International Journal of Scientific Research and Management (IJSRM)
||Volume||07||Issue||01||Pages||MP-2019-118-127||2019||
Website: www.ijsrm.in ISSN (e): 2321-3418
Index Copernicus value (2016): 93.67, (2017):89.90, DOI: 10.18535/ijsrm/v7i1.mp01

Prognostic factors of poor renal outcomes in renal amyloidosis patients: Systematic review and meta-analysis

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Abstract

Background: Renal involvement by systemic amyloidosis is one of the most common poor outcomes of the disease, usually manifested as nephrotic range proteinuria and can progress to end-stage renal disease(ESRD) with negative effects on the quality of life and survival of the patients. The objective of this meta-analysis was to determine prognostic factors of poor renal outcome in renal amyloidosis patients. The findings of this study may provide a clearer indication of the possibility of worsening state of renal function, which affect monitoring and therapeutic decisions.

Methods: We searched for studies reporting on the renal outcomes in systemic amyloidosis, and cohort studies related to systemic amyloidosis prognosis and/or outcomes. Pooled mean differences, odds ratios and95% confidence intervals were computed using random-effect approach in Rev Man5.3®. Clinical, laboratory and renal biopsy prognostic factors were tested for heterogeneity and for overall effect. P-value<0.05 was considered statistically significant.

Results: Our search resulted in 7 eligible articles involving 3016 participants in total. Five prospective cohort studies were included. 861 patients had poor renal functional outcomes which included deteriorating estimated glomerular filtration rate, progressing to chronic kidney disease or end-stage renal disease and ESRD-related mortality. Male gender AL (OR 1.58; 95% CI 0.16,15.52, p=0.70) and AA (OR 1.36; 95% CI0.09, 20.71, p=0.81), proteinuria (OR 1.03; 95% CI 0.40-1.66), serum creatinine (OR1.23; 95%CI 0.65-1.80), eGFR for AA (OR 0.42; 95% CI 0.24-0.72) and eGFR for AL (OR 0.33; 95% CI 0.12-0.91) were poor prognostic factors renal amyloidosis. There were insufficient data to systematically assess age a poor out come.

Conclusion: The odds of having poor renal prognosis was increased in the male gender, the presence of proteinuria, elevated serum creatinine and decreased eGFR filtration rate. These results highlight the role of aggressive control of modifiable factors like proteinuria, the role of close medical monitoring of patients,t hat present with fatigue, edema, hypotension, and nephrotic syndrome. These clinical features are strongly associated with renal amyloidosis. Such patients should have a renal biopsy as soon as possible thus to minimize the risk of irreversible kidney damage that adversely affects the renal outcomes.

Keywords: Prognostic factors, Renal amyloidosis, Meta-analysis, Renal outcomes

Introduction

Renal amyloidosis is one of the commonest outcomes of systemic amyloidoses, which involves many other organs.[1] Systemic amyloidoses contain a series of diseases characterized by multi-organ deposition of misfolded proteins and aggregated autologous proteins of β-pleated sheet fibrils.[2]

The epidemiology of amyloidosis is still not well known [3] and mostly due limited to case reports and mortality data for AL and/or autopsy studies for AA.[3–6]

The incidence of systemic amyloidoses is not well reported but apparently falls between 5 and 13 per million per year.[7]

Amyloid deposition on the kidney usually deposits in the glomeruli, but arteries, tubules, and interstitium can also get involved. This can result in chronic kidney disease (CKD) characterized by glomerulosclerosis, tubular atrophy, interstitial fibrosis, and inflammation, leading to end stage renal disease.[8] It is occasionally associated with the severe nephrotic syndrome and proteinuria presents as a first symptom. There are two main types of renal amyloidosis which are primary or immunoglobulin light chain (AL) amyloidosis, which is associated with plasma cell dyscrasia, and amyloid A (AA) amyloidosis secondary or reactive to chronic inflammatory conditions.[9] The diagnosis is usually made by doing an autopsy or biopsy, and then examined by immunofluorescence (IF), immunohistochemistry, or mass spectrometry.[10]

