney transplantation in patients with SLE. Hence, in this analysis, we aimed to compare the complications associated with kidney transplantation, causes of graft failure and causes of mortality following kidney transplantation in patients with SLE.

Methods

Data sources

The sources of data included http://www.ClinicalTrials.gov, EMBASE (www.sciencedirect.com), MEDLINE including Pubmed as a subset, Google Scholar, Web of Science and Cochrane databases. It is to be noted that reference lists of suitable publications were also checked for any relevant studies.

Search strategies

During this search process, the following search terms were used:

(a) Systemic lupus erythematosus and kidney transplantation;
(b) Systemic lupus erythematosus and end-stage kidney disease;
(c) SLE and kidney transplantation;
(d) Lupus nephritis and kidney transplantation;
(e) Systemic lupus erythematosus and kidney replacement therapy;
(f) Systemic lupus erythematosus and kidney transplantation and complications;
(g) Systemic lupus erythematosus and kidney transplantation and graft failure; and
(h) Systemic lupus erythematosus and kidney transplantation and mortality.

Criteria for inclusion

The criteria for inclusion were:

(a) Studies that compared kidney transplantation outcomes in patients with SLE versus a control group;
(b) Studies that reported complications of kidney transplantation and/or causes of graft failure and/or causes of mortality after kidney transplantation;
(c) Studies which were published in English language.

Criteria for exclusion

The criteria for exclusion were:

(a) Studies that despite reporting the outcomes of renal transplantation in patients with SLE, did not have any control group for comparison;
(b) Studies that were literature or systematic reviews and meta-analyses;
(c) Studies that were repeated in electronic databases, or which were based on the same trial or cohort study.

Definitions of terms

SLE [18] is defined as a rare rheumatic inflammatory disease, which is also an autoimmune disorder most commonly manifesting among women of child-bearing age and is often associated with a higher rate of organ-based complications which are often fatal and life threatening.

Lupus nephritis [19] is defined as inflammation of the kidneys as a consequence of SLE.

Allograft failure [20] is defined as non-functioning or failure of the graft function for different reasons due to which renal replacement therapy including dialysis or re-transplantation would be required. Renal allograft biopsy is a useful tool in the presence of allograft dysfunction. This allograft biopsy is the gold standard tool for the diagnosis and prognosis as soon as vascular and surgical causes have been excluded.

Delayed graft function [21]: is defined as the need to continue dialysis during the first week after transplant due to the graft taking more time than required to start functioning.

Acute graft rejection [22] is defined as a rising serum creatinine level after having excluded other causes of graft dysfunction followed by a sudden decrease in glomerular filtration rate and kidney function.

Chronic graft rejection is defined as an increasing serum creatinine level with gradually declining kidney allograft function; it is the leading cause of late graft loss in renal transplantation.

Graft thrombosis [23]: is defined as a serious complication of kidney transplantation which might result in early allograft loss in renal transplantation due to occlusion.

Chronic allograft nephropathy [24] is defined as a histopathological diagnosis used to denote features of chronic interstitial fibrosis and tubular atrophy within the renal allograft.

The experimental group included renal transplantation patients with SLE whereas the control group included renal transplantation patients without SLE.

Data extraction and quality assessment

The authors independently extracted data from the selected studies. The abstracts and full-text articles were carefully assessed prior to data extraction. The surnames of authors, the time frame for patients' enrolment and number of participants assigned to the SLE and control group, as well as the number of events representing each outcome, were extracted. In addition, the methodological quality of the studies, information about type of study, baseline features and country where participants were enrolled, were also extracted.

All the extracted data were cross checked by all the authors. Any disagreement or any doubt which arose during this data extraction process was carefully discussed among the authors, and a final decision was made by the corresponding author.

The quality assessment of the observational studies was carried out by the Newcastle Ottawa Scale (NOS) [25].

Statistical analysis

Revman software version 5.4 was used for the data analysis, whereby risk ratio (RR) with 95% confidence intervals (CI) were used to represent the data following analysis.

In addition, the Q statistic test and the I^2 statistic test were used to assess heterogeneity. A subgroup outcome with a *P*-value less than 0.05 was considered statistically significant. Heterogeneity increased with the increasing value of I^2.

A random effect statistical model was used during statistical analysis.

Sensitivity analysis was also carried out using a method of exclusion, and publication bias was visually observed using funnel plots.

Ethical approval

This is a meta-analysis of studies which have previously been published. Hence, a consent for ethical approval or board review approval was not required for this study.

Results

Search outcomes

The Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guideline [26] was followed. On the basis of this search process through electronic databases, a total number of 1280 publications was obtained. Following a careful assessment of the titles and abstracts, a total number of 1092 publications was eliminated since they were not related to the title of this research topic; thus, 188 full-text articles were assessed for eligibility.

After a careful assessment of the 188 full-text articles, further eliminations were carried out on the basis of the inclusion and exclusion criteria:

(a) Studies that did not have a control group ($n=12$);
(b) Studies that did not report the corresponding outcomes ($n=14$); and
(c) Studies that were replicated and repeated in different search databases ($n=141$).

Finally, only 21 studies [12, 15, 17, 27–44] were selected and confirmed to be used in this analysis. Figure 1 represents the flow diagram for the study selection.

General features of the studies

Table 1 represents the main features of the included studies. A total number of 149,330 participants were included in this analysis, with 7534 participants with SLE. Patients' enrolment time period ranged from the years 1968 to 2018. Chelamcharla' study consisted of the highest number of participants with SLE, followed by Bunnapradist' study and Ward's study, as presented in Table 1. Participants were enrolled from Europe, the USA, Spain, Iran, Greece, Korea and so on.

Complications reported following kidney transplantation, aetiology of graft failure for kidney transplantation and causes of mortality after kidney transplantation

The complications following kidney transplantation which were reported in the original studies have been listed in Table 2. In addition, the causes of graft failure and the causes of mortality were also reported in Table 2.

The following complications of kidney transplantation were assessed:

(a) Mortality;
(b) Graft failure; and
(c) Delayed graft function.

