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REVIEW

Redefining kidney transplantation procedure among adult Lupus nephritis: Expedient review approach and meta-analysis from the last couple of decades

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Summary

Background: *The actual prognostic impact of prior lupus nephritis (LN) diagnosis on end-stage kidney disease (ESKD) patients remains questionable, especially in relation to outcomes of kidney transplantation (KTx) We aim to determine the survival of the graft and recipient after the KTx procedure among patients with ESKD due to LN in comparison to non-LN.*

Methods: *This meta-analysis included retrospective studies from the last two decades, focusing on the KTx's outcomes among ESKD due to LN in comparison to non-LN. We establish the graft/recipient survival rate at different follow-up intervals as the primary outcome, and acute graft rejection and pooled graft failure rate as secondary outcomes. All analyses were performed with the random-effect model (REM) and were presented as odd ratio (OR; within 95% confidence interval (CI)). The protocol of this study was registered in PROSPERO: CRD42023394310.*

Results: *A total of 1,299 KTx (368 LN patients) from 10 studies with >10 years of follow-up were thoroughly reviewed. All checkpoints (at 1-, 5-, 10, and 15-year post-KTx) on graft survival rate demonstrated comparable outcomes in either LN or non-LN (e.g., at 10-year follow up (OR, 1.08 [0.40, 2.91]; p = 0.88). Similar findings at all checkpoints for recipient survival rate were also observed without statistically significant difference between LN and non-LN arm (e.g., at 10-year checkpoint; OR, 0.99 [0.68, 1.46]; p = 0.98). Both of our secondary analyses also presented insignificant differences (p = 0.70 and = 0.16, respectively).*

Conclusions: *Our findings suggested that prognosis of ESKD due to complicated LN is equal compared to ESKD associated with non-LN etiologies, suggesting the impact of LN as the inducing cause of ESKD on KTx outcome is relatively neglectable.*

KEY WORDS: *Graft survival; Kidney transplantation; Lupus nephritis; Systemic lupus erythematosus; Recipient survival.*

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INTRODUCTION

Advancing into 3rd decade of the new millennium, progress of organ replacement care is rapidly evolving due to its promising prospect as the next definitive treatment for degenerative and chronic diseases. *Kidney transplantation* (KTx) is currently the state-of-art procedure to attenuate symptoms of *end-stage kidney disease* (ESKD), offering nearly "*permanent*" restoration despite requiring long-term close observation on the recipients (1, 2). The etiologies of ESKD are diverse, often resulted from multisystem damage and longstanding pathologic involvement of the kidney as observed in *systemic lupus erythematosus* (SLE) (3). Immune-complex deposition plus abnormal interplay of immune cells' response in SLE may cause persistent kidney damage termed *lupus nephritis* (LN), which is clinically confirmed by laboratory and biopsy evaluation (4).

The prevalence of SLE among the global population is estimated to be between 48 to 366.6 per 100.000 individuals, with at least 50% of cases developing LN at some point, and 10-30% progressing further into ESKD (5, 6). ESKD is the most aggravating complication of LN, that primarily affects young female population (mean diagnosis age of 31.2 years old) and has a 10-20% probability to progress into ESKD within 15 years from diagnosis (7). As a kidney replacement therapy, KTx offers major prospects on treatment's effect longevity, although individuals with SLE/LN might possess higher risk for developing worse prognostic value. Although outcomes of KTx had been generally associated to other factors as ethnic/racial differences, related to the genetical susceptibility and local lifestyle, the apparent influence on KTx outcome of prior LN diagnosis, as the underlying etiology, remains questionable, specifically in the last couple of decades with some remarkable breakthroughs in transplant-molecular science (8, 9).

Regardless its distinctive autoimmune origin and subse-

quent requirement of systemic management, should the general transplant care be extended to LN-related KTx? Is the outcome of KTx recipients remarkably worse than general population, hence requiring early robust observation? Should the current research progress be focused on preventing SLE-related flare after KTx?

This review is aimed to define the prognostic aspect of kidney-transplanted individuals after ESKD following complicated LN in comparison with non-LN etiologies, by focusing on the grafts and recipients' survival plus the overall rejection status.

Materials and methods

Registration and protocol

The protocol of this review had been approved and registered in PROSPERO: International Prospective Register of Systematic Reviews under issue ID CRD42022376362.

Study design, search strategy, and eligibility criteria

We conducted this study based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) protocol to address our main clinical question on whether the KTx's outcomes among individuals with LN with ESKD are different to those of ESKD due to other etiologies. Online electronic databases e.g., *PubMed, ScienceDirect, Cochrane Library* and *ProQuest* were thoroughly searched to retrieve all eligible literatures (in English) until November 2022. We employed Boolean method to connect the keywords on abstract/title-based identification i.e. ("*Lupus Nephritis*") AND ("*Systemic Lupus Erythematosus*") AND ("*Kidney Transplantation*"). Each keywords derivatives or synonyms e.g., '*renal transplantation*' for the '*kidney transplantation*' phrase was also included through "OR" keywords in between. Duplicate documents were automatically identified by using Mendeley (version 1.19.8) software, and subsequently removed. The literatures were initially screened by two authors (S.M.W. and N.N.F.) through relevant abstract-to-full text identification, followed by group discussion with other co-authors for any identified discrepancies.

To date, most of the studies investigating KTx were designed as either cohort or case-control analysis, considering that the procedure itself is a "*personalized approach*" for both donor (either living or deceased) and recipient, therefore assumption to organize a trial-based investigation is impractical in this case. Consequently, the reviewed literatures mainly consisted of studies with aforementioned designs (cohort and/or case-control), covering an adequate period of time (≥ 10 years of coverage from either single- or multi-centre records) in a geographical region (or nation), but not restricted to specific continent or race. Studies older than a decade are included in this review since we aimed to synthesize reliable evidences from previous years (or the new millennia i.e., > year 2000), capturing how the progress had evolved over time. However, we also excluded nationwide cohort, which might solely rely on medical records and were often conducted by independent investigators (outside of the KTx-eligible centres) to reduce "*gap*" in population size and avoid potential statistical bias.

Risk of bias assessment and data extraction

The *risk-of-bias* (RoB) were collectively assessed by three authors (N.N.F., A.J.V., and S.C.S.), using a criteria appraisal tools by *Joanna Briggs Institute* (JBI), each specifically designed for estimating the bias level of both cohort and case-control studies (10, 11). Discrepancies between each interpretation were resolved through a re-assessment of respective studies in an internal discussion with the first author (S.M.W.). To systematically summarize our finding, we extracted the following information from each study: its design, region and period, diagnosis of included patients and controls, both arm's characteristics (age, donor status, pretransplant dialysis status, and pretransplant dialysis duration (in months)).

In the quantitative analysis, we applied proportional-odds model to compare each group which focused on graft and patient survival analysis as the primary outcomes. We also secondarily investigate the acute graft rejection (< 1 month) to represent short-term graft-host interaction and overall graft-failure, accumulated throughout the full-duration of cohort and case-control studies.

Effect measures and statistical analysis

Variations might be observed considering both cohort and case-control studies were included in the final analysis (as indicated by I square (I2) value). Therefore, this meta-analysis will be conducted by a *random-effect model* (REM) to reduce the heterogeneity's impact on the final estimation. The statistical analysis was performed by *Review Manager* (RevMan) 5.4 to capture our review model on Forest plots whilst estimating *odd-ratio* (OR) value in 95% confidence interval (CI; P value of < 0.05 was considered to be statistically significant). This review also attempted to conduct sub-group analysis on graft- and patient-survival based on time-point of follow-up (e.g., 1-year, 5-year, 10-year, and 15-year after KTx.). However, it should be noted that not all studies provide complete reports from the aforementioned checkpoints due to limitations in the observation period and reporting model.