The treatment of renal amyloidosis is mainly based on chemotherapy and autologous hematopoietic stem cell transplantation (ASCT). Novel agents such as (thalidomide, lenalidomide, and bortezomib) alone and in combination with steroids and alkylating agents have shown some efficacy and continue to be explored.[9] As survival in these patients improves, those that develop renal failure are now faced with a longer time on dialysis. The early experience of kidney transplantation patients was complicated by graft loss due to disease recurrence and early death of the patient. [11,12]

Definitive outcome assessment is debarring by lacking a comprehensive system or registry for follow-up. Safety remains in obscurity because of the inferences at single centers with limited generalizability, restrictive sample size, and inappropriate comparison groups. All these findings cause concerns about renal amyloidosis outcomes with a special focus on the remnant kidney. For this reason, we conducted a systematic review and meta-analysis to investigate the prognostic factors of poor renal outcome in renal amyloidosis patients.

Methods

Search strategy and study selection

Two independent reviewers conducted a database search using EMBASE, Google scholar and MEDLINE (PubMed) reporting our items for a systematic review and meta-analysis. The search investigated all retrospective, prospective and cohort studies related to the renal outcomes and prognostic factors in systemic amyloidosis. Studies were identified using a combination of MeSH terms related to systemic amyloidosis and prognosis, such as: ‘‘amyloidosis’’ [MeSH] or (‘‘AL’’ or ‘‘AA” or “primary’’ or ‘‘systemic’’) and (‘‘prognosis’’ or‘‘proteinuria’’ or ‘‘outcomes’’) [subheading] and “retrospective study” also ‘‘amyloidosis’’ [MeSH] and ‘‘clinical trial’’ [MeSH] as publication type or clinical trial as to clarify the factors influencing renal outcomes and prognostic factors in renal amyloidosis patients.

Inclusion criteria

We mainly focused on the following: renal outcomes or response, the prognostic factors of renal amyloidosis. Publications, which included data from 1st January 1990 to 31st December 2017, were considered. Populations of age >17 years, any sex or ethnicities were included for analysis. Renal Outcomes of interest were: eGFR, male gender, proteinuria, serum creatinine and ESRD.

Exclusion criteria

Studies that were excluded were: letters, duplicates, animal studies, editorial reviews, case reports, studies with fewer individuals such as <30, and studies that did not report outcomes of our interest. Non-English articles were excluded.

Initially, we downloaded 315 full-text articles of inherent studies, of which 252 publications were excluded due to not meeting our demands (Fig. 1). After a detailed evaluation, 52 more studies were excluded according to our inclusion and exclusion criteria. Eventually, 7 studies published from 1990 to 2017, and from 5 different countries involving a total of 1,539 participants were included in this meta-analysis.

Statistical Analysis

RevMan 5.3 ® was used to conduct statistical analyses of the results from the pooled data. Continuous variables were mean age, mean follow up, baseline and mean creatinine, mean eGFR and mean proteinuria.

The mean differences between renal amyloidosis (AA and AL) patients with poor renal outcome and stable renal outcome were compared. Dichotomous variables were male gender, end stage renal disease and dialysis. The odds ratio between renal amyloidosis patients with poor renal outcome and renal amyloidosis patients with stable renal outcome were compared.

Pooled event rates and 95% confidence intervals (CIs) were computed using random-effect approach. Each variable was tested for heterogeneity study and test for overall effect. Between-study heterogeneity we evaluated by calculation of I^2 statistics. We considered heterogeneity low if I^2 was ≤50%, moderate if >50% to <75%, and high if ≥75%. P <0.05 was considered statistically significant.

Results

Our literature search yielded 315 studies, where 252 were excluded due to containing animal studies, non-English and irrelevant tittle or abstract. The remaining 63 were further reviewed, independently assessed and finally seven studies fulfilled our criteria. Four cohorts were from Europe, two from Middle East and one from Asia. The median number of patients used was 220 (range, 81-461) and the median follow-up was 39months (range, 15-50 months). The mean or median eGFR was ≥45 ml/min/1.73 m2 in two of seven studies. Only one study had a mean eGFR of 10ml/min/1.73 m2. Three studies reported a proteinuria mean range of 2.92-11.7g/d.