The following causes of graft failure were assessed:

(a) Acute graft rejection;
(b) Chronic graft rejection;
(c) Graft thrombosis;
(d) Recurrence of disease; and
(e) Chronic allograft nephropathy.

The following causes of mortality were assessed:

(a) Cardiac death;
(b) Sepsis;
(c) Malignancy; and
(d) Cerebrovascular attack.

Mean age and percentage of female participants

Table 3 lists the mean age and the percentage of female participants in each study. The participants in the SLE group had a mean age ranging from 19.0 to 43.5 years, whereas the participants in the control group had a mean age ranging from 15.0 to 50.7 years, as presented in Table 3. The mean percentage of female participants in the SLE group ranged from 66.7% to 100% whereas for the control group it was from 32.5% to 100%. The studies by Bartoshs, Bunnapradist and Deegens did not report mean age of general participants and age of the participants in those studies were not available. The studies by Considine, Roozbeh, Naranjo and Stone did not report the percentage of female participants and that information was therefore not included in this study.

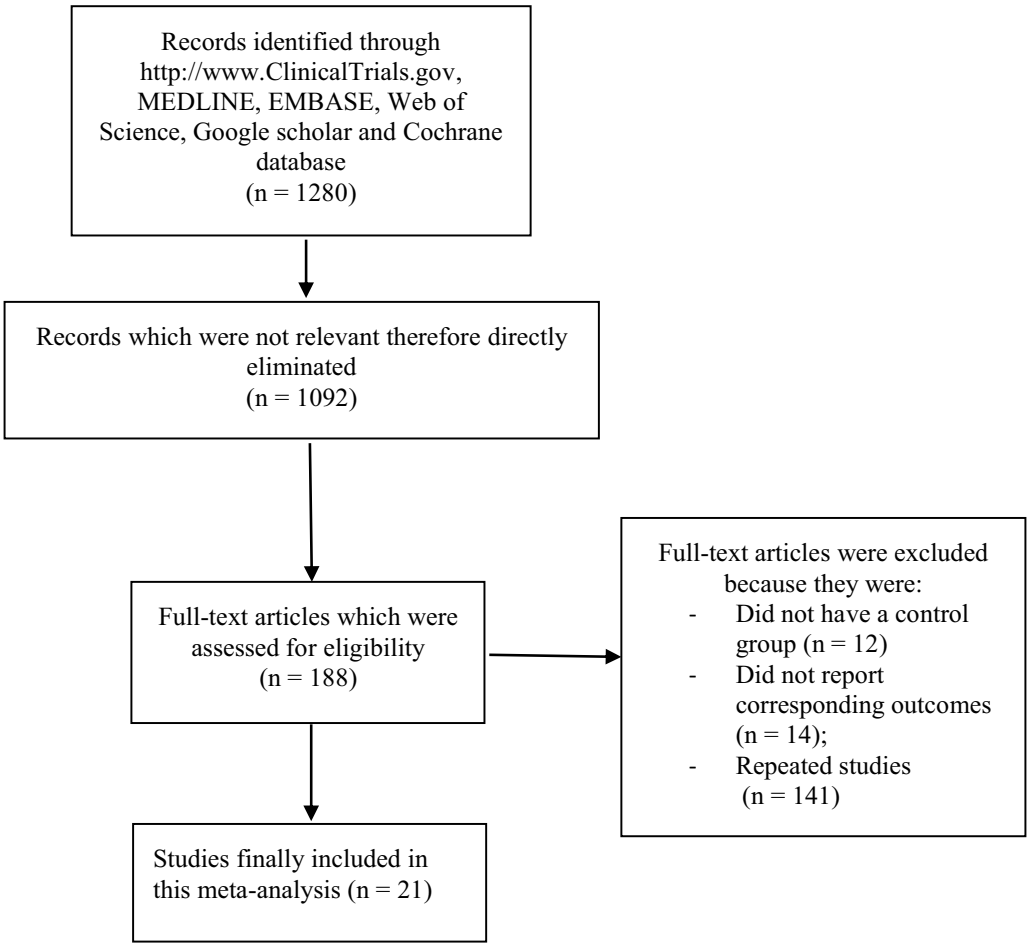

Fig. 1 Flow diagram representing the selection of study

Results of this analysis

A total number of 2250 out of 7484 patients with SLE died, whereas a total of 33,178 out of 141,744 non-SLE participants who were enrolled in this analysis died. In addition, 3480 out of 7439 participants with SLE suffered graft failure, whereas 51,737 out of 141,616 non-SLE participants suffered the same. Results of this analysis showed that mortality (RR 1.07, 95% CI 0.89–1.29; $P=0.45$; $I^2=82\%$), graft failure (RR 1.22, 95% CI 0.99–1.52; $P=0.07$; $I^2=97\%$) and delayed graft function (RR 1.01, 95% CI 0.44–2.34; $P=0.98$; $I^2=64\%$) were not significantly higher in renal transplant patients with SLE versus a control group, as shown in Fig. 2. Since a *P*-value greater than 0.05 was obtained in each subgroup analysis, respectively, the results were not statistically significant on the basis of this Q statistic test.

For the sub-groups analysing mortality, graft failure and delayed graft function, a higher I^2 value was obtained showing a highly heterogeneous result, indicating the use of a random effects statistical model during analysis.

For the causes of graft failure, 95 out of 299 participants with SLE and 178 out of 655 non-SLE participants suffered acute graft rejection, and 49 out of 202 participants with SLE and 122 out of 404 non-SLE participants suffered chronic graft rejection, while 409 out of 2114 participants with SLE and 3742 out of 16,544 non-SLE participants suffered graft thrombosis. Moreover, 15 out of 199 participants with SLE and 5 out of 354 non-SLE participants suffered recurrence of disease, and 15 out of 30 participants with SLE and 10 out of 20 non-SLE participants suffered chronic allograft nephropathy.