We prefer OR over *risk ratio* (RR) parameter since our review also comprised of case-control study, in which the latter study model is basically tracking the exposure from cases and controls populations (rather than identifying the exposure, then analyzing the subsequent outcomes); thus OR is more preferrable in this situation (12). Inclusion of case-control study in this review is justifiable, considering KTx procedure among LN patients are relatively uncommon requiring an individualized care, hence we prioritize to synthesize as much evidence as possible. A meta-epidemiological study by *Lanza et al.* suggested that meta-analysis with both cohort and case-control studies included might possess no statistically significant difference in estimating treatment effects, which can be applied as well in our study (13). A set of sensitivity analysis was conducted as well by restricting the analysis to investigations which included only adult age populations (> 18 years old), performed the KTx from living donor source > 50.0% of the total, cohort-only analysis, and applying leave-one-out approach by removing individual studies one at a time to confirm its overall influence in pooled estimation.

Results

After thorough identification of studies from literature (Figure 1), we included 10 studies (8 retrospective cohorts) from multiple regions with at least 10 years of investigation period (Table 1).

Uncontrolled studies, nationwide investigations, studies that included general rheumatic diseases other than SLE-LNs, and those with different aims (e.g., focusing on ethnic/race influence, re-transplantation, etc.) were excluded from the final analysis (Figure 1). All patients were diagnosed with ESKD due to LN's complication following SLE diagnosis, and were compared to a control group (i.e., ESKD resulting from any other disease except for LN or SLE's kidney manifestation). All studies enlisted > 50 individuals in total, though the participant's distributions were not always in 1:1 ratio and the study population might be compared to a control group twice it size (e.g., 25 *vs.* 50 individuals) (14-23).

A total of 368 KTx procedure from LN arm were compared to 931 controls, with majority of studies consisting of females (mostly > 70.0% of the total study size), except for a cohort by *Pampa-Saico* in 2019. The mean ages (or median) of the populations were relatively homogenous, ranging from 3rd to 5th decade of life. Though variability in population's age occurred, inclusion of all the cohorts is still within our review scope since specific limitation on studied population's age was not applied. The donor status of the transplanted kidney included both living (either related or unrelated donor) and deceased donor. Five studies (*Ghafari et al.*, *Horta-Baas et al.*, *Lionaki et al.*, *Park et al.*, *Ramirez-Sandoval et al.*, and *Roozbeh et al.*) reported living donors to be > 50.0% of organ source. Pretransplant dialysis method and duration were also provided on Table 1 though significant difference on baseline characteristics was not observable. The RoB assessment results in Table 2 demonstrated the majority of confounding aspects in our studies were completely reported based on the JBI-based quality scoring.

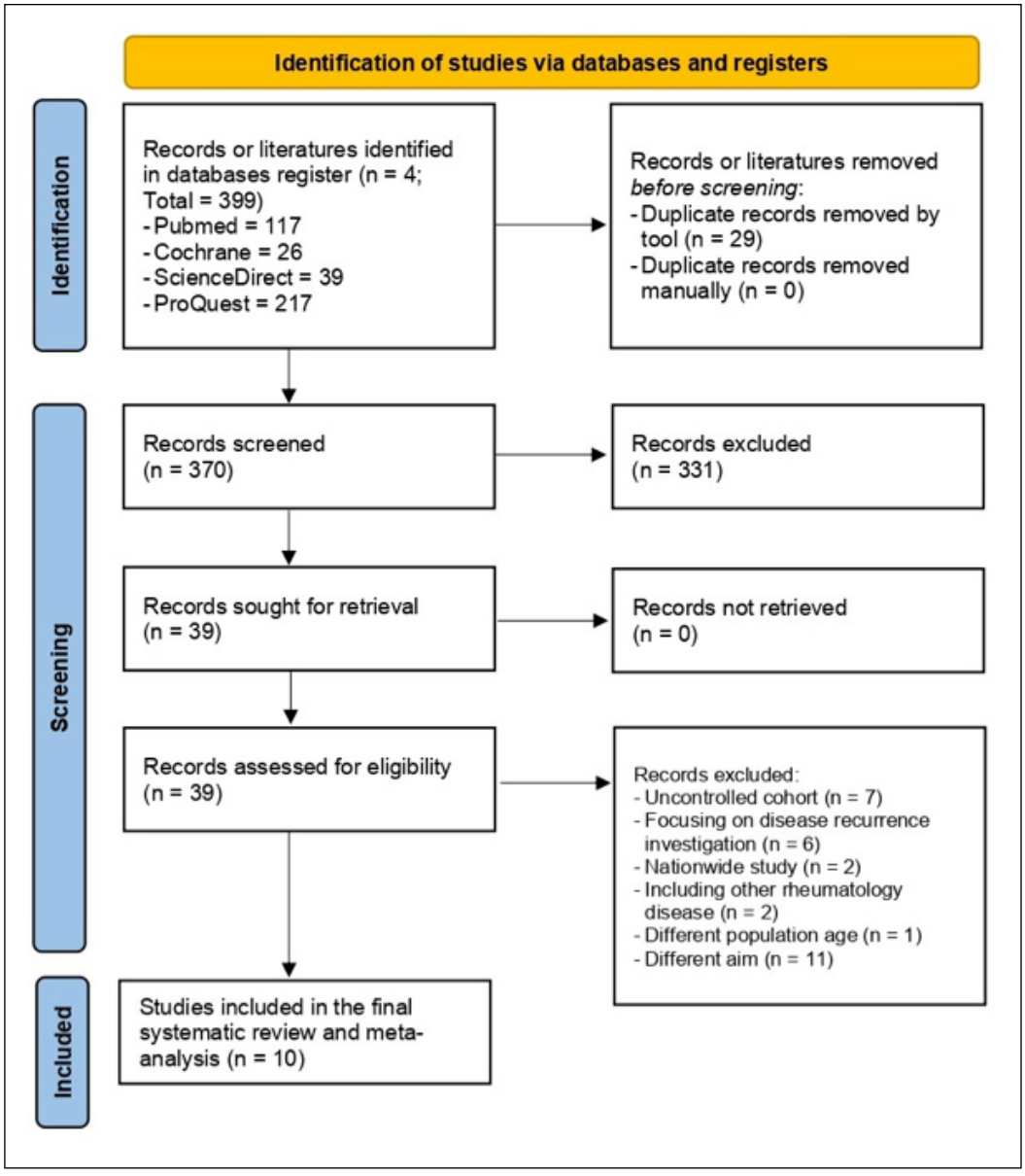


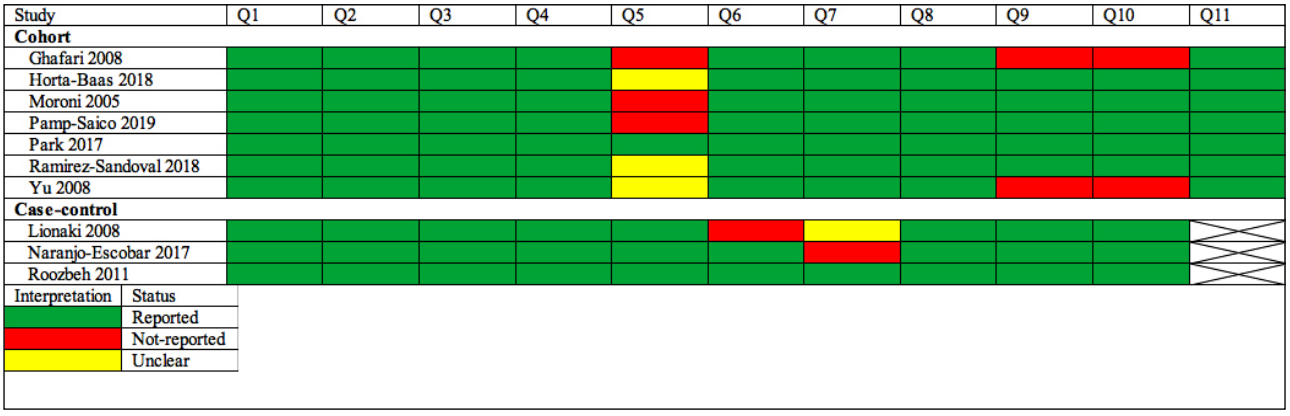
Figure 1. *Process of identifying the eligible studies by utilizing PRISMA 2020 flow diagram.*

Table 1.
Summary of the included studies of this review.