All seven studies had a serum creatinine range of 0.87-12.4mg/dL. **Table 1** shows the individual study characteristics and its results. One study was prospective cohort, four were retrospective cohort and one was not reported. One retrospective study was divided and conducted into two different retrospective cohorts, done by the same author. The seven studies included a total of 1,539 patients with 207 patients showing poor renal functional outcome. **Figure 1 illustrates the flowchart of selected studies.**

The variables of interest were as follows: age, baseline and mean creatinine, proteinuria, mean eGFR, male gender and onset of renal amyloidosis from diagnosis and progressing to end stage renal disease. Pooled mean difference or odds ratio was determined for each variable.

The studies that described the variables mentioned were sufficiently heterogeneous.

Subgroup analyses were performed for male gender that had AL amyloidosis was OR 1.58(95% CI 0.16,15.52, p=0.70) **(Figure 2)**. Analyses for male gender that had AA amyloidosis was OR 1.36(95% CI 0.09, 20.71, p=0.81) **(Figure 3)**. Thus the odds of having poor renal prognosis were increased with male gender.

The pooled means of proteinuria in both AL and AA studies (p=0.02; 95% CI 0.40-1.66 gram/24-hours) **(Figure 4)**, and baseline creatinine (p < 0.00001; 95% CI 0.65-1.80 mg/dL) **(Figure 5)** of renal amyloidosis patients with poor renal outcome were significantly elevated than those with stable renal status when subgroup analyses were performed. There is no significant dependence of eGFR as a prognostic factor in AA amyloidosis, p=0.30 **(Figure 6)** but significance is seen in AL amyloidosis p=0.02 **(Figure 7).** In dispersion through the studies included, the odds of progressing to end stage renal disease and doing dialysis was 0.96 (95% CI 0.32,2.86, p=0.94) **(Figure 8).**