When the causes of graft failure were analysed in renal transplant patients with SLE versus without SLE, acute graft rejection (RR 1.20, 95% CI 0.98–1.47; $P=0.07$; $I^2=0\%$), chronic graft rejection (RR 0.76, 95% CI 0.57–1.03; $P=0.08$; $I^2=9\%$), graft thrombosis (RR 1.47, 95% CI 0.83–2.63; $P=0.19$; $I^2=48\%$), disease recurrence (RR 3.08, 95% CI 1.00–9.47; $P=0.05$; $I^2=0\%$) and chronic allograft nephropathy (RR 1.08, 95% CI 0.60–1.95; $P=0.80$; $I^2=0\%$) were not significantly higher in patients

Table 1 General features of the studies

Studies	No. of participants with SLE (*n*)	No. of participants without SLE (*n*)	Type of study	Enrolment time period + country	Type of patient
Bartosh [27]	94	470	Retrospective analysis	1987–1998 USA	Young patients with SLE
Bunnapradist [28]	1959	63,879	Observational study	1996–2000 USA	Patients with LN
Chelamcharla [15]	2886	23,393	Retrospective analysis	1990–1999 USA	Patients with SLE
Considine [29]	55	37	Retrospective review	1982–2017 Ireland	Patients with SLE
Deegens [30]	23	23	Observational study	1968–2001 Netherlands	Patients with SLE
Derner [12]	559	2795	Retrospective cohort	1992–2016 Europe	Patients with SLE
Ghafari [31]	23	60	Retrospective study	1989–2006 Iran	Patients with LN
Gipson [32]	254	7672	Observational study	1987–1997 USA	Children with LN
Lionaki [33]	26	26	Case control study	1985–2005 Greece	Patients with LN
Lopez [34]	34	34	Case control study	2010–2015 Germany	Patients with SLE
Mai [35]	457	10,097	Observational study	2000–2016 USA	Children and adolescent with SLE
Martinez [36]	21	32	Retrospective study	1980–2018 Spain	Patients with LN
Moroni [37]	33	70	Observational study	1982–2004 Italy	Patients with LN
Naranjo [38]	65	65	Retrospective case study	1996–2014 Columbia	Patients with LN
Nieto [39]	27	109	Retrospective study	2005–2013 Columbia	Patients with LN
Park [17]	19	18	Retrospective review	2005–2016 Korea	Patients with LN
Ramirez [40]	74	148	Retrospective cohort	1979–2015 Mexico	Patients with LN
Roozbeh [41]	33	33	Case–control study	1990–2004 Iran	Patients with SLE
Stone [42]	97	97	Observational study	1984–1996 San Francisco	Patients with SLE
Ward [43]	772	32,644	Observational study	1987–1994 USA	Patients with LN
Yu [44]	23	94	Retrospective study	1984–2007 USA	Patients with LN
Total number of participants (*n*)	7534	141,796			

SLE, systemic lupus erythematosus; LN, lupus nephritis

with SLE, as shown in Fig. 3. Similarly, since a *P*-value greater than 0.05 was obtained in each subgroup analysis, respectively, the results were not statistically significant on the basis of this Q statistic test.

The causes of mortality were also analysed. On the basis of the analysis, mortality from any cardiac cause (RR 0.82, 95% CI 0.67–1.01; $P=0.06$), sepsis (RR 1.19, 95% CI 0.93–1.53; $P=0.17$), malignancy (RR 0.79, 95% CI 0.51–1.24; $P=0.31$) and cerebrovascular attack (RR 0.76, 95% CI 0.44–1.30; $P=0.31$) were not significantly different in kidney transplantation patients with SLE versus without SLE, as shown in Fig. 4.

For the sub-groups analysing the causes of graft failure and causes of mortality in these patients, a low I^2 value

Table 2 Complications following kidney transplantation, aetiology of graft failure and possible causes of mortality after kidney transplantation which were reported

Studies	Complications reported following KT	Aetiology of graft failure for KT	Causes of mortality after KT
Bartosh	Overall death, re-hospitalisation after transplantation, graft failure	Thrombosis, primary non-function, acute rejection, chronic rejection, non-compliance, recurrence	Infection, malignancy, cardiopulmonary, other causes
Bunnapradist	Graft failure, patient death, delayed graft function, re-transplant graft failure, re-transplant patient death		–
Chelamcharla	Graft failure, mortality	Acute rejection, graft thrombosis, hyper-acute rejection, infection	Myocardial infarction, cardiac arrest, stroke, cardiac arrhythmia, cardiomyopathy, septicaemia, pneumonia, malignancies
Considine	Overall graft failure, overall patients mortality	Patient death, chronic allograft nephropathy, recurrence of primary disease, death with functional graft, discontinuation of immunosuppression	Malignancy
Deegens	Patient mortality, graft failure	Acute rejection, death with functional grafts, recurrent lupus nephritis, chronic rejection, thrombosis	Infection, brain haemorrhage, myocardial infarction, malignancies
Derner	Patient mortality, graft failure	–	Cardiovascular disease, myocardial infarction, heart failure, cardiac arrest, cerebrovascular events, infection, malignancy, unknown
Ghafari	Patient mortality, graft failure	Thrombosis	Cardiovascular diseases, infections, others
Gipson	Allograft failure, patient mortality, allograft rejection	–	Infection, cardiovascular disease, malignancy
Lionaki	Graft failure, patient mortality	Chronic allograft nephropathy, acute rejection, recurrence of lupus nephritis, unknown	Sepsis, cardiovascular cause, cerebrovascular cause, unknown
Lopez	Any complication, graft failure	Thrombotic microangiopathy, acute rejection	–
Mai	Mortality, graft failure	–	–
Martinez	Mortality	Allograft dysfunction, acute rejection, graft loss	Cardiovascular disease, sepsis and neoplasm
Moroni	Delayed graft function, thrombosis, mortality, graft failure	Acute rejection, chronic rejection, thrombosis	–
Naranjo	Mortality, graft dysfunction/failure	Vascular thrombosis, urological complications, acute rejection, recurrence of disease, chronic graft nephropathy, acute rejection	Infection
Nieto	Delayed function of the kidney, graft failure, mortality	Thrombosis of graft, acute rejection, death, chronic transplant nephropathy	–
Park	Graft failure, renal flare up of SLE	Acute rejection, chronic rejection	–
Ramirez	Mortality, recurrence of lupus, graft failure	Acute rejection, chronic rejection, mechanical, others	Unknown causes, malignancy, infection, vascular events including cardiovascular disease
Roozbeh	Mortality, graft failure	–	Cardiopulmonary arrest, myocardial infarction, sepsis, pulmonary oedema, hypovolemic shock, uraemia
Stone	Loss of allograft, allograft failure, mortality	Acute rejection, chronic rejection, recurrence of disease, thrombosis, death, infection	Cardiopulmonary arrest, infection, hypertensive stroke, liver failure, hypovolemic shock
Ward	Graft failure, patients mortality	–	–
Yu	Mortality, graft failure, avascular necrosis, malignancy	Acute rejection, thrombosis, chronic graft nephropathy, unknown	Infection

