

Meta-analysis on Prognostic Factors of Poor Renal Outcome in Patients with Lupus Nephritis

Erick Mendoza, M.D.*; Nikki Rillon-Tabil M.D.*; Melanie Payte, M.D.* and Sandra Navarra, M.D.*

Abstract

Background and objective: Lupus nephritis is the strongest predictor of poor outcome in systemic lupus erythematosus. Up to 60% of patients develop renal involvement with 10-20% progressing to end-stage renal disease. The objective of the meta-analysis was to determine prognostic factors of poor renal outcome in lupus nephritis patients. The findings of the study may provide a clearer indication of the likelihood of worsening state of renal function thus affect monitoring and therapeutic decisions.

Methodology: Two independent reviewers searched electronic databases from Pub Med and Science Direct. Predetermined criteria were used to include eligible studies. Pooled mean differences, odds ratios and 95% confidence intervals were computed using fixed-effect approach in Rev Man7®. Clinical, laboratory and renal biopsy prognostic factors were tested for heterogeneity and for overall effect. P-value <0.05 was considered statistically significant.

Results: Nine studies with a total 794 patients were included. Two hundred and seven had poor renal functional outcome

which included deteriorating estimated glomerular filtration rate, progression to chronic kidney disease or end-stage renal disease and ESRD-related mortality. Male gender (OR 1.83; 95% CI 1.02-3.26), hypertension (OR 1.97; 95% CI 1.02-3.81), nephrotic syndrome (OR 1.71; 95% CI 1.04-2.82) and high chronicity index on renal biopsy (OR 4.39; 95% CI 2.63-7.33) were poor prognostic factors in lupus nephritis. Systolic blood pressure and proteinuria were significantly elevated in lupus nephritis patients with poor renal outcome.

Conclusion: The odds of having poor renal prognosis was increased in the presence of hypertension, nephrotic syndrome and high chronicity index on renal biopsy. The results of the study highlight the role of aggressive control of modifiable factors like hypertension and proteinuria, and the prognostic role of a kidney biopsy to minimize irreversible kidney damage. Lupus nephritis patients with poor prognostic factors merit closer monitoring and more aggressive treatment.

Keywords: prognostic factors, lupus nephritis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune pathology with a complex set of immunologic abnormalities involving multiple mechanisms of dysregulation and diverse clinical manifestations representing the prototype of autoimmune connective tissue disease. It is often characterized by development of glomerulonephritis.^{1,2} Renal disease represents a frequent manifestation of SLE as well as the strongest determinant of poor outcome in these patients. Up to 60% of SLE patients develop renal involvement, usually within five years of disease onset.^{3,4} Of these patients, 10-20% of patients with lupus nephritis go on to develop end stage renal failure. Mortality rate is higher in patients with lupus nephritis than in those without renal disease.⁵

Most renal abnormalities commonly emerge within the first six to 36 months of diagnosis of SLE. Although an elevated plasma creatinine concentration eventually develops in approximately 30 percent of all patients with SLE, evidence of decreased renal function is an uncommon manifestation within the first few years of diagnosis. In patients with SLE, the presence of nephritis is suspected by an abnormal urinalysis and/or elevation of the serum creatinine, and the diagnosis is confirmed by histopathologic findings on renal biopsy.^{2,6}

There is a paucity of clinical trial data in lupus nephritis and the present literature lacks definite description that may determine renal functional outcome in patients with this condition. Elevated creatinine is the most frequently reported clinical predictor of progression towards end-stage renal disease (ESRD). Other clinical factors including marked proteinuria, delay between the onset of nephritis symptoms and performance of renal biopsy, young and old age, male gender, smoking and hypertension have also been observed to predict adverse renal outcome, but less consistently so.^{7,8}

*Section of Rheumatology, Clinical Immunology and Osteoporosis, Department of Medicine, University of Santo Tomas Hospital, Manila Philippines

Corresponding Author: Erick Mendoza, M.D., University of Santo Tomas Hospital, Ermita, Manila, Philippines
Email address: ericksmendoza@gmail.com

The World Health Organization (WHO) renal biopsy classification has been widely employed to date. However, prognosis based on this classification alone is highly variable and is subject to treatment response. While some investigators found that biopsy findings add important prognostic information, others concluded that histological data do not increase the predictive strength of models based exclusively on clinical and routine laboratory variables. Frequently reported histological predictors of ESRD encompass diffuse proliferative histopathology, severe active glomerular and tubulointerstitial abnormalities and their presence of chronic parenchymal injury.^{7,5}

The objective of this study is to perform a systematic literature review and meta-analysis of the association of various clinical and histopathologic factors with poor renal outcome in patients with lupus nephritis. Even though renal biopsy is readily performed in tertiary care settings, correlation of clinical, laboratory and histopathologic features would be the most effective method for monitoring lupus nephritis patients. The findings of the study may provide a clearer indication of the likelihood of progression to worse states of renal function thus affect future therapeutic decisions. Our meta-analysis is limited to clinical and histopathologic factors. Although the patients underwent standard treatment based on renal biopsy results and following American College of Rheumatology guidelines, we did not included treatment factors.

Methodology

Literature Search

A comprehensive search for analytical studies investigating the association between different prognostic factors and development of poor renal outcome was conducted by using PubMed and Science Direct. Search strategies used the following medical subject headings (MeSH): systemic lupus erythematosus, lupus nephritis, prognostic factors and poor functional renal outcome. The electronic search was supplemented by a manual review of reference lists. The search was limited to studies published in English.

Study Selection and Criteria Inclusion

Full texts of potentially relevant citations were retrieved and assessed for eligibility by two independent reviewers (E.M. and N.T.) according to the predetermined criteria. Study quality was assessed using the study validation score developed by the investigators.