Study	Design, region, and studied period	LN/non-LN KTx characteristics						
		Study size (n) and female percentage (%)	Age (years)		Living donor (%)	Pretransplant dialysis % (HD, PD)		Pre-transplant dialysis duration (months)
			LN	non-LN		LN	non-LN	
Ghafari 2008	Retrospective cohort, Iran (SC; 1989-2006)	23(78.2)/60(81.6)	22.5 ± 16.0	26.2 ± 18.0	(77 [a]/23b)/(40 [a]/60 [b])	NA		NA
Horta-Baas 2018	Retrospective cohort, Mexico (SC; 2003-2014)	25(76.0)/50(74.0)	20.5 (10-50)		(84 [a]/8b)/(43 [a]/3 [b])	36/48/12 [c]	22/62/6 [c]	NA
Lionaki 2008	Case-control, Greece (SC; 1985-2005)	(26/26; 89.0)	34.4 ± 9.2	36.9 ± 10.5	54 [a]/54 [a]	NA		30.0 ± 29.0/42.7 ± 48.7
Moroni 2005	Retrospective cohort, Italy (SC; 1982-2004)	33(78.8)/70(80.0)	34.6 ± 9.9	35.8 ± 9.8	26/26	73/27	83/17	42.0 ± 38.4/47.6 ± 45.9
Naranjo-Escobar 2017	Case-control, Colombia (SC; 1996-2014)	65(85.0)/65(85.0)	34 (27-43)		31/25	48/15/31 [c]/6d	49/22/18 [c]/11 [d]	35 (16-62)/31 (20-49)
Pampa-Saico 2019	Retrospective cohort, Mexico (SC; 1980-2014)	47(39.5)/367(36.2)	38.5 ± 13.4	44.0 ± 14.0 *	NA	NA	30.1 ± 27.7/30.8 ± 31.5	
Park 2017	Retrospective cohort, Korea (SC 2005-2016)	(19/18; 100.0)	43.5 ± 10.2	43.6 ± 10.5	(79 [a]/5b)/(39 [a]/6 [b]) *		74/21/5d	43.3 ± 47.9/50.3 ± 43.8
Ramirez-Sandoval 2018	Retrospective cohort, USA (SC 1979-2015)	74(83.0)/148(80.0)	31.5 ± 10.2	32.1 ± 10.4	66/65	NA		NA
Roozbeh 2011	Case-control, Iran (SC; 1990-2004)	33(NA)/33(NA)	26.8 ± 8.0	26.7 ± 8.0	(18 [a]/45 [b]; both arm)	NA		24.3 ± 24.0/14.3 ± 8.9
Yu 2008	Retrospective cohort, Taiwan (SC; 1984-2007)	23(87.3)/94(81.7)	33.7 ± 10.3	33.6 ± 11.6	4/7	70/30	78/22	29.7 ± 28.4/26.1 ± 32.2

*[a] Living-related donor; [b] Living-unrelated donor; [c] Both HD-PD; [d] No pretransplant dialysis at all; * Significant baseline difference (p < 0.05).*
ESRD: End-stage renal disease; GN: Glomerulonephritis; LN: Lupus nephritis; NA: not available.

Table 2.
Risk of bias assessment by checklists provided by Joanna-Briggs Institute (10, 11).