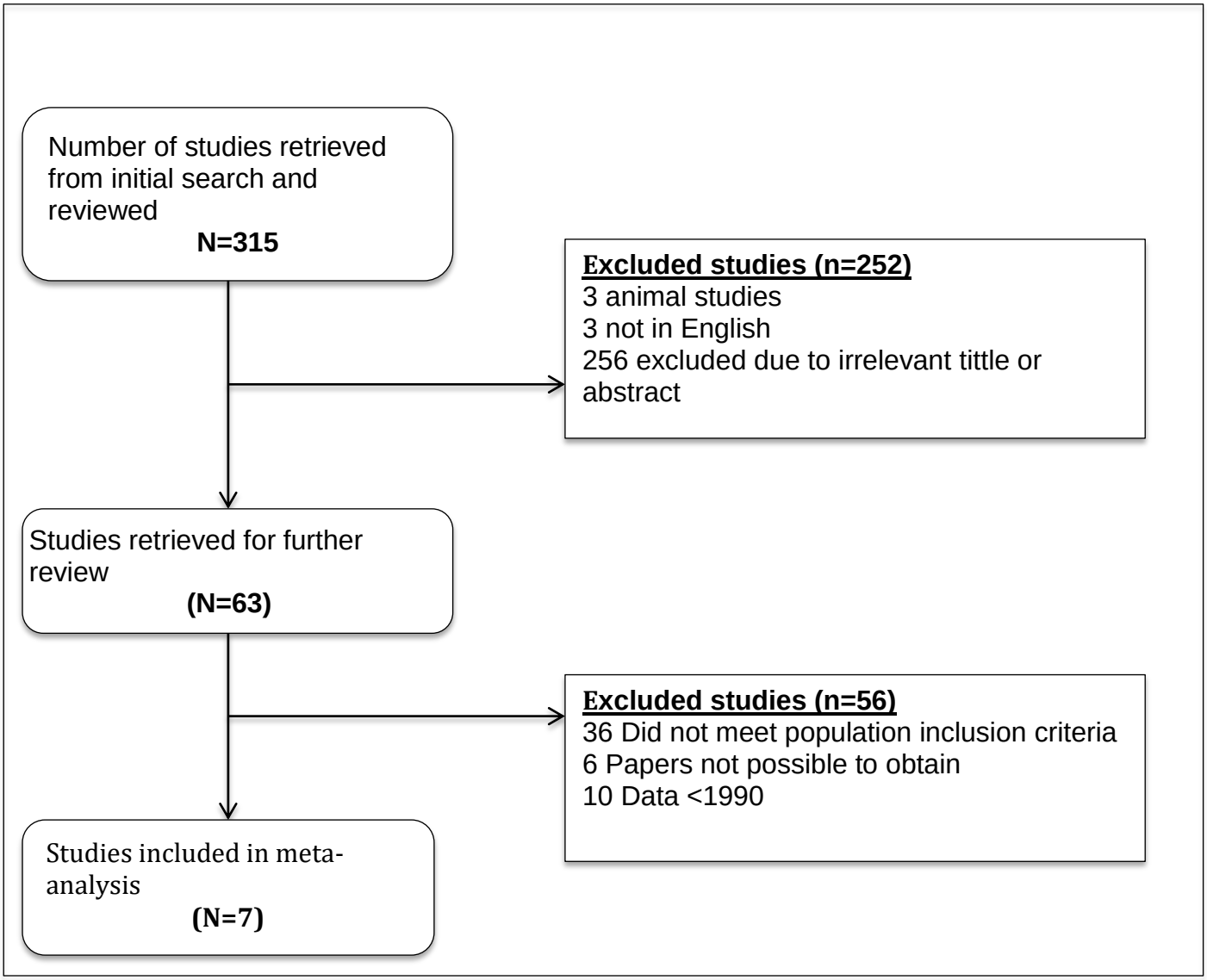

Figure 1. Flowchart of selected studies in the meta-analysis

Table 1. Clinical, pathological features and renal outcomes of the included studies.

Author	Location of Study	Study period	Sample Size	No.of Patients used	Age	Median Follow up (m)	No. of deaths	Survival	Scr (mg/dL)	Protein-uria (g/d)	eGFR (ml/min per 1.73 m2)	Type of R-A
X. Huang, 2015	China	2003-2011	269	231	56.02 ± 9.51	15.2	101	36.3m (10pts alive)	1.21 ± 0.94	4.92 ± 2.92	N	AL
G.Palladini, 2014a	Italy	2004-2012	461	461	64 (56-61)	40	226	NR	1.11 (0.87-1.70)	5.1 (2.3-9.4	62 (38-84)	AL
F.Bergesio 2008	Italy	1995-2000	373	290	NR	NR	87 AL 34 AA	NR	1.2 (0.6–10.3) AL, 1.6 (0.5	NR	NR	AA, AL
T.Rezk 2015	UK	2009-2015	1000	84	68 (40–86)	NR	NR	84pts	NR	NR	10	AL
E. Ahbap, 2017	Turkey	2001-2013	121	121	38.2 ± 3.3	50	64.7 ± 6.3 m	32.3 ± 0.1	6.7 ± 0.4	NR	NR	AA
G.Palladini 2014b	Germany	2004-2012	271	271	61 (54-68)	50	136	NR	1.1 (0.83-1.63)	6.0 (3.3-9.0)	64 (42-88)	AL
Y.Ayar, 2017	Turkey	2006-2014	531	81	50 (19–83)	NR	NR	10.4m	1.1 (0.9–2.2)	7.0 (4.4–11.7)	NR	AL