Standardized forms were used to assess the study eligibility according to the following predefined criteria: (a) study population described as adults and/or minimum age specified as 19 years old; (b) diagnosis of systemic

lupus erythematosus made by the American College of Rheumatology Criteria; (c) evidence of lupus nephritis in the urinalysis and/or creatinine; (d) outcome of lupus nephritis reported as deterioration of renal function i.e. significant doubling of creatinine, chronic kidney disease, end-stage renal disease and/or mortality related to lupus nephritis.

Statistical Analysis

RevMan 7 ® was used to conduct statistical analyses of the results from the pooled data. Continuous variables were age, onset of lupus nephritis from diagnosis of SLE, systolic and diastolic blood pressure, baseline creatinine and mean proteinuria. The mean differences between lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome were compared. Dichotomous variables were male gender, presence of nephrotic syndrome and acute renal failure from the onset, anti-ds DNA positivity, low C3 level, activity index ≥ 2 , chronicity index ≥ 4 and interstitial fibrosis on renal biopsy. The odds ratio between lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome were compared.

Pooled event rates and 95% confidence intervals (CIs) were computed using fixed-effect approach, which reflects only the specific studies included in the analysis. Each variable was tested for heterogeneity study and test for overall effect. $P < 0.05$ was considered statistically significant.

Results

Our literature search yielded 102 studies, of which 76 deemed unsuitable by title alone. The remaining 26 were independently assessed and nine fulfilled study eligibility criteria. Five studies were prospective cohort and four were retrospective cohort. The nine studies included a total of 794 patients with 207 patients showing poor renal functional outcome. Figure 1 illustrates the literature search. See Appendix A for the summary of studies included in the meta-analysis.

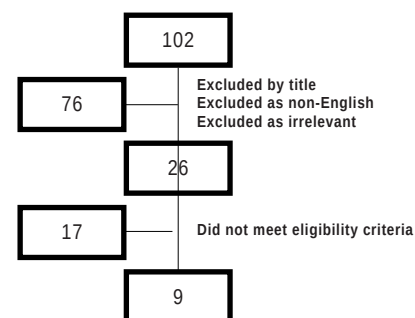


Figure 1. Flow diagram of studies assessed and used in this meta-analysis.

The 1982 American College of Rheumatology criteria for the diagnosis of systemic lupus erythematosus were used for the diagnosis. All studies mentioned which subsets of patients have lupus nephritis, the target population in this research. For the purposes of this study, we defined having nephritis as those patients with clinical, laboratory, and/or histologic evidence of lupus nephritis (i.e. abnormal urinalysis, elevated creatinine and/or abnormal renal biopsy).

The variables of interest were as follows: age, male gender, onset of lupus nephritis from SLE diagnosis, presence of hypertension, systolic and diastolic blood pressure, baseline creatinine, mean proteinuria, nephrotic syndrome, baseline acute renal failure, anti-ds DNA positivity, low C3 level, activity index, chronicity index and interstitial fibrosis on renal biopsy. Pooled mean difference or odds ratio was determined for each variable. See Appendix B for the plots of individual prognostic factors.

Among the studies included, the odds of having a poor renal prognosis was increased in the presence of nephrotic syndrome (POR 1.71; 95% CI 1.04-2.82), high chronicity index on renal biopsy (POR 4.39; 95% CI 2.63-7.33) and interstitial fibrosis on renal biopsy (POR 3.18; 95% CI 1.60-6.30). The studies that described the variables mentioned were sufficiently homogeneous.

Subgroup analyses were performed for male gender and hypertension. The odds of having poor renal prognosis was increased with male gender (POR 1.83; 95% CI 1.02, 3.26) and hypertension (POR 1.97, 95% CI 1.02, 3.81). There is no significant dependence of baseline acute renal failure, low C3, anti-ds DNA positivity and activity index ≥ 12 on renal biopsy with poor renal outcome in lupus nephritis patients (Table I).

The pooled means of systolic blood pressure ($p=0.04$; 95% CI 0.11-8.69 mm Hg), baseline creatinine ($p=0.0005$; 95% CI 33.6-65.1 $\mu\text{mol/liter}$) and proteinuria ($p < 0.0001$; 95% CI 0.7-1.9 gram/24-hours) of lupus nephritis patients with poor renal outcome were significantly elevated than those with stable renal status when subgroup analyses were performed. There were no significant differences between the age, onset of lupus nephritis, diastolic blood pressure and baseline creatinine of lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome (Table II).

Discussion

The findings of this meta-analysis demonstrated that the most valuable and informative prognostic factors in patients with lupus nephritis were primarily the presence

Table I. Summary of dichotomous prognostic variables

Prognostic Factor	Odds Ratio, 95% CI	Heterogeneity	Overall Effect
Male gender	1.83 (1.02, 3.26)	$p=0.32$	$p=0.04$
Hypertension	1.97 (1.02, 3.81)	$p=0.28$	$p=0.04$
Nephrotic syndrome	1.71 (1.04-2.82)	$p=0.46$	$p=0.04$
Baseline ARF	1.64 (0.78, 3.48)	$p=0.17$	$p=0.19$
Anti-dsDNA positivity	2.20 (1.21,4.01)	$p=0.01$	$p=0.01$
Low C3	0.87 (0.34, 2.26)	$p=0.17$	$p=0.78$
Activity index ≥ 12	0.85 (0.43, 1.65)	$p=0.10$	$p=0.62$
Chronicity index ≥ 4	4.39 (2.63, 7.33)	$p=0.98$	$p<0.00001$
Interstitial fibrosis	3.18 (1.60, 6.30)	$p=0.38$	$p=0.0009$