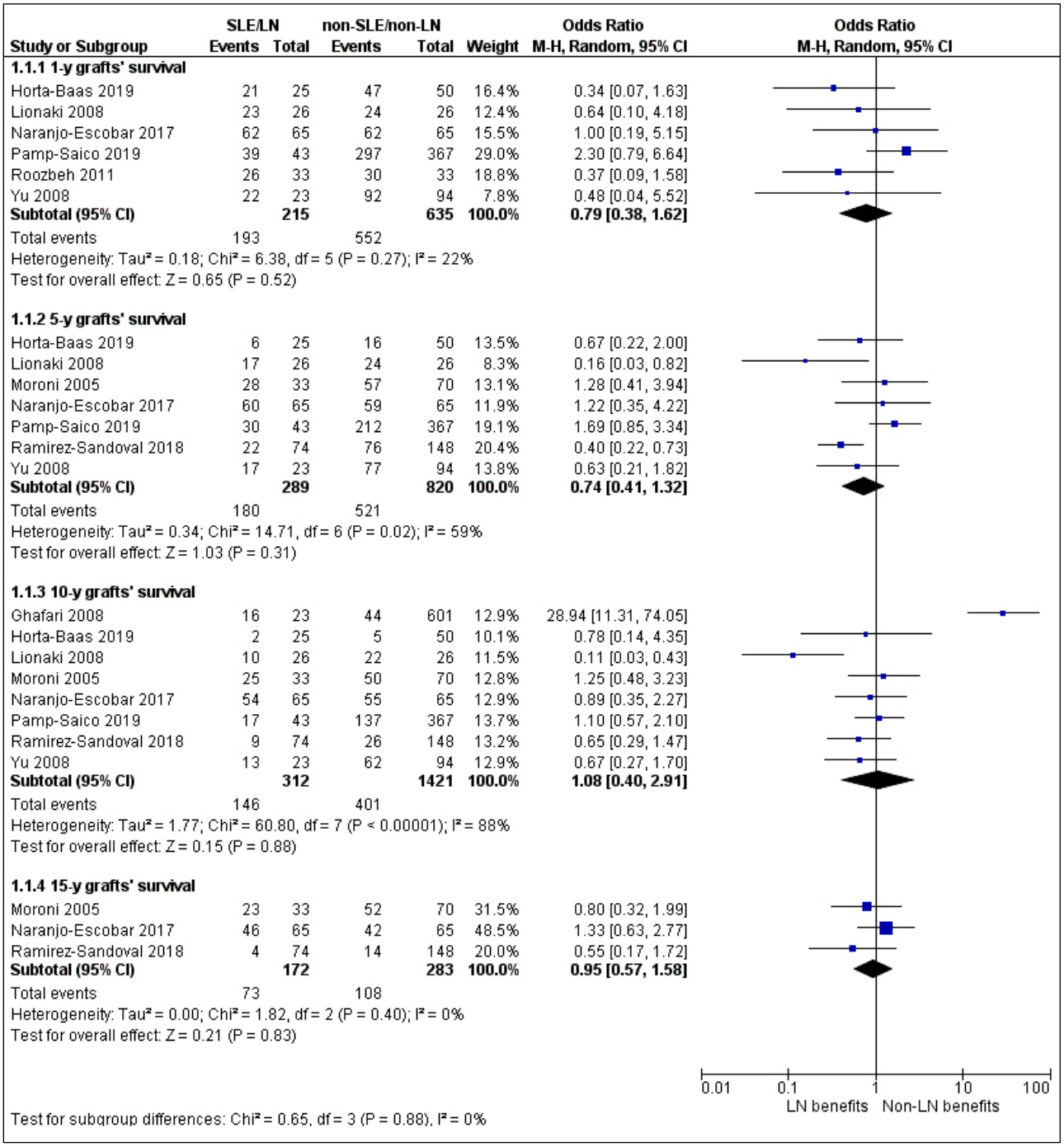


Graft and recipients' survival

Our first primary analysis on graft survival demonstrated that there was not any statistically meaningful difference between the two arms based on the modelled proportional-odd estimation (Figure 2). On sub-group analysis at 1-year post-KTx, the estimated OR value was 0.79 [0.38, 1.62] in 95% CI (p > 0.05), slightly favouring LN population though statistical difference was not significant. However, analysis at the following checkpoint (5-year post-KTx) revealed a lower OR of 0.74 [0.41, 1.32] in 95% CI (p = 0.31).

The latter results represent a lower possibility of longer surviving grafts among non-LN population despite this change does not directly translate into a significant finding upon 95% CI estimation. Further analysis on 10- and 15-year post-KTx demonstrated that the long-term follow-up of graft survival does not show any difference between the two groups. Moreover, our analysis also depicted a progressively reduced graft survival rate throughout the observation period (only 46.8% *vs.* 28.2% of the transplanted kidney will survive after 10 years in LN *vs.* non-LN etiology, respectively). Comparison of those rates with those observed at earlier checkpoints (e.g., 1st year (89.7% *vs.* 86.9; p = 0.52, and 5th year 62.3% *vs.* 63.5%; p = 0.31) revealed consistent reductions on graft survival, which even lower rates at 15th year with only 42.4% (LN) *vs.* 38.2% (non-LN); p = 0.83. Those percentages were congregated from the Figure 2 by calculating the event-to-total rate in each arm (i.e., grafts' survival rate per total KTx performed). Overall analysis on the recipient survival comparison demonstrated similar outcomes to the corresponding graft status after several years of follow-up (Figure 3). On 1-year

Figure 2.
Graft survival after 1, 5, 10, and 15 years of follow-up post-kidney transplantation.

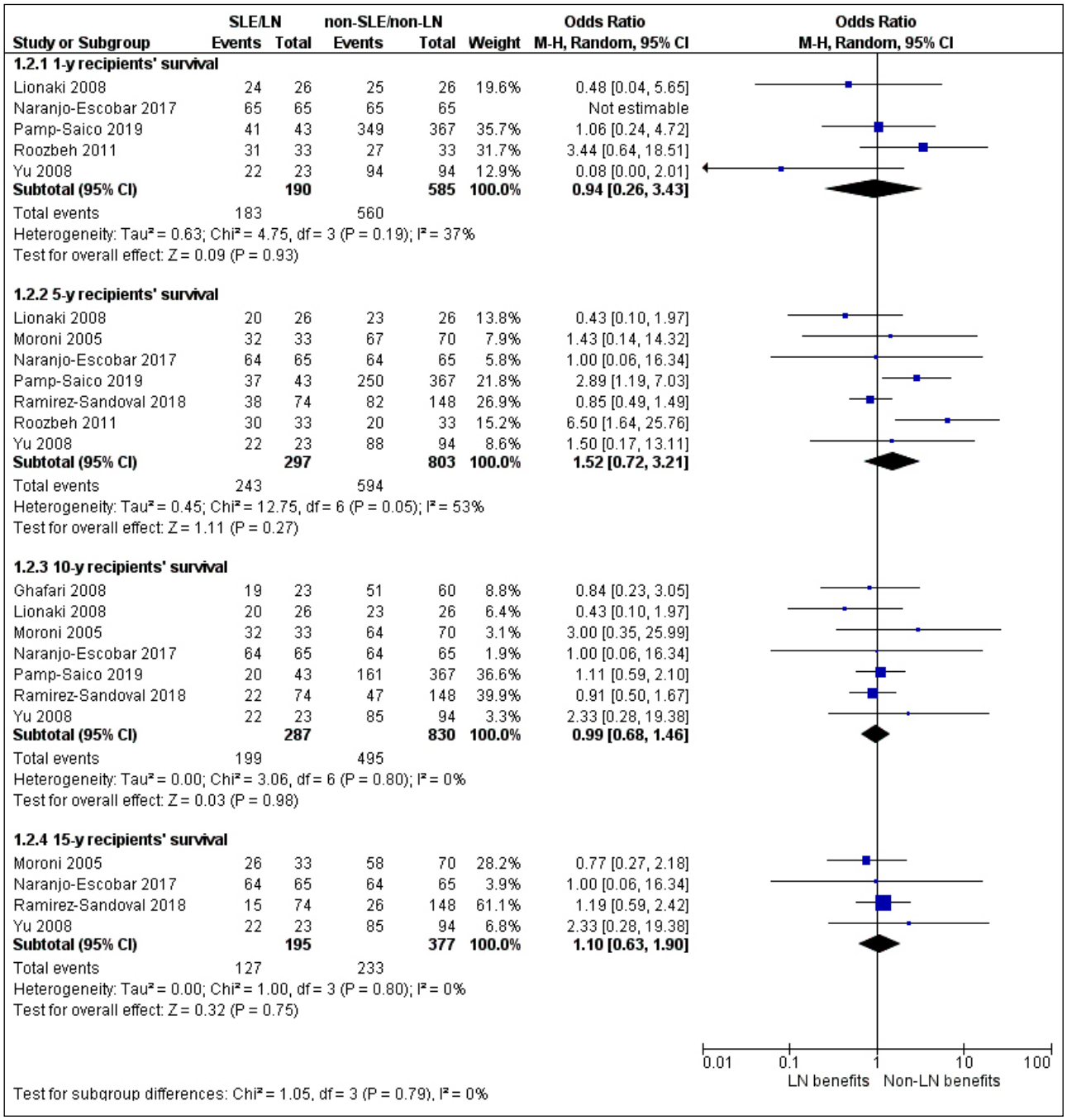


post-KTx, the estimated OR value was 0.94 [0.26, 3.43] in 95% CI ($p > 0.05$). Conversely to the previous analysis, we observe that after 5 years of KTx the OR value of recipient survival is slightly favouring non-LN population (1.52 [0.72, 3.21] in 95% CI ($p = 0.27$)). Nevertheless, this finding does not possess any significance in our estimation model though the findings are interesting to be elaborated further. Further analysis on 10- and 15-year post-KTx disclosed similar results with those observed for graft, as this analysis failed to show any difference (both $p > 0.05$). Additionally, we observed a remarkable challenge of transplantation care in relation to the progressively reduced recipient survival rate after years of observation. In comparison, the 1st year survival rate was 96.3% *vs.* 95.7% ($p = 0.93$) in LN and non-LN arm, respectively. However, the patients' survival rate was massively affected throughout the years with reduced values at 5th year (80.8% *vs.* 74.0%; $p = 0.27$), 10th year (69.3% *vs.* 59.6%; $p = 0.98$), and 15th year (65.1% *vs.* 61.8%; $p = 0.75$).

Acute and chronic graft rejection status

Secondary investigation was conducted on the recorded

Figure 3.
Recipient survival after 1, 5, 10, and 15 years of follow-up post-kidney transplantation.