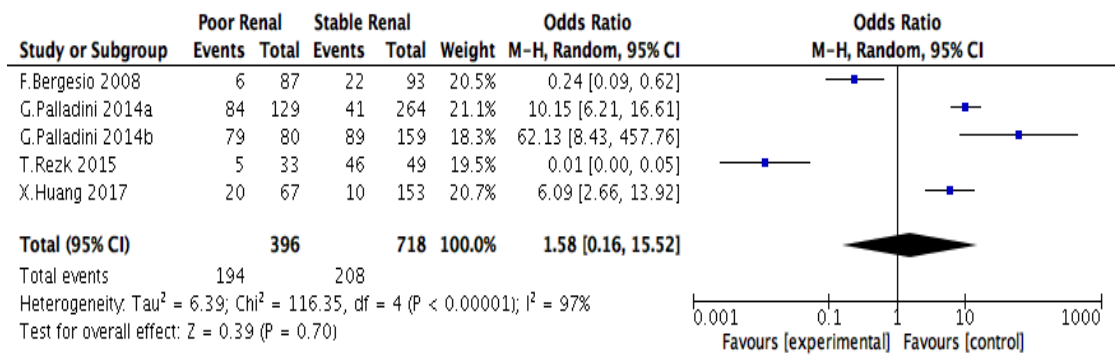

Figure 2: Male gender as prognostic factor for poor renal outcome in AL amyloidosis

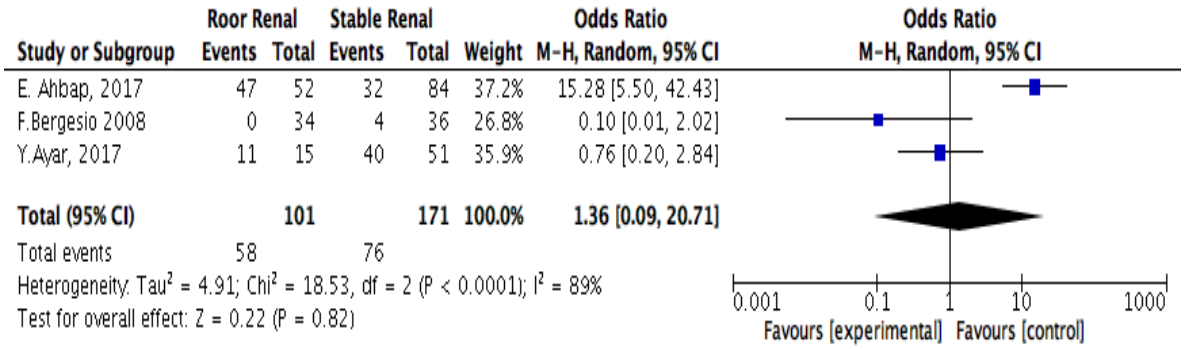

Figure 3: Male gender as prognostic factor for poor renal outcome in AA amyloidosis

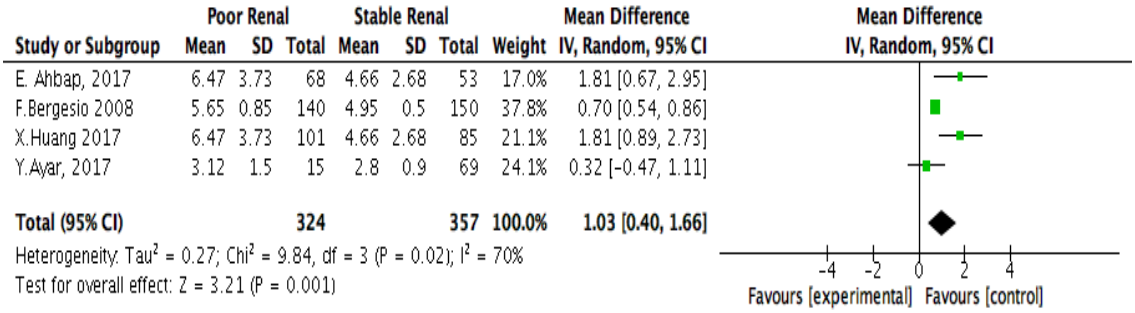

Figure 4: Mean proteinuria (gram/24-hours) as prognostic factor for poor renal outcome