Table II. Summary of continuous prognostic variables

Prognostic Factor	Mean Difference, 95% CI	Heterogeneity	Overall Effect
Age (years)	-1.08 (-2.29, 0.13)	$p=0.24$	$p=0.08$
Onset of LN (years)	6.63 (-0.93, 14.19)	$p=0.22$	$p=0.09$
Systolic BP (mm Hg)	4.40 (0.11, 8.69)	$p=0.07$	$p=0.04$
Diastolic BP (mm Hg)	1.62 (-1.17, 4.41)	$p=0.05$	$p=0.26$
Creatinine ($\mu\text{mol/L}$)	49.35 (33.57, 65.12)	$p=0.0005$	$p=0.00001$
Proteinuria (g/24-h)	1.30 (0.71, 1.89)	$p=0.07$	$p<00001$

of nephrotic syndrome and high chronicity index on renal biopsy. Likewise, male gender, the presence of hypertension and heavy proteinuria were all associated with poor renal outcome.

Young age and male gender have been described as poor prognostic factors.⁹ Male sex was shown to be predictive of therapeutic resistance and reduction of renal survival.¹⁰ Our pooled results agreed that males were at a disadvantage when considering renal functional outcome. However, renal outcome was unaffected by age and onset of lupus nephritis from the diagnosis of SLE. Old age as a clinical factor for renal function deterioration and mortality might be related to higher prevalence of co-morbid conditions that negatively influence the outcome of SLE such as cardiovascular diseases.¹¹

Several studies concluded that the longer delay of diagnosis of lupus nephritis established by renal biopsy was associated with unopposed renal inflammation, occurrence of chronic renal lesions and hence poor renal outcome.^{5,7} The meta-analysis did not find any positive correlation between onset of lupus nephritis from diagnosis of SLE and poor renal outcome. The likely explanation is that the probability of developing ESRD was more associated with deteriorated renal function at the onset of lupus. Likewise, the delay in kidney biopsy could also adversely affect the renal outcome.

Hypertension is a consistent risk factor in the development of chronic kidney disease and ESRD. Hypertension is associated with poor renal outcome and mortality in lupus nephritis patients.¹² Hypertension had a higher prevalence in lupus nephritis patients who developed renal failure as well as in those who had mortality related to kidney disease.¹¹ Systolic blood pressure was more significantly associated with deterioration of renal function than diastolic blood pressure based on our results.

Like in previous studies, the prognostic value of elevated creatinine at onset of lupus nephritis has also been established in this meta-analysis. An elevated serum creatinine at the time of diagnosis of lupus nephritis was identified as strong predictor of ESRD. Despite the significant heterogeneity contributed by the studies of Chrysochou et al., and Woo Yoo et al, serum creatinine remains to be a significant prognostic factor. Hence, elevated creatinine in conjunction with other contributing factors can assess the extent of overall kidney dysfunction and estimate the potential benefits of aggressive immunosuppressive and renoprotective treatment.⁵

Interestingly, our pooled results did not show significant dependence of poor renal outcome in patients with WHO

Class IV. This unexpected result may be due to more aggressive treatment received by this subset of patients as well as their dramatic response to treatment.³ Patients with proliferative glomerulonephritis had a greater potential for entering into remission compared with other patients within the category of severe lupus nephritis.¹⁹ Immunosuppressive treatment generally reduced the risk of renal injury and altered the prognostic significance of histologic features in lupus nephropathy.¹³ The poor outcome of patients with WHO Class IV lupus nephritis may further be attributed to severe hypertension and renal vasculopathy in this particular subset of patients.¹⁴

A significant association was noted between proteinuria and poor renal outcome. These observations support the measurement of proteinuria as a clinical indicator of nephritis activity in patients with SLE. The quantity of proteinuria at baseline correlates with the rate of progression to ESRD.^{3,19} Likewise, the likelihood of achieving remission and improved renal prognosis is significantly less for patients with greater levels of proteinuria at baseline.¹¹ Although not included in this meta-analysis, the presence of profound hypoalbuminemia was considered a risk factor for ESRD.¹⁵ The relationship of persistent proteinuria and progression of glomerular injury is based on the hypothesis that severe proteinuria, carrying activated cytokines and lipoproteins producing reactive oxygen species, triggers a downstream inflammatory cascade in and around epithelial cells. These effects induce tubulointerstitial injury along with fibrosis and atrophy.¹⁶

Low C3 complement level was of traditional prognostic importance but it was not in agreement in this meta-analysis. The contribution of low C3 level diminishes in the presence of other important clinical and histological factors.¹⁷ Serological markers for SLE often provide conflicting prediction of outcome.¹⁹

High chronicity index is a powerful prognostic factor of poor renal functional outcome. It has a stronger correlation with ESRD than serum creatinine and proteinuria because it estimates the extent and duration of renal injury. This meta-analysis also supported the findings of Howie et al¹⁸ that the histological chronicity index was more predictive of renal functional outcome than WHO classification. This may be more useful as a clinical marker of eventual renal functional outcome decline.^{5,18} In contrast, activity index did not prove to be a significant predictor of progression toward terminal renal failure. Even other components of activity index like inflammatory cell infiltrates were not considered significant factors.⁵ This is in congruence with the pattern observed in most glomerular diseases in which chronic glomerular and tubulointerstitial lesions are the most important determinants of poor outcome.¹⁶ Interstitial

fibrosis, a component of chronicity index, came out as a strong prognostic factor of poor renal status. Moderate to severe interstitial fibrosis and the presence of cellular crescents on renal biopsy identified patients particularly at high risk for doubling serum creatinine.¹⁷

From a clinical point of view, our finding underscores the need for close medical monitoring of patients with SLE and frequent urinalyses. Patients with SLE should have a renal biopsy as soon as clinical signs of nephritis are evident in order to accelerate treatment decisions and minimize risk of inflammation-induced irreversible kidney damage.