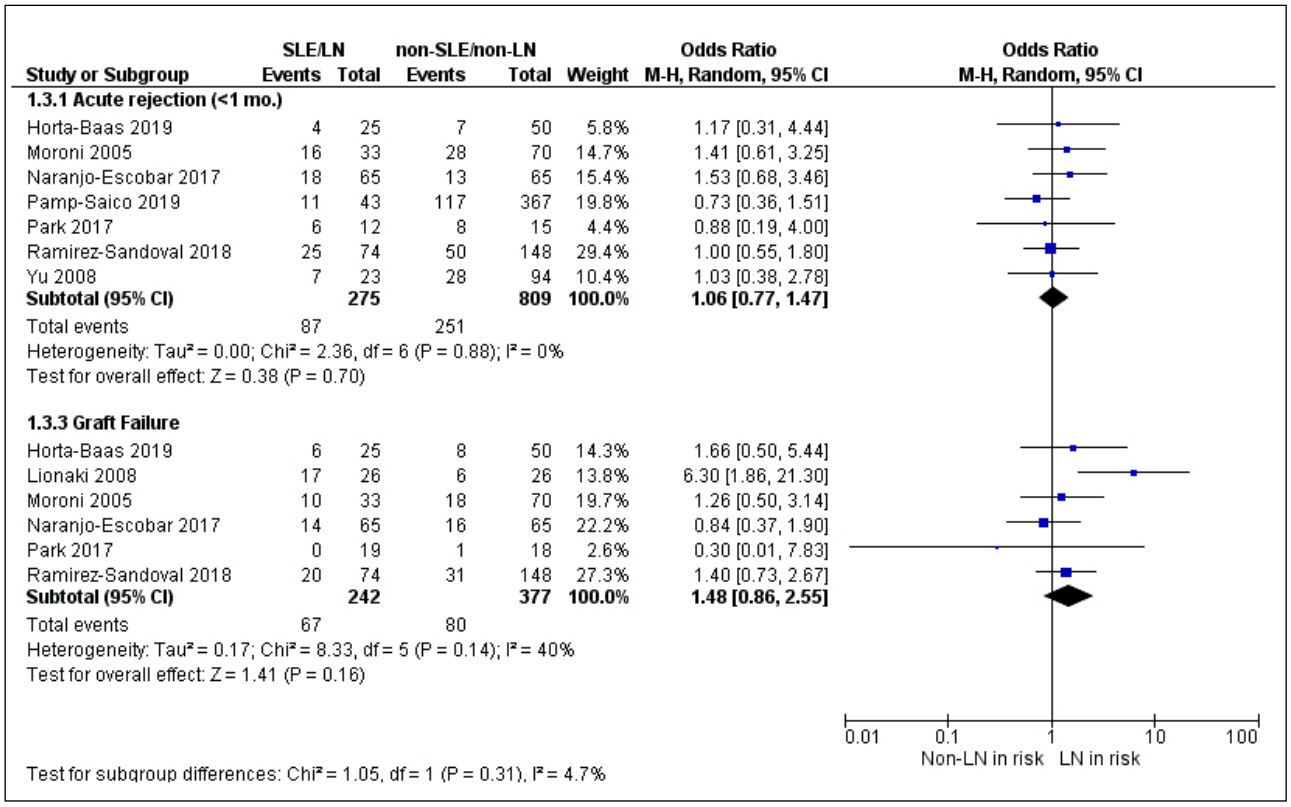
rejection rate within acute graft reaction period (< 1 month) and pooled graft failure during each complete study period (Figure 4).

The estimation of acute rejection demonstrated an OR value of 1.06 [0.77, 1.47] in 95% CI (p = 0.70). The following analysis on pooled graft failure disclosed similar outcomes which delineated insignificant difference among both groups, as represented by a OR value of 1.48 [0.86, 2.55]; 95% CI (p = 0.16). For that reason, our results concluded that the etiology of LN hardly influence the grafts' reaction rate in both short- and long-term observation.

Sensitivity analysis

The influence of living-donor graft status was not observed on all analysis, since most of the sub-group estimation remain statistically insignificant. However, at 5-year post-KTx checkpoint of grafts' survival analysis, we observe a significant finding (p < 0.05) with the OR value at 0.41 [0.24, 0.69] in 95% CI, favouring the LN arm by only including studies with > 50.0% living-donor percentage. Further sensitivity analysis on pooled rejection status also demonstrated similar outcomes to our primary report, with neither LN nor non-LN having better estimation on both acute rejection (OR 1.01 [0.61, 1.68]; p = 0.98) and graft

Figure 4.
Meta-analysis of graft's reaction on acute- and chronic-phase post-renal transplantation after maximum follow-up period in each study.