KT, kidney transplantation

Table 3 Mean age and percentage of female participants

Studies	Mean age (years) SLE/non-SLE	Female participants (%) SLE/non-SLE
Bartosh	–	82.0/–
Bunnapradist	–	81.9/39.7
Chelamcharla	36.6/43.5	82.0/38.0
Considine	42.5/42.5	–
Deegens	–	91.3/–
Derner	39.1/39.2	82.2/82.2
Ghafari	22.5/26.2	78.3/81.6
Gipson	19.0/15.0	79.0/40.0
Lionaki	34.4/36.9	89.0/89.0
Lopez	32.0/33.0	79.4/79.4
Mai	18.0/10.0	80.3/38.1
Martinez	39.8/46.6	66.7/43.8
Moroni	34.6/35.8	78.8/80.0
Naranjo	34.0/34.0	–
Nieto	32.5/50.7	88.8/32.5
Park	43.5/43.6	100/100
Ramirez	31.5/32.1	83.0/80.0
Roozbeh	26.8/26.7	–
Stone	35.0/38.0	–
Ward	36.1/43.9	81.1/37.1
Yu	33.7/33.7	78.3/71.3

SLE, systemic lupus erythematosus

was obtained, representing a lower heterogeneity along the sub-groups indicating, the use of a fixed effect statistical model during analysis.

The results have been summarised in Table 4.

Consistent results were obtained throughout during sensitivity analysis. Publication bias was visually represented in Figs. 5, 6 and 7.

Discussion

In this meta-analysis, we aimed to show the complications following kidney transplantation in patients with SLE. In addition, we also demonstrated the causes of mortality and the causes of graft failure in these patients. Our results showed that mortality, graft failure and delayed graft function were not significantly different with patients with SLE following kidney transplantation when compared with the control group. The causes of graft failure including acute and chronic rejection, graft thrombosis, recurrence of disease and chronic allograft nephropathy were not significantly different in the SLE group versus the control group. The causes of mortality were also similarly manifested.

Several studies have published results comparable to this meta-analysis. Experience from a single retrospective university centre including 21 participants with lupus nephritis showed that kidney transplantation might be a safe alternative for patients with SLE with end-stage renal disease, and this therapy might be associated with long-term survival in these patients with SLE [45]. In addition, in a Brazilian cohort, the authors demonstrated that lupus nephritis was the major cause of morbidity in patients with SLE, and stated that despite concerns regarding the recurrence of lupus nephritis after kidney transplantation, this procedure was an acceptable and safe alternative in patients with SLE [46]. Another case–control study based in Málaga composed of patients with SLE with chronic kidney disease undergoing renal transplantation showed no significant difference in mortality and graft failure among SLE versus control group [36]. The authors also pointed out that after the year 2000, better outcomes were obtained following kidney transplantation, which might have been due to better immunosuppressive therapies and other factors.

Our study has shown acute/chronic graft rejection, graft thrombosis, chronic allograft nephropathy and recurrence of disease to be the causes for graft failure in both participants with SLE and those without. However, another study including 361 patients with lupus nephritis has proven poor compliance and non-adherence to immunosuppressive agents to be associated with an increased rate of graft failure [47].

Immunosuppression is vital in patients with SLE and kidney transplantation. Our current analysis considered patients which were extracted from studies published between 1968 and 2018. There have been major changes related to immunosuppressive agents recently [48]. It would be good to mention that the immune system can cause damage to the kidneys through different mechanisms leading to acute kidney injury which can further aggravate to chronic kidney injury and kidney failure thus requiring the need for immunosuppressants to abate these immune processes. However, other factors including pregnancy and infertility should be taken into consideration while prescribing those immunosuppressive agents. In SLE and kidney transplantation, immunosuppressive agents' aim should be focussed on achieving disease control and minimising any treatment-related adverse drug event. Today, cyclophosphamide, an alkylating agent, and anti-CD 20 therapy including rituximab, calcineurin inhibitors, complement inhibitors, steroids and intravenous immunoglobulin, have shown good response in similar patients. In patients with SLE with kidney transplantation [49], nowadays the immunosuppression with a calcineurin inhibitor, mycophenolate mofetil and prednisolone could be more appropriate to prevent clinically overt recurrent disease. However, this might not be sufficient to prevent chronic allograft nephropathy. If a patient with SLE with