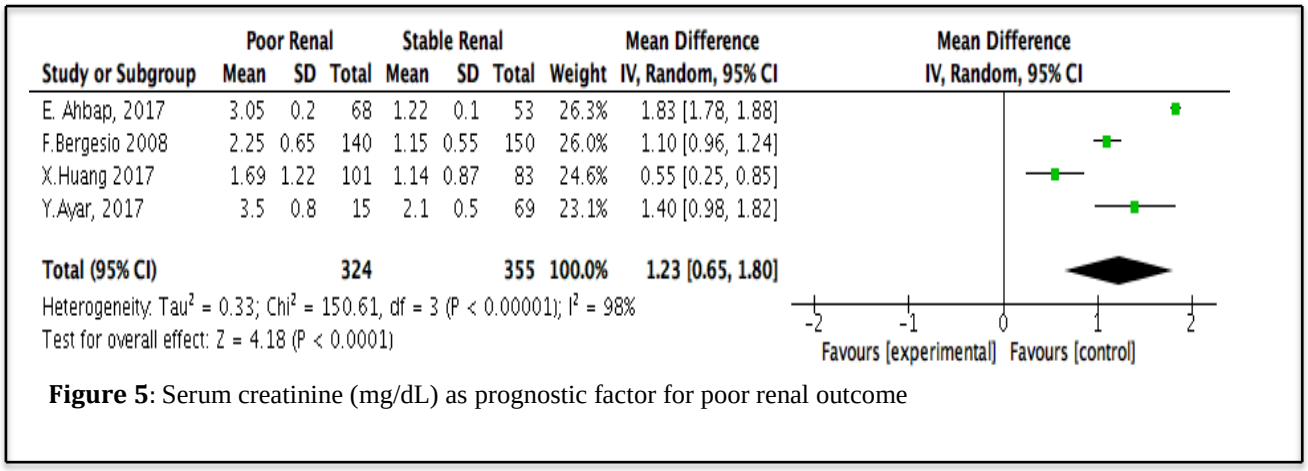

Figure 5: Serum creatinine (mg/dL) as prognostic factor for poor renal outcome

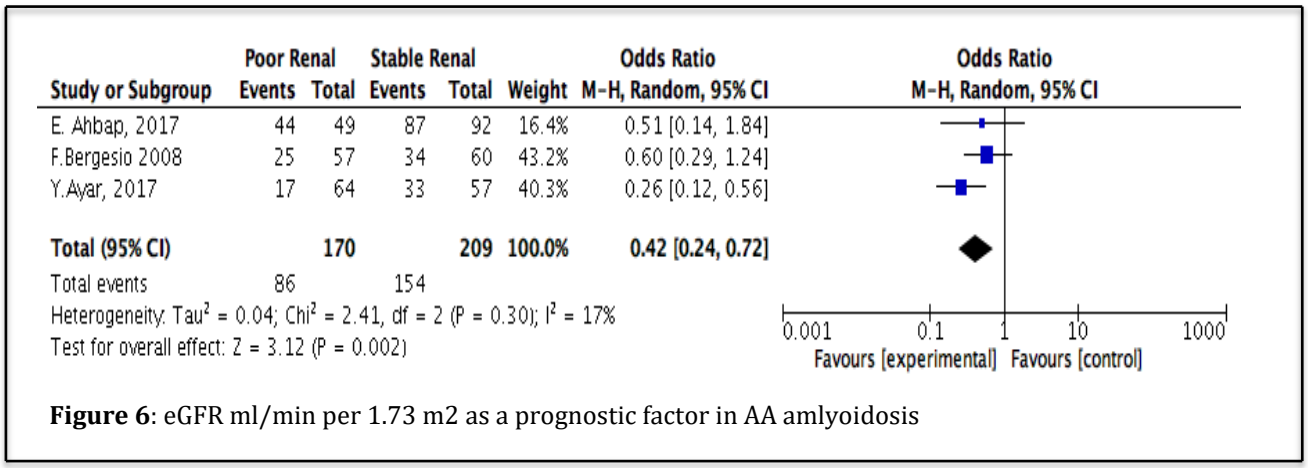

Figure 6: eGFR ml/min per 1.73 m2 as a prognostic factor in AA amlyoidosis