Conclusion

The odds of having poor renal prognosis was increased in the presence of hypertension, nephrotic syndrome and high chronicity index on renal biopsy. The results of the study highlight the role of aggressive control of modifiable factors like hypertension and proteinuria, and the prognostic role of a kidney biopsy to minimize irreversible kidney damage. Histological chronicity index proves to be a dominant predictor of renal functional outcome than serum creatinine or WHO classification. This may be more useful marker of eventual renal functional decline. Lupus nephritis patients with poor prognostic factors merit closer monitoring and more aggressive treatment.

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Appendices

Appendix A: Characteristics of included studies

Deteriorating renal function: reduction of estimated GFR of >1 ml/min/year deterioration over the period of follow up. This definition was chosen as previous studies have shown that the ageing process in the general population can be associated with decline in estimated GFR of 0.5-1 ml/min/year deterioration.

End-stage renal disease (ESRD): need for chronic dialysis or kidney transplant

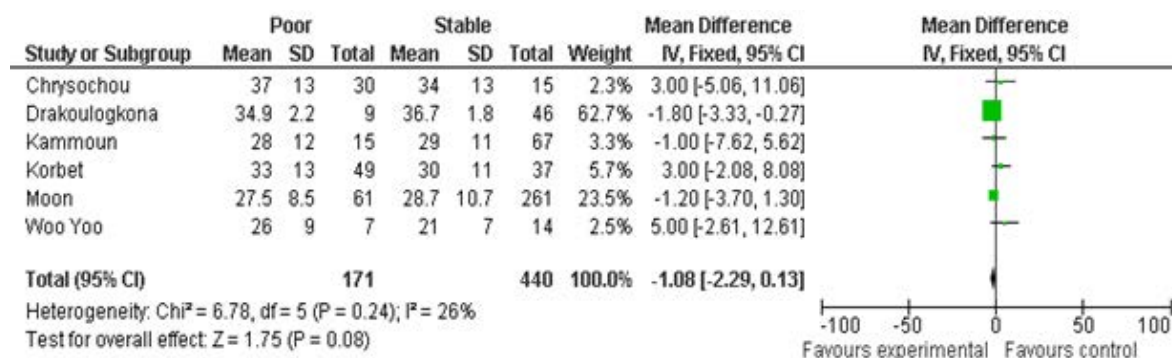
End-stage renal failure (ESRF): bilateral small kidneys with serum creatinine ≥ 8 mg/dl and had received renal replacement therapy for more than 3 months.

Non-remission: serum creatinine >1.4 mg/dL and proteinuria >330mg/d of protein after induction therapy.

Appendix B: Forrest Plots of Prognostic Factors

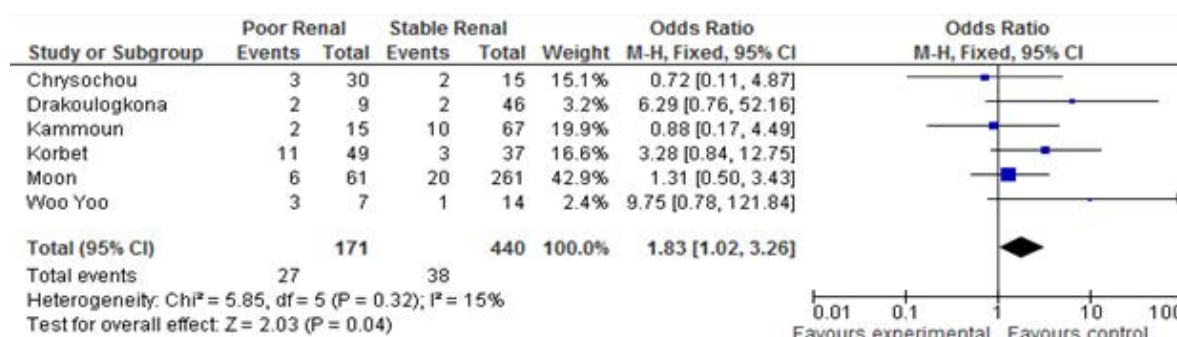
Author (reference)	Date of Publication	Study Design	Study population	Sample size	Outcome(s)
Chrysochou et al.	February 2008	Retrospective	Lupus nephritis	45	Deteriorating GF
Drakoulogkona et al.	Nov 2011	Prospective	Lupus nephritis	55	ESRD related mortality
Faurschouet al.	March 2006	Prospective	Lupus nephritis	91	ESRD
Hu et al.	May 2010	Retrospective	Lupus nephritis	26	ESRF
Kammoun et al.	July 2011	Retrospective	Lupus nephritis	82	ESRD mortality
Korbetet al.	December 1999	Prospective	Lupus nephritis	86	Non-remission
Mercadalet al.	October 2002	Prospective	Lupus nephritis	66	ESRD mortality
Moon et al.	June 2011	Retrospective	Lupus nephritis	322	Chronic kidney disease
Woo Yooet al.	July 2000	Prospective	Lupus nephritis	21	Renal Progression