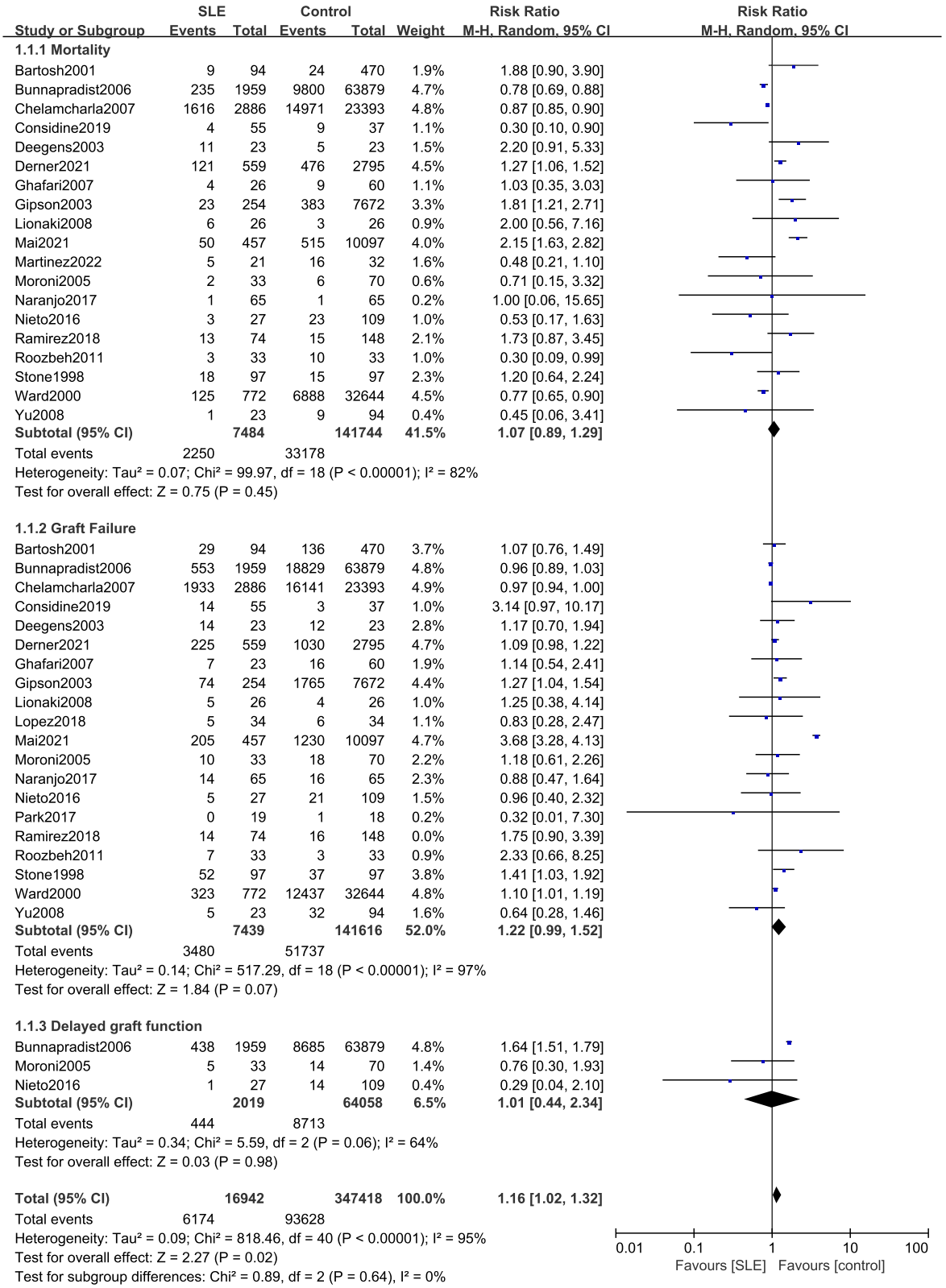

Fig. 2 Complications of kidney transplantation in patients with SLE

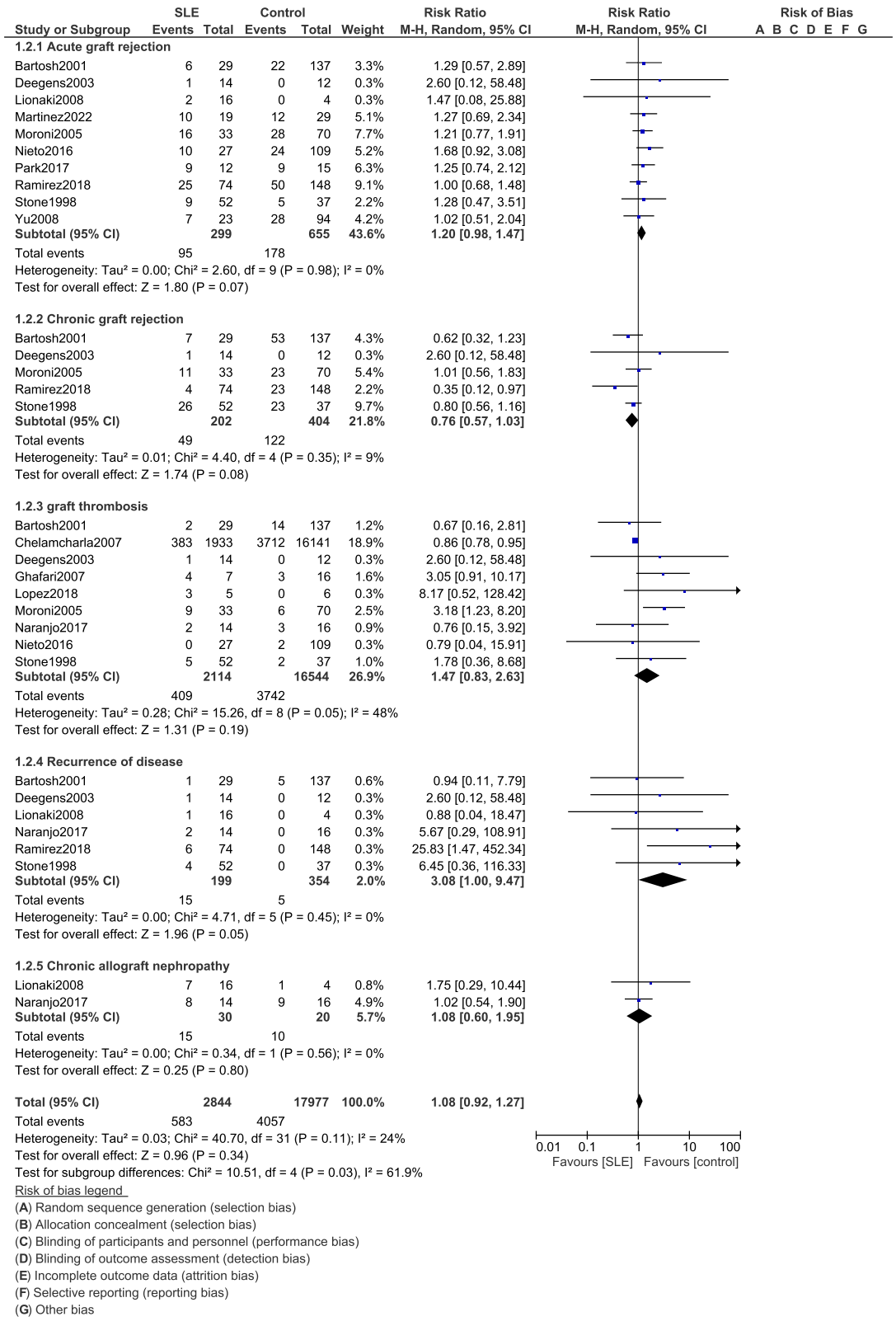

Fig. 3 Causes of graft failure in patients with SLE following kidney transplantation

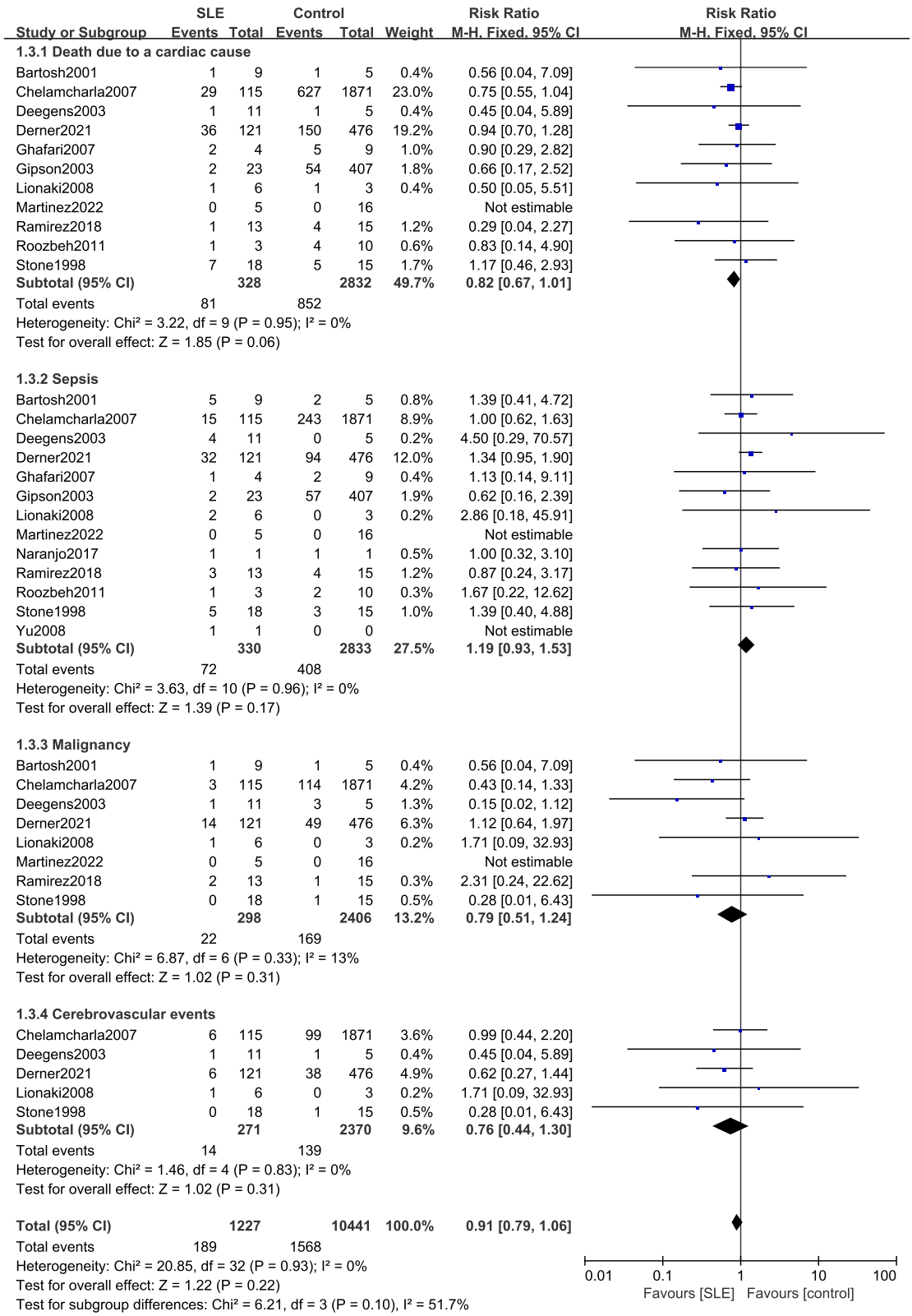

Fig. 4 Causes of mortality in patients with SLE following kidney transplantation

Table 4 Results of this analysis

Endpoints	RR with 95% CI	*P*-value	I^2 value (%)
Complications following kidney transplantation			
Mortality	1.07 [0.89–1.29]	0.45	82
Graft failure	1.22 [0.99–1.52]	0.07	97
Delayed graft function	1.01 [0.44–2.34]	0.98	64
Causes of graft failure			
Acute graft rejection	1.20 [0.98–1.47]	0.07	0
Chronic graft rejection	0.76 [0.57–1.03]	0.08	9
Graft thrombosis	1.47 [0.83–2.63]	0.19	48
Recurrence of disease	3.08 [1.00–9.47]	0.05	0
Chronic allograft nephropathy	1.08 [0.60–1.95]	0.80	0
Causes of mortality			
Cardiac cause	0.82 [0.67–1.01]	0.06	0
Sepsis	1.19 [0.93–1.53]	0.17	0
Malignancy	0.79 [0.51–1.24]	0.31	13
Cerebrovascular events	0.76 [0.44–1.30]	0.31	0

RR, risk ratios; CI, confidence intervals

kidney transplantation is suffering from resistant recurrent lupus nephritis despite the use of cyclophosphamide and mycophenolate mofetil, then rituximab in addition to corticosteroids could be beneficial. Moreover, the existing immunosuppressive regimen could be modified in the case of worsening proteinuria or severe proliferative lesions in grafts and with deterioration of renal function. In such cases, high doses of mycophenolate mofetil or intravenous cyclophosphamide accompanied by glucocorticoids for 3 days following a tapering of corticosteroid therapy could be a better option.