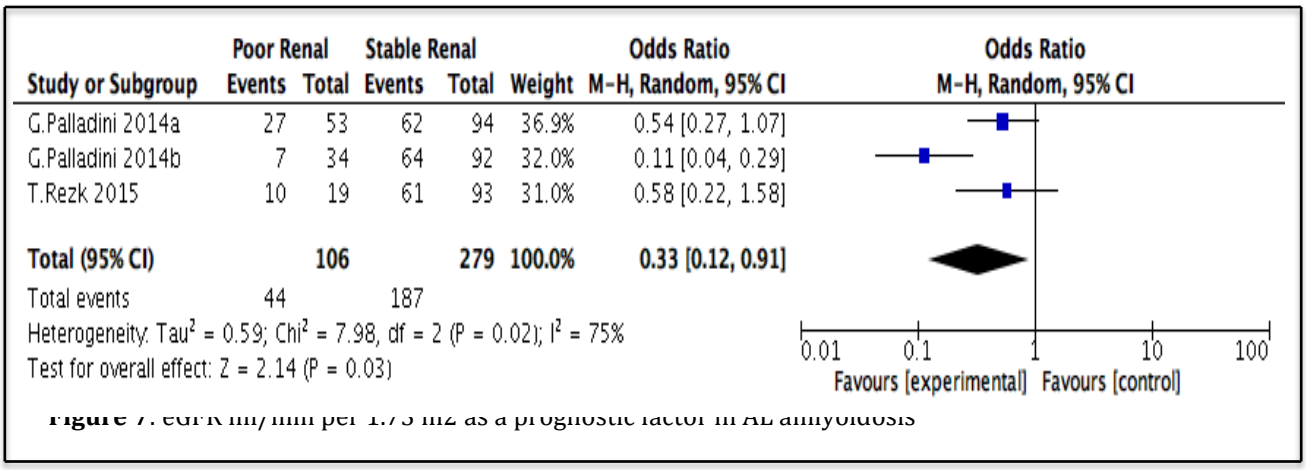

Figure 7: eGFR ml/min per 1.73 m2 as a prognostic factor in AL amlyoidosis

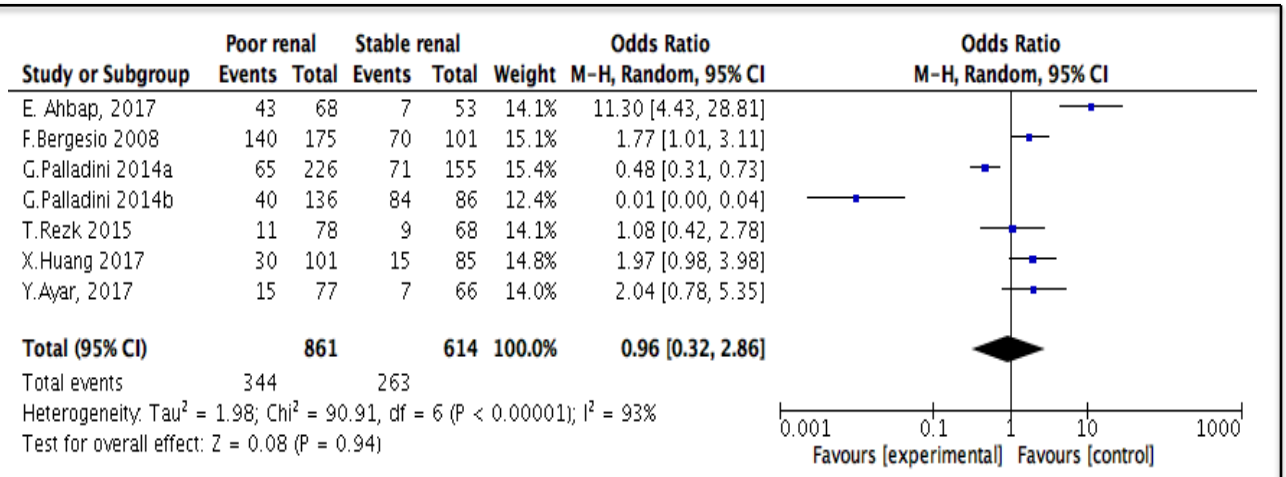

Figure 8: Progression of patients reaching end stage renal disease and doing dialysis