Age (years) as prognostic factor for poor renal outcome



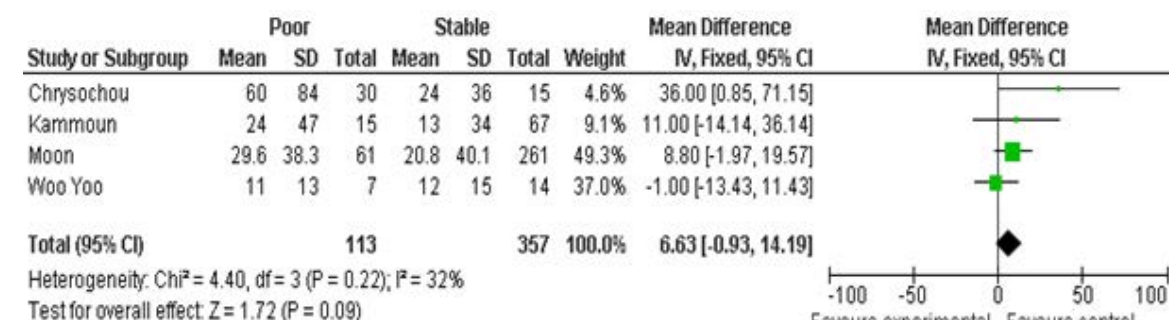
The studies are sufficiently homogeneous ($p=0.24$) however there is no significant difference between ages of lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome ($p=0.08$).

Male gender as prognostic factor for poor renal outcome



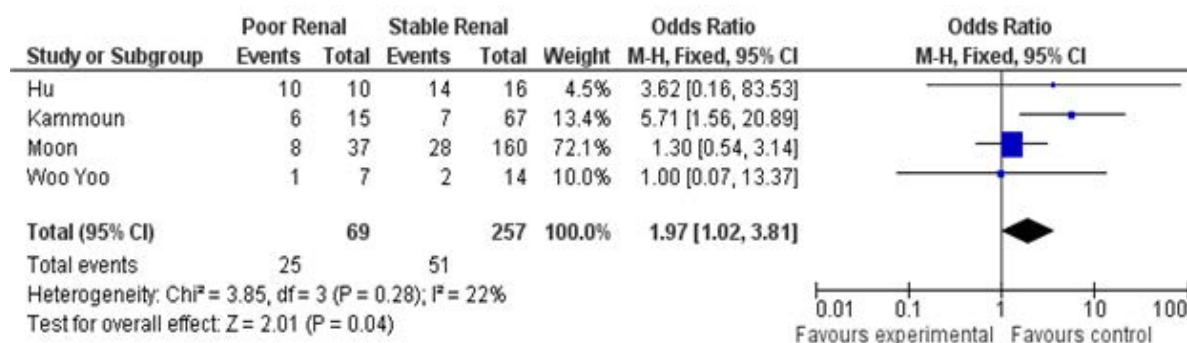
A subgroup analysis was done. The studies are sufficiently homogeneous ($p=0.17$) and there is no significant difference between male lupus nephritis patients with poor renal outcome and male lupus nephritis patients with stable renal outcome ($p=0.19$).

Onset of lupus nephritis from diagnosis of SLE (months) as prognostic factor of poor renal outcome



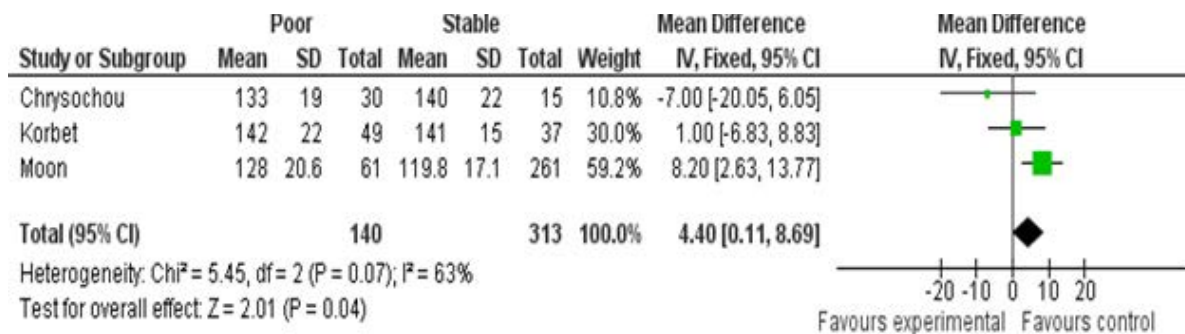
The studies are sufficiently homogeneous ($p=0.22$) however there is no significant difference in the duration from the diagnosis of SLE to onset of lupus nephritis between lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome ($p=0.09$).

Hypertension as prognostic factor for poor renal outcome



A subgroup analysis was done. The studies are sufficiently homogeneous ($p=0.28$) and there is a significant dependence of hypertension and poor renal outcome in lupus nephritis patients ($p=0.04$). For every 1 hypertensive patient with stable renal outcome, there are about 2 hypertensive patients with poor renal outcome.

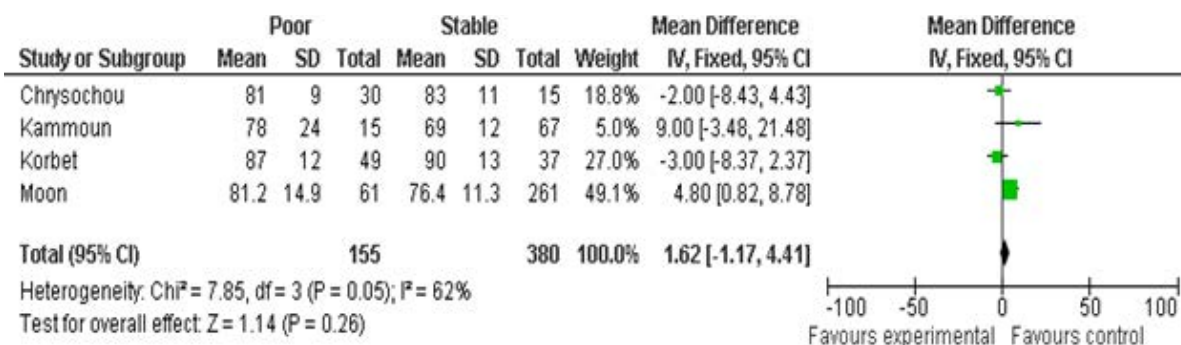
Systolic blood pressure (mm Hg) as prognostic factor for poor renal outcome



The studies are heterogeneous ($p=0.009$) however there is a significant difference between the mean systolic blood pressure of lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome at 95% confidence interval ($p=0.004$). Mean systolic blood pressure of lupus nephritis patients with poor renal outcome was higher by 2 to 10 mm Hg.