Renal transplantation has an excellent long-term outcome in patients with SLE, with higher rates of graft survival and lower rates of recurrent nephritis among 53 patients with SLE who underwent kidney transplantation [50]. Renal transplant has now been accepted as an alternative mode of treatment to dialysis in patients with SLE with end-stage renal disease [51]. Remaining now is to compare kidney transplantation with dialysis in patients with SLE. Future studies should focus on this particular comparison.

The strength of this study is the fact that this is the first meta-analysis to assess patients from the years 1968 to 2018 comparing kidney transplantation in patients with SLE versus without SLE. The search process was thoroughly carried out using concise key terms and the abstracts and titles were independently assessed by the authors to select relevant studies for this meta-analysis. We believe that data were carefully extracted and analysed. The Newcastle Ottawa scale was used to assess the methodological quality in each original study since all the studies which were included were observational studies.

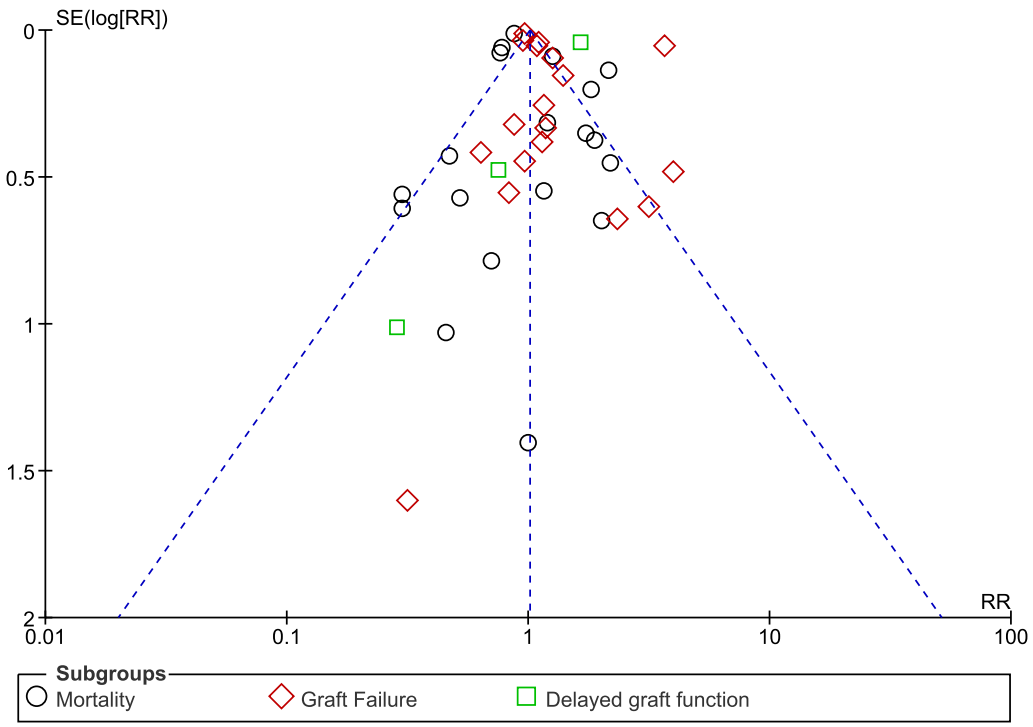

Fig. 5 Funnel plot showing publication bias (A)

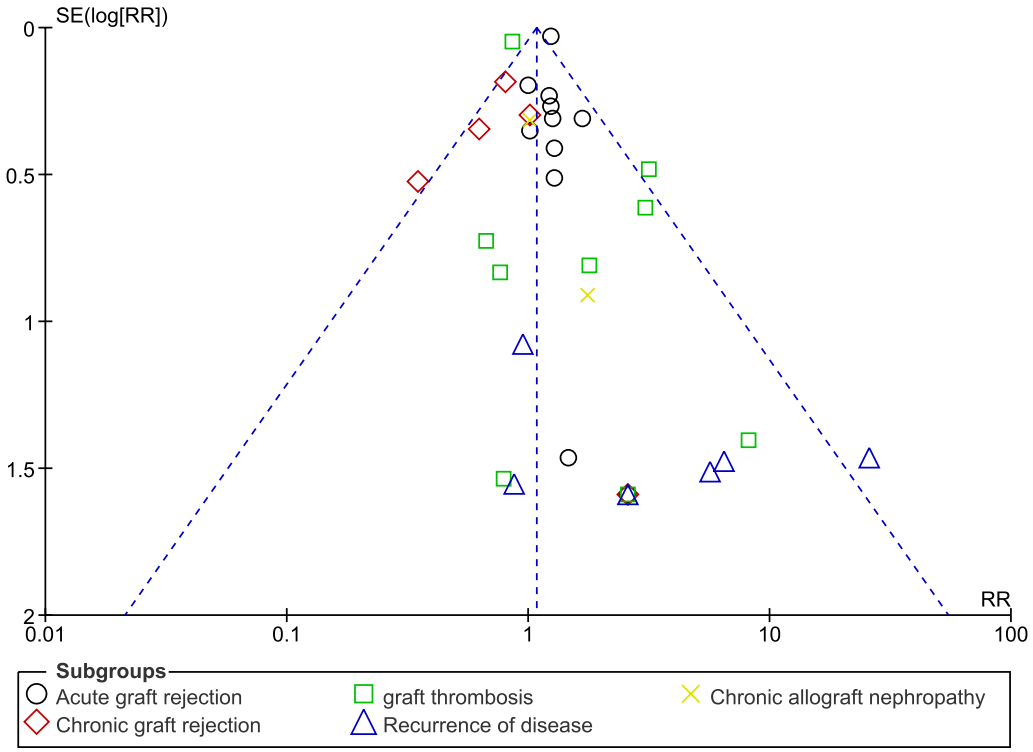

Fig. 6 Funnel plot showing publication bias (B)