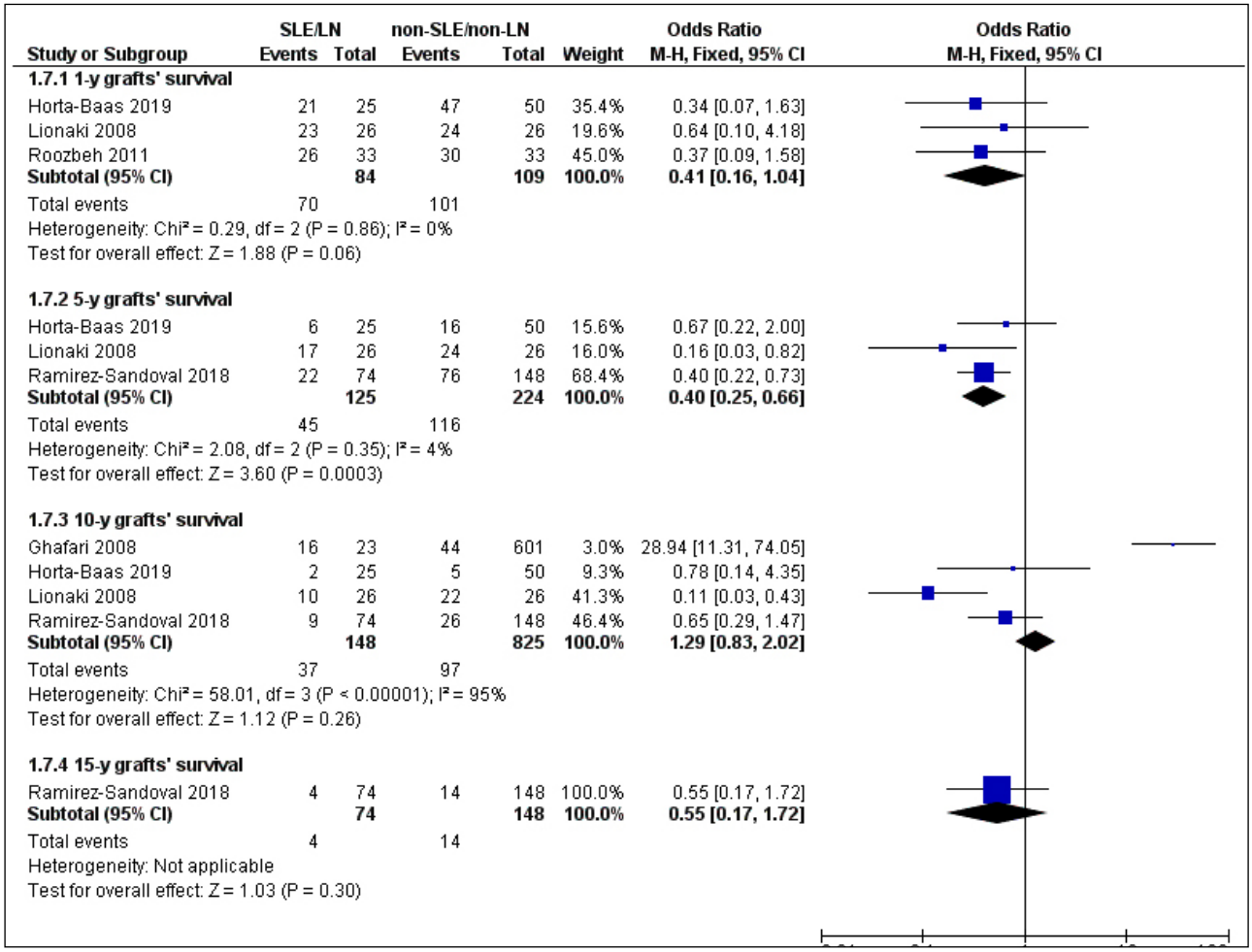


failure variable (OR 1.97 [0.84, 4.60]; p = 0.12) in 95% CI. Those sensitivity analysis draw a confounding question on LN-etiology influence; how does the population has better grafts' survival in 5-year post-KTx checkpoint, but also possess similar pooled graft failure risk?
(The Forest plot outcomes of these sensitivity analysis are available on ***supplementary data***).

Discussion

Current research in transplantation care is focused on improving the prognosis, by avoiding graft rejection or subsequent organ failure. The transplant procedure is a demanding task in modern medicine, and issues need to be addressed beforehand, as donor organ shortage and preservation, recipients' compatibility, technological limitation, and the main issue reviewed in this study that was graft and recipient survival in a special population (2, 24, 25). The role of other *renal replacement therapy* (RRT) is considered to be pivotal and often deemed to be the only regular ESKD 'treatment' option available in remote regions. Both haemodialysis and peritoneal dialysis hold much advantages in early-cost effectiveness and are relatively "*attainable*" in short-term, yet their advantages remain controversial in continuous and long-term run (26). The patient may discontinue the dialysis and proceed to KTx option since its overall outcomes are significantly better than prolonged and routine dialysis, which eventually involves pitfalls on the individuals' quality of life (1, 27). However, transplantation may involves the risk of early (< 1 month) or longer-term host-graft reaction, though it is generally accepted that the patient may achieve high survival rate in case of minimal rejection event (28). Moreover, chronic graft rejection will eventually lead into lower graft survival, creating the necessity to identify the outcome-influencing factors.
Donor transplantation procedure requires a complex collaboration to establish recipient eligibility and organ availability. Eligible recipients are placed on a "*waiting list*" and selected based on several "*qualifications*" related to life expectancy (26, 29). The statement "*different ESKD's etiology might manifest unique outcomes*" is related to the personalized medicine program, based on the theoretically reasonable idea that a pathology might induce a specific reaction in a specific patient. Though the recurrence-related concern is relatively rare among LN, it was presumed to be correlated with high-titers of anti-phospholipid antibodies, therefore the immunosuppressive options of post-KTx care may significantly reduce its impact (30, 31). The 2020 clinical guideline by *Kidney Disease Improving Global Outcomes* (KDIGO) placed the recommendation "*not excluding*" for selection of LN patients to KTx but also assessed that minimal disease activity should be achieved prior to the procedure (32). Even though the recommended waiting time to transplant among LN patients is ideally as short as possible, *European League Against Rheumatism and European Kidney Association-European Dialysis and Transplant Association* (EULAR/ERA-EDTA) suggested that the patients should achieve controllable disease for at least 3-6 months prior

Figure S1.
Graft's survival after 1, 5, 10, and 15 years of follow-up post-renal transplantation limited to studies which included 50.0% living-donor.



to be eligible for KTx (33). Considering its autoimmune course, combination of the underlying dysfunctional immune reaction plus expected host-graft' reaction could theoretically drive the prognostication of much worse outcomes of RTx for LN patients. Requirements of standardized induction and maintenance therapy for both LN and transplantation procedures is another issue to be resolved. Performing KTx on serologically active SLE might involve an higher risk of subsequent recurrence and lower graft/recipient survival, thus, apart from its complicated LN, the underlying lupus should be quiescent or stable within minimal or no immunosuppressive influence (34, 35).

The main objective of our study was to determine whether LN may significantly influence KTx outcomes, so we solely scoped the survival-related outcomes without describing much of its influencing factors from each study. To our knowledge, this is the first systematic review and meta-analysis to compare LN versus non-LN etiology among ESKD patients which received KTx. Revisiting the outcomes of this demanding procedure is unquestionably essential to establish the impact of this variable in patients who underwent KTx.

This review basically concluded that there are no significant differences ($p > 0.05$) between LN versus non-LN arm, according to proportional-odds estimation at different timing of follow-up (1-, 5-, 10-, and 15-years post-KTx). The results are relatively consistent throughout each observation period, though the latter checkpoint only involved 3-4 studies at the most. If the analysis was aimed solely to OR values, fluctuations at each checkpoint, were statistically inconsistent. Throughout each checkpoint estimation, our analysis was unable to observe even a slightest suggestion to differentiate the outcomes, excluding the hypothesis that LN might negatively influence the graft/recipient survival. This lack of differences might be originated from diverse etiologies included in non-LN population or other factors such race/ethnicity or others, although our simplified conclusion is that LN might, in fact, did not involve a worse prognostic value compared to KTx procedures in general. Several controversies around possible factors influencing graft and patients' survival after KTx had been elaborated, and yet, the most commonly described variables are the absence of induction treatment, multiple immunosuppressant medication, pre-existing comorbidities, higher body mass index, donor/recipient of Afro-American race, non-living donor, longer dialysis time, prior dialysis

Figure S2.
Meta-analysis of recipients' survival after 1, 5, 10, and 15 years of follow-up post-renal transplantation limited to studies which included 50.0% living-donor.