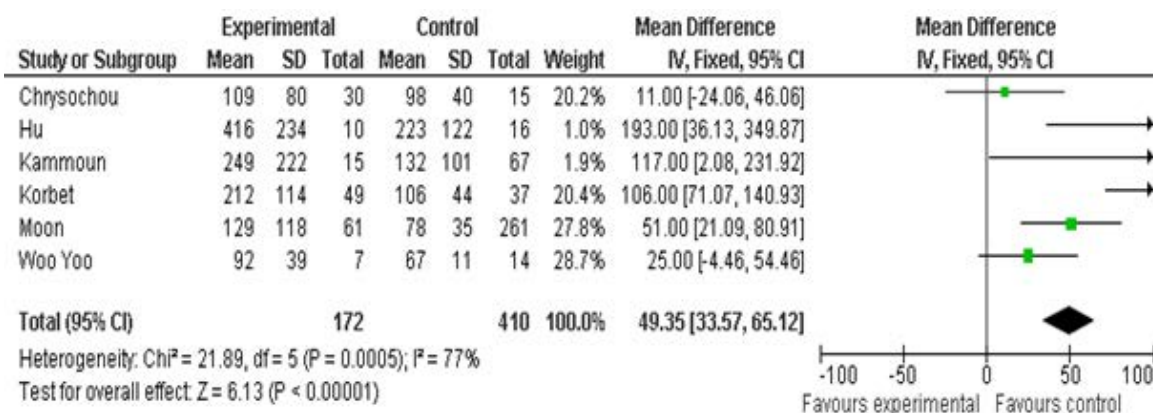
A subgroup analysis was done. The studies are sufficiently homogeneous ($p=0.07$) and there is a significant difference between the mean systolic blood pressure (SBP) of lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome ($p=0.04$). SBP of lupus nephritis patients with poor renal outcome was higher by a mean of 4.4 mm Hg.

Diastolic blood pressure (mm Hg) as prognostic factor for poor renal outcome



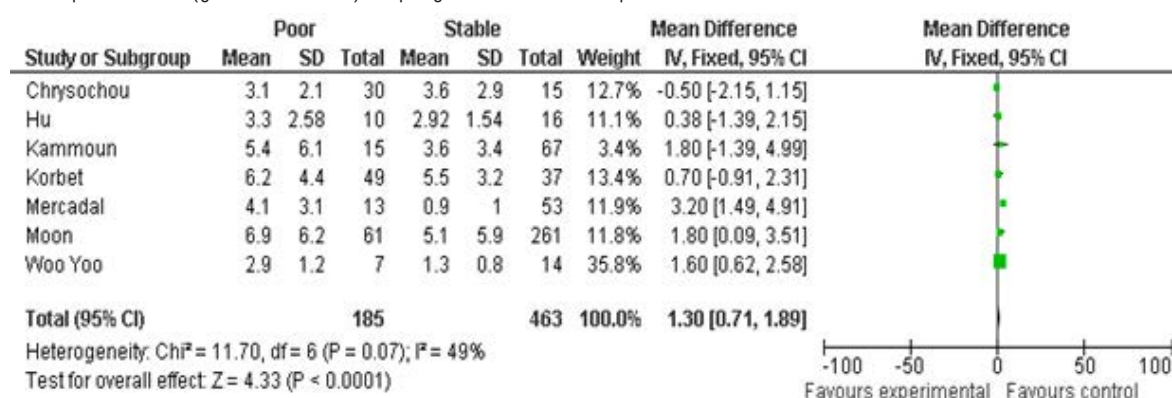
The studies are heterogeneous ($p=0.05$) and there is no significant difference between the mean diastolic blood pressure of lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome ($p=0.26$).

Baseline creatinine ($\mu\text{mol/liter}$) as prognostic factor for poor renal outcome



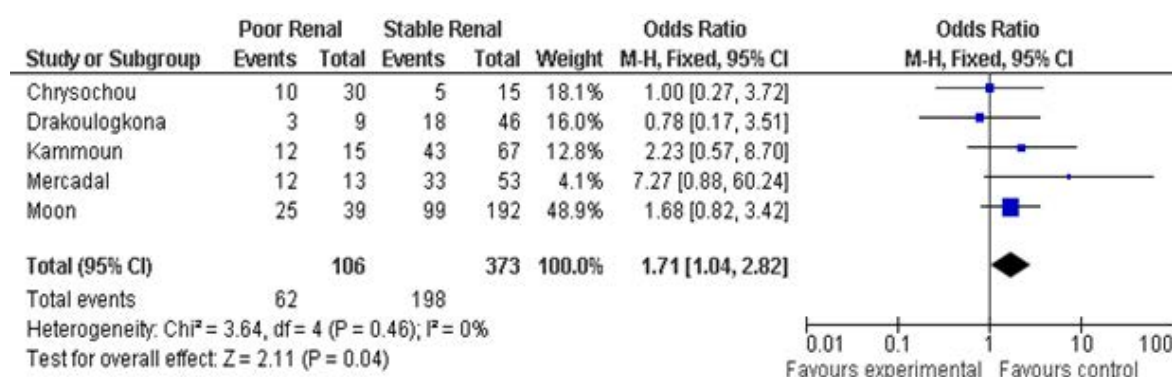
The studies are heterogeneous ($p=0.009$) however there is a significant difference between the baseline mean creatinine of lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome ($p=0.0005$). Mean creatinine of lupus nephritis patients with poor renal outcome was higher by 33.6 to 65.1 $\mu\text{mol/liter}$.