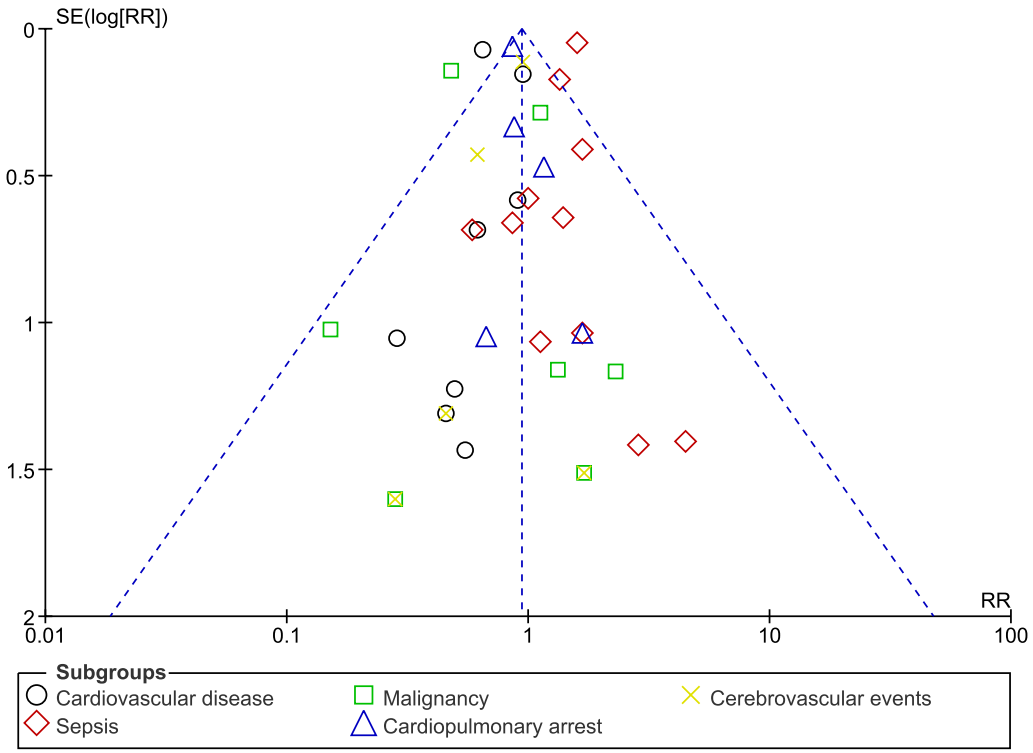

Fig. 7 Funnel plot showing publication bias (C)

Following an assessment of the methodological quality in each study, a moderate risk of bias was observed. The causes of graft failure and causes of mortality were also analysed. Therefore, this study has answered several questions which were trapped in controversies. The total number of participants was also significantly high to provide robust results. In addition, the results of this study might be vital clinically when considering renal transplant as an option in patients with SLE, who deserve the same chance of transplantation treatment when compared with other patients without SLE. Even though medical knowledge shows patients with SLE to be clinically weaker with impaired immune system when compared with non-SLE patients, renal transplantation might equally be considered in such patients.

Limitations

This study also has limitations. First, data were extracted from retrospective studies, which could result in the introduction of several types of bias contributing to higher heterogeneity. Another limitation could be the fact that the follow-up period was not considered during data analysis. In addition, one study included patients with only diabetes mellitus in the control group. Moreover, the duration of SLE and the pre-transplantation treatments were not considered during analysis. Furthermore, even though several factors including ethnicity, severity of SLE during kidney transplantation and use of immunosuppressive agents could have influenced the results, it was not possible to demonstrate the impact of these factors on the outcomes with the data available. In addition, even though allograft biopsy was used to diagnose allograft dysfunction/failure, the indication and threshold to carry out transplant biopsy have not yet been standardised. Therefore, different protocols are used by different transplantation centres, which include either protocol biopsy at specified time or indicated biopsy when allograft dysfunction has been observed. The guidelines for transplant biopsy should be more standardised. This could have an impact on the allograft failure outcomes due to a guideline which is not same everywhere. In addition, the type of dialysis prior to renal transplantation was not taken into consideration. One or two studies were also based on children/adolescents with SLE while the other studies were based on adults with SLE.

Conclusions

Complications associated with kidney transplantation including mortality, graft failure and delayed graft function were not significantly higher in patients with SLE when compared with a control group. The causes of graft failure and mortality after kidney transplantation were also comparable in both groups. Therefore, kidney transplantation represents a promising treatment in patients with SLE with ESRD.

Abbreviations

SLE	Systemic lupus erythematosus
LN	Lupus nephritis
KT	Kidney transplantation
GF	Graft failure
ESRD	End-stage renal disease

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Not applicable.

Author contributions

Authors X.L., C.X.C. and J.C. were responsible for the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the initial manuscript and revising it critically for important intellectual content. The final draft was written by authors X.L. and C.X.C. All authors gave their approval to the final manuscript as it has been written.

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Availability of data and materials

Data which have been used in this study can freely be accessed and are included in the original published articles. References of the original papers involving the data source which have been used in this paper have been listed in the main text of this current manuscript. All data are publicly available in electronic databases.

Declarations

Ethics approval and consent to participate

Ethical approval and consent to participate were not applicable for this systematic review and meta-analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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