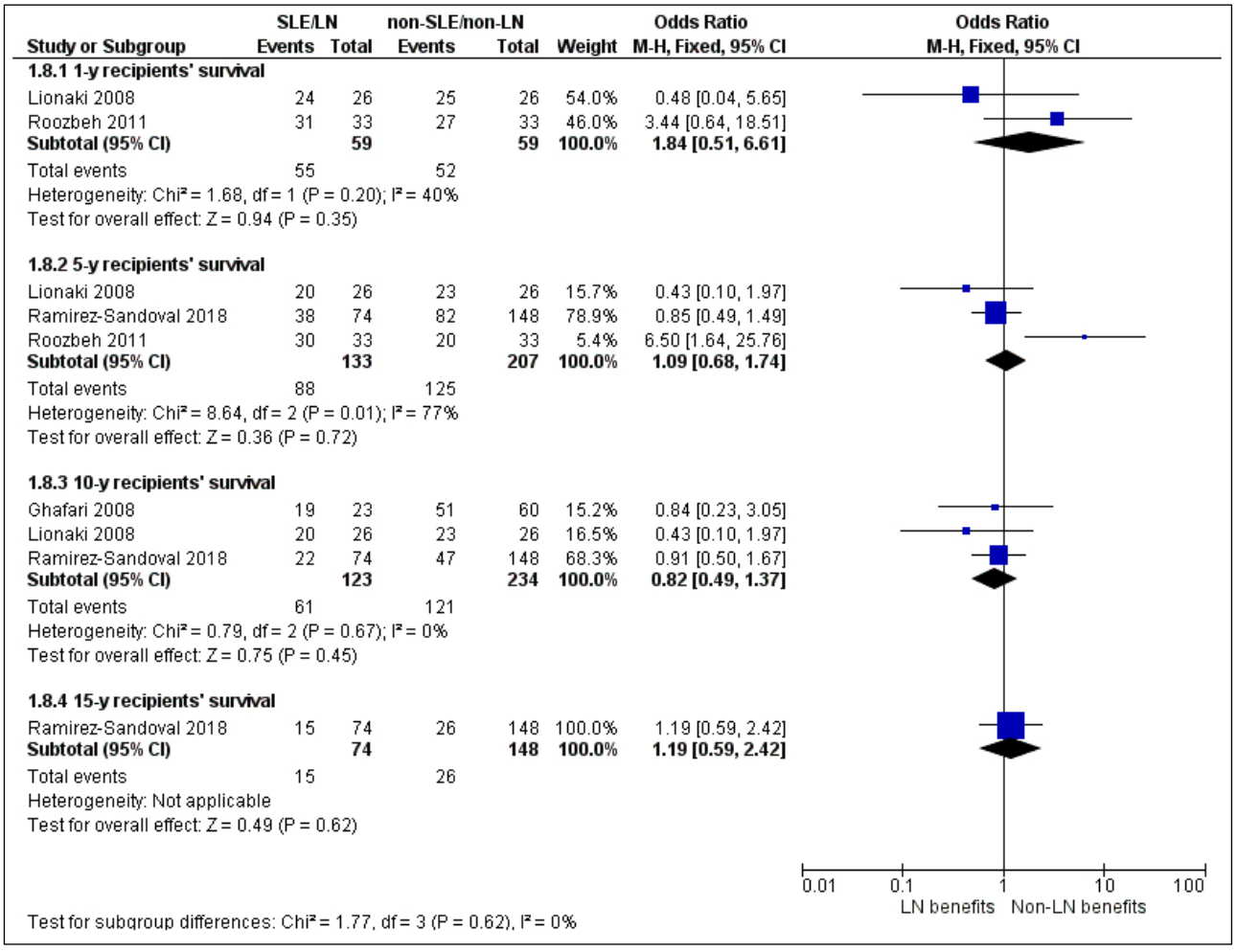
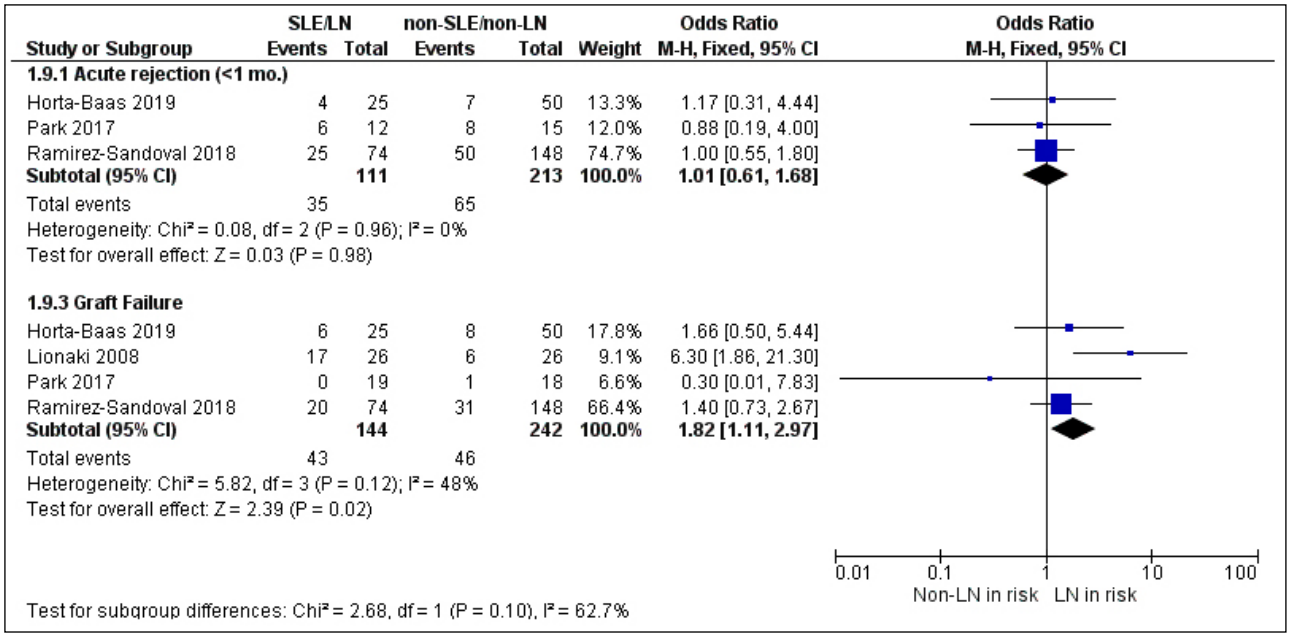


Figure S3.
Meta-analysis of graft's reaction on acute- and chronic-phase post-renal transplantation after maximum follow-up period in each study; limited to studies which included 50.0% living-donor.



method, lower adherence to treatment or routine control, and delayed graft function (36-38).

It is highly perceivable that the concomitant SLE might theoretically worsen outcome of KTx procedures considering the similarity of risk factors between graft loss and the SLE (37, 39, 40). Specific evaluation on the causes of graft loss was not performed in this study, even though chronic graft nephropathy was the most common etiology, followed by thrombotic events which are related to *anti-phospholipid antibody* (APA) positivity or pregnancy. The population age was younger in LN arm, raising the hypothesis that this might affect the outcome of the procedure. Did it favour the survival or early onset translated into more severe course of disease?

Another issue is the statistical design of the studies which estimated the prognosis by *hazard-ratio* (HR) value in Kaplan-Meier curve. Since not all studies provided those details, we adapted our approach to the proportional-odds model evaluating values corresponding to each checkpoint of follow-up, although this choice is our main limitation in providing more accurate estimation in survival rate, Our review primarily consisted of retrospective studies that lack the advantages of randomization and all the benefits of trial-investigation.

We incorporated both case-control and cohorts into the same pooling of analysis because of the scarcity of the included studies that obliged us to perform a meta-analysis of all the studies available at that point. Only 3 case-control studies (*Lionaki et al.*, *Naransjo-Escobar et al.*, and *Roozbeh et al.*) were included in the final analysis (16, 18, 22), however it should be underlined that differences in design compared to other retrospective cohorts may act as an important selection bias (originated from case-control studies) in this review (41). Nevertheless, our primary outcome was statistical confirmation of KTx outcome to justify KTx among LNs, since it might offer better quality of life or superior survival rate compared to individuals in routine dialysis schedule.

We encourage future original studies on LN-ESKD-KTx subjects to be focused on identifying factors preceding grafts loss and subsequent recipient mortality in order to evaluate not only grafts rejection rate but also the best modality of control of SLE activity and prevention of LN recurrence by managing the most appropriate immunosuppressants.

Conclusions

KTx procedure in ESKD with LN etiology is equally beneficial in short- and long-term outcomes compared to procedure in patients with non-LN etiologies since no statistically significant difference of outcomes were observed. Hence no special care was practically required on the LN population. Recommendation to perform KTx among eligible participants including individuals with SLE should be advocated considering that current transplantation care had progressed into more specific and personalized approach. Therefore, this review is expected to assist global transplant community in tailoring better strategies and preventing KTx's-related pitfall among complicated-LN patients.