Mean proteinuria (gram/ 24-hours) as prognostic factor for poor renal outcome



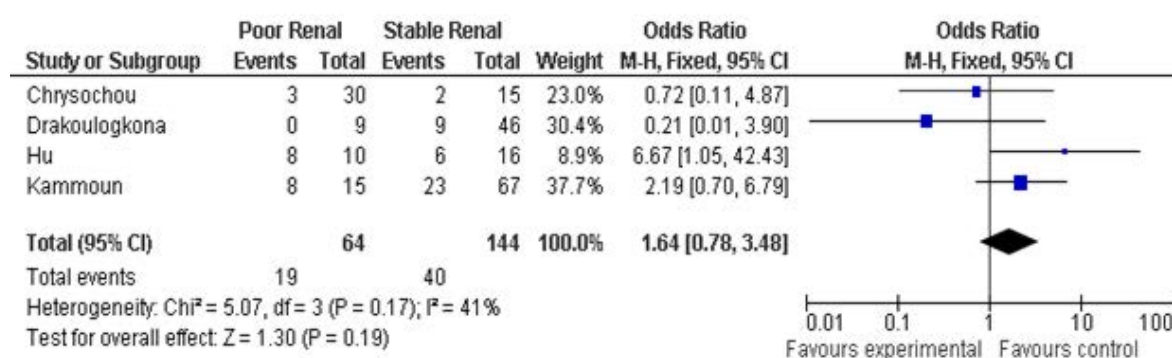
The studies are sufficiently homogeneous ($p=0.07$) and there is a significant difference between the mean proteinuria of lupus nephritis patients with poor renal outcome and lupus nephritis patients with stable renal outcome ($p < 0.0001$). Mean proteinuria of lupus nephritis patients with poor renal outcome was higher by 0.71 to 1.89 g/24-hours.

Nephrotic syndrome as prognostic factor for poor renal outcome



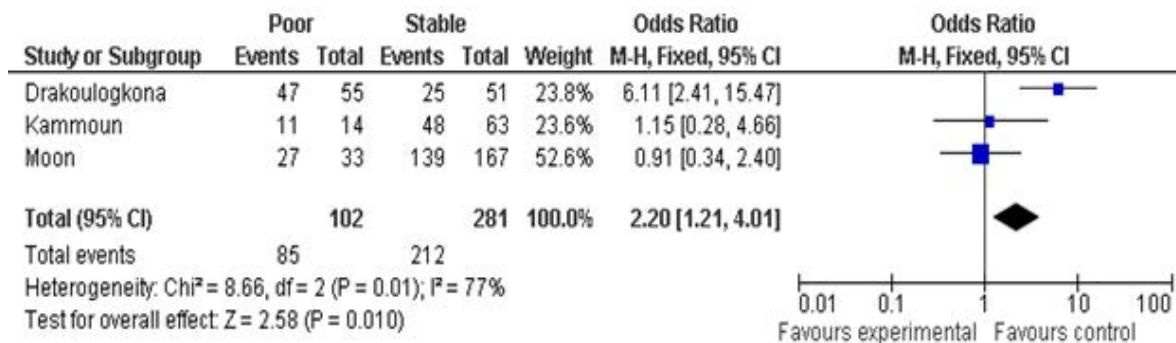
The studies are sufficiently homogeneous ($p=0.46$) and there is a significant dependence of nephrotic syndrome and poor renal outcome in lupus nephritis patients ($p=0.04$). For every 1 nephrotic patient with stable renal outcome, there are about 2 nephrotic patients with poor renal outcome.

Baseline acute renal failure as poor prognostic factor for poor renal outcome



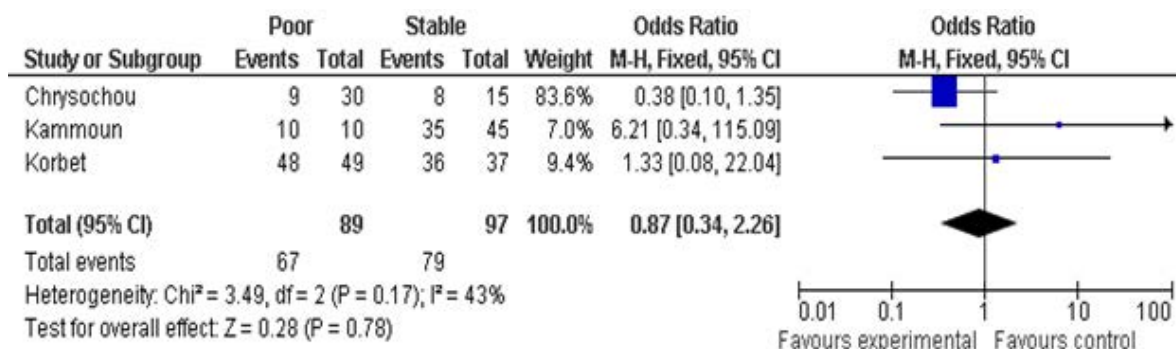
The studies are heterogeneous ($p=0.17$) and there is no significant dependence of acute renal failure and poor renal outcome in lupus nephritis patients ($p=0.19$).