References

1. Wang JH, Skeans MA, Israni AK. Current Status of Kidney Transplant Outcomes: Dying to Survive. Adv Chronic Kidney Dis 2016; 23:28

2. Chapman JR. What are the key challenges we face in kidney transplantation today? Transplant Res. 2013; 2:1-7.

3. Chan TM, Yung S, Yap DYH. A review of advances in the understanding of lupus nephritis pathogenesis as a basis for emerging therapies. F1000Res. 2020; 9:F1000 Faculty Rev-905

4. Hahn BH, McMahon M, Wilkinson A, et al. American College of Rheumatology Guidelines for Screening, Case Definition, Treatment and Management of Lupus Nephritis. Arthritis Care Res. 2012; 64:797-808.

5. Barber MRW, Drenkard C, Falasinnu T, et al. Global epidemiology of systemic lupus erythematosus. Nat Rev Rheumatol [Internet]. 2021; 17:515-32.

6. Almaani S, Meara A, Rovin BH. Update on Lupus Nephritis. Clin J Am Soc Nephrol [Internet]. 2017; 12:825-35.

7. Tektonidou MG, Dasgupta A, Ward MM. Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971-2015: A Systematic Review and Bayesian Meta-Analysis. Arthritis Rheumatol 2016; 68:1432-41.

8. Newman KL, Fedewa SA, Jacobson MH, et al. Racial/Ethnic Differences in the Association between Hospitalization and Kidney Transplantation among Waitlisted End Stage Renal Disease Patients. Transplantation. 2016; 100:2735-45.

9. Rybicka-Kozlowska E, Andreoni K, Kozlowski T. Racial differences in renal transplantation: How do we bridge the gap? Surg (United States) [Internet]. 2021; 170:333-5.

10. Joanna Briggs Institute. Checklist for Cohort Studies [Internet]. jbi.global; 2020. Available from: https://jbi.global/sites/default/files/2021-10/Checklist_for_Cohort_Studies.docx

11. Joanna Briggs Institute. Checklist for Case Control Studies [Internet]. jbi.global; 2020. Available from: https://jbi.global/sites/default/files/2021-10/Checklist_for_Case_Control_Studies.docx

12. Ranganathan P, Aggarwal R, Pramesh C. Common pitfalls in statistical analysis: Odds versus risk. Perspect Clin Res. 2015; 6:222.

13. Lanza A, Ravaud P, Riveros C, Dechartres A. Comparison of estimates between cohort and case-control studies in meta-analyses of therapeutic interventions: A meta-epidemiological study. PLoS One. 2016; 11:1-12.

14. Ghafari A, Etemadi J, Ardalan MR. Renal Transplantation in Patients With Lupus Nephritis: A Single-Center Experience. Transplant Proc. 2008; 40:143-4.

15. Horta-Baas G, Camargo-Coronel A, Miranda-Hernández DG, et al. Renal transplantation in systemic lupus erythematosus: Comparison of graft survival with other causes of end-stage renal disease. Reumatol Clin. 2019; 15:140-5.

16. Lionaki S, Kapitsinou PP, Iniotaki A, et al. Kidney transplantation in lupus patients: A case-control study from a single centre. Lupus. 2008; 17:670-5.

17. Moroni G, Tantardini F, Gallelli B, et al. The long-term prognosis of renal transplantation in patients with lupus nephritis. Am J Kidney Dis. 2005; 45:903-11.

18. Naranjo-Escobar J, Manzi E, Posada JG, et al. Kidney transplantation for end-stage renal disease in lupus nephritis, a very safe procedure: A single Latin American transplant center experience. Lupus. 2017; 26:1157-65.

19. Pampa-Saico S, Marcén-Letosa R, Fernández-Rodríguez A, et al. Kidney transplantation in systemic lupus erythematosus: Outcomes and prognosis. Med Clin 2019; 153:460-3.

20. Park H, Park WY, Kang SS, et al. Clinical Outcomes of Kidney Transplantation in Patients With Biopsy-Proven Glomerulonephritis. Transplant Proc. 2018; 50:1009-12.

21. Ramirez-Sandoval JC, Chavez-Chavez H, Wagner M, et al. Long-term survival of kidney grafts in lupus nephritis: a Mexican cohort. Lupus. 2018; 27:1303-11.

22. Roozbeh J, Eshraghian A, Raeesjalali G, et al. Outcomes of kidney transplantation in patients with systemic lupus erythematosus. Iran J Kidney Dis. 2011; 5:53-6.

23. Yu TM, Chen YH, Lan JL, et al. Renal outcome and evolution of disease activity in Chinese lupus patients after renal transplantation. Lupus. 2008; 17:687-94.

24. Kupiec-Weglinski JW. Grand Challenges in Organ Transplantation. Front Transplant. 2022; 1:1-5.

25. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21st century. Ann Transl Med. 2018; 6:409-409.

26. Kaballo MA, Canney M, O'Kelly P, et al. A comparative analysis of survival of patients on dialysis and after kidney transplantation. Clin Kidney J. 2018; 11:389-93.

27. Yngman-Uhlin P, Fogelberg A, Uhlin F. Life in standby: Hemodialysis patients' experiences of waiting for kidney transplantation. J Clin Nurs. 2016; 25:92-8.

28. Neild GH. Life expectancy with chronic kidney disease: an educational review. Pediatr Nephrol [Internet]. 2017; 32:243-8.

29. NHS Blood and Transplant. Kidney acceptance criteria Available from: https://www.odt.nhs.uk/transplantation/kidney/kidney-acceptance-criteria/#

30. Pramudya D, Hertanto DM, Pitaloka AT, Tjempakasari A, Pranawa. Lupus nephritis and kidney transplantation: past, present and future. Bali Med J. 2023; 12(2):1802-7.

31. Pattanaik D, Green J, Talwar M, Molnar M. Relapse and Outcome of Lupus Nephritis After Renal Transplantation in the Modern Immunosuppressive Era. Cureus. 2022; 14:e20863.

32. Chadban SJ, Ahn C, Axelrod DA, et al. KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. Transplantation. 2020; 104(4S1 Suppl 1):S11-S103.

33. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020; 79:S713-23.

34. Wilhelmus S, Bajema IM, Bertsias GK, et al. Lupus nephritis management guidelines compared. Nephrol Dial Transplant. 2016; 31:904-13.

35. Morales E, Galindo M, Trujillo H, Praga M. Update on Lupus Nephritis: Looking for a New Vision. Nephron. 2021; 145:1-13.

36. Rodelo J, González LA, Ustáriz J, et al. Kidney transplantation outcomes in lupus nephritis: A 37-year single-center experience from Latin America. Lupus. 2021; 30:1644-59.

37. Legendre C, Canaud G, Martinez F. Factors influencing long-term outcome after kidney transplantation. Transpl Int. 2014; 27:19-27.

38. Albuquerque BC, Salles VB, Tajra RDP, Rodrigues CEM. Outcome and Prognosis of Patients With Lupus Nephritis Submitted to Renal Transplantation. Sci Rep. 2019 Aug 12; 9(1):11611.

39. Gergianaki I, Bortoluzzi A, Bertsias G. Update on the epidemiology, risk factors, and disease outcomes of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2018; 32:188-205.

40. Nee R, Jindal RM, Little D, et al. Racial differences and income disparities are associated with poor outcomes in kidney transplant recipients with lupus nephritis. Transplantation. 2013; 95:1471-8.

41. Palumbo SA, Robishaw JD, Krasnoff J, Hennekens CH. Different Biases in Meta-Analyses of Case-Control and Cohort Studies: An Example from Genomics and Precision Medicine. Ann Epidemiol. 2021; 58:38-41.

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