Anti- ds DNA positivity as prognostic for poor renal outcome

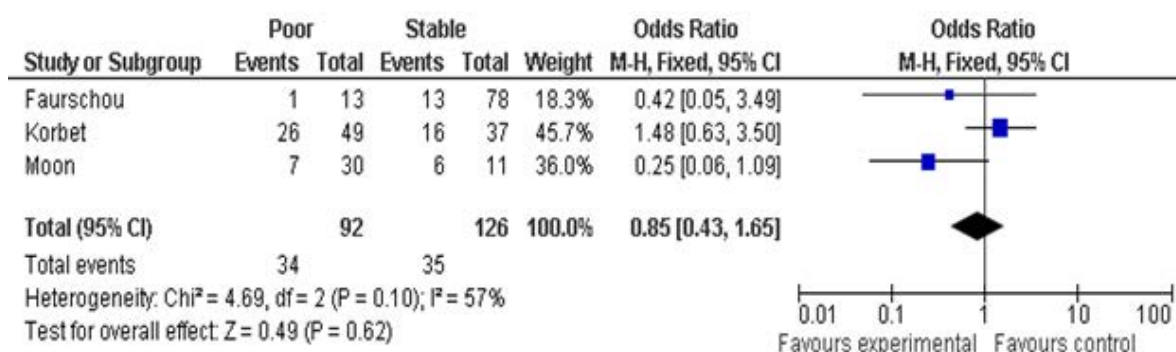


The studies are heterogeneous ($p=0.01$) however there is a significant dependence of anti-ds DNA positivity and poor renal outcome in lupus nephritis patients ($p=0.010$). For every 1 anti-ds DNA positive patient with stable renal outcome, there are 2 anti-ds DNA positive patients with poor renal outcome.

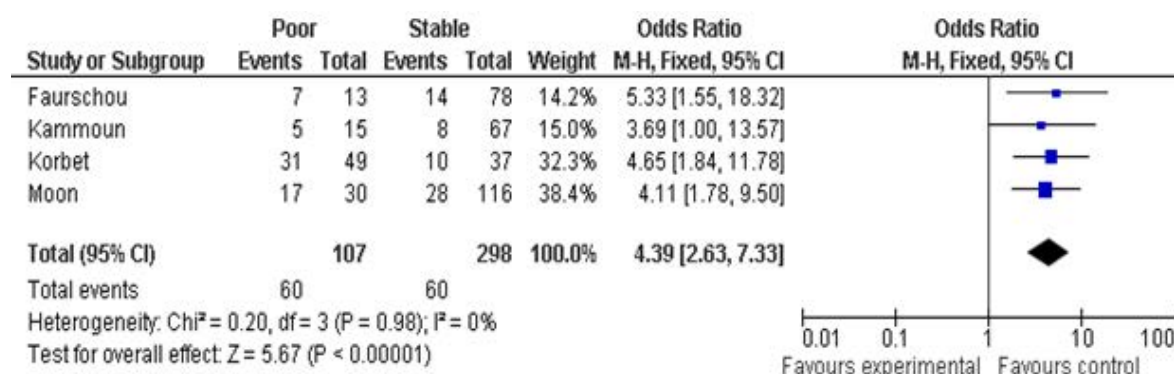
Low C3 as prognostic factor for poor renal outcome



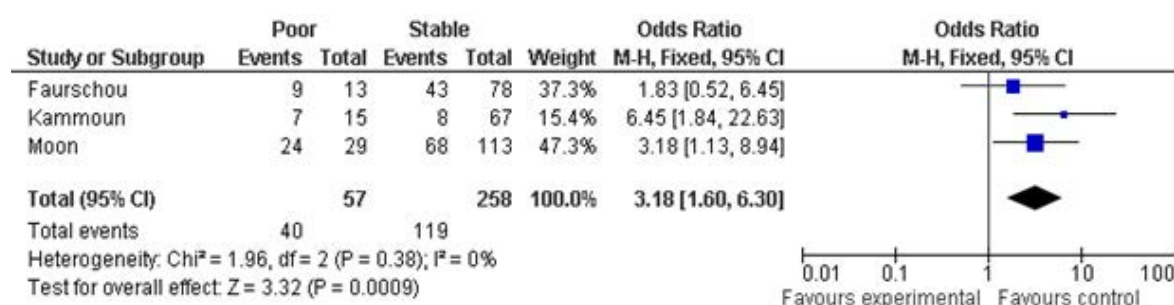
The studies are homogeneous ($p=0.01$) however there is no significant dependence of low C3 and poor renal outcome in lupus nephritis patients ($p=0.010$).

Activity index ≥ 12 as prognostic factor for poor renal outcome

The studies are homogeneous ($p=0.01$) however there is no significant dependence of high activity index (≥ 12) and poor renal outcome in lupus nephritis patients ($p=0.62$).

Chronicity Index ≥ 4 as prognostic factor for poor renal outcome

The studies are sufficiently homogeneous ($p=0.01$) and there is a significant dependence of high chronicity index (≥ 12) and poor renal outcome in lupus nephritis patients ($p < 0.00001$). For every 1 patient with high chronicity index on renal biopsy and stable renal outcome, there are 4 patients with high chronicity index on renal biopsy and poor renal outcome.

Interstitial Fibrosis as prognostic factor for poor renal outcome

The studies are sufficiently homogeneous ($p=0.38$) and there is a significant dependence of interstitial fibrosis on renal biopsy and poor renal outcome in lupus nephritis patients ($p=0.0009$). For every 1 patient with interstitial fibrosis on renal biopsy and stable renal outcome, there are 3 patients with interstitial fibrosis on renal biopsy and poor renal outcome.