Discussion

This is the first systematic review and meta-analysis examining the prognostic factors of poor renal outcome in renal amyloidosis patients. We believe that it comprises the totality of data published to date: 7 moderate to good quality prospective and retrospective cohort studies that included people across the full spectrum of renal amyloidosis.[13–19]

The findings of this meta-analysis demonstrated that the most valuable and informative prognostic factors in patients with renal amyloidosis were primarily male gender; proteinuria, serum creatinine and low eGFR were all associated with poor renal outcome. Three studies mentioned older age as a poor prognostic factor.[14,20,21]

Several studies concluded that the early increases in proteinuria did not significantly alter renal outcomes. Severe proteinuria and nephrotic syndrome are strongly related to the amount and pattern of amyloid deposition.[22] Despite, it is possible that later increases in proteinuria in case of relapse can have a larger effect. In addition, it was proposed by the 2005 ISA panel of experts, that an early decrease of equal or more than 25% in eGFR predicts a poor renal outcomes and survival.

The meta-analysis combined studies of AL and AA amyloidosis, Bohle et al.[23] reported that in the first 5 years after diagnosis, patients with amyloidosis AL showed a more rapid deterioration of renal function than those with AA. Yet, except for cases receiving special therapy, there were no significant clinical differences between cases with AA and those with AL in the present study.

Serum creatinine was significantly associated with poor renal outcomes and in previous studies it was reported that, median survival of patients with creatinine levels of atleast 1.69 mg/dL (150 µmol/L) was found to be 18 months in a study from 1989.[22]

Patients with severe vascular, glomerular amyloidosis and interstitial inflammatory infiltrate showed the highest levels of serum creatinine concentrations, urine protein concentrations and glomerulosclerosis.[20]

A rise in Scr (>25%) did not negatively cause poor outcomes in renal amyloidosis patients once they achieved a >75% reduction in proteinuria. One-way to interpret this is that reductions in proteinuria by >75% would mean the kidney is recovering.[24]

From our pooled findings, the likely explanation is that the probability of developing ESRD and doing dialysis was more associated with declined renal function at the onset of renal amyloidosis. Long-term prognosis would evolve terrible outcomes if patients with renal amyloidosis had other organs involvements.

Complications of end- stage renal disease are the main causes of death and median survival after diagnosis varies between 4 and 10 years.[25,26]

From a clinical point of view, our finding underscores the need for close medical monitoring of patients, which presents with fatigue, edema, hypotension and nephrotic syndrome. These clinical features are strongly associated with renal amyloidosis. Moreover, Patients with such features should have a renal biopsy as soon as possible thus to minimize risk of irreversible kidney damage. The delay in kidney biopsy could also adversely affect the renal outcomes.

This study was designed to evaluate poor renal outcomes of patients with AL or AA amyloidosis with renal involvements thus, response of other organs will not be used. Cardiac biomarkers were not included in the analysis of this study. There is no doubt that cardiac biomarkers are quite useful as markers of response in amyloidosis, but not all patients have cardiac involvement.

Study Limitations

Meta-analysis could overcome the limitation that not every individual study had a sufficient number of enrolled patients and adequate occurrence of hard endpoints. However, several factors decreased the quality of the evidence. Selective outcome reporting bias was the major limitation. None of the included seven studies reported all of the ORs from univariate and multivariate analyses of the association of each renal outcome feature with the development of renal insufficiency and progression to ESRD. The studies varied among included studies and could be partially responsible for the heterogeneity of the summarized results. The results of our meta-analysis should be interpreted with caution because of these inherent limitations. More methodologically sound and sufficiently powered prospective, retrospective and randomized cohort studies with adequate number of patients and length of follow-up are still urgently needed to address the questions regarding prognostic utility of renal amyloidosis patients.

Conclusions

The odds of having poor renal prognosis in both groups was increased in the presence of older age, male gender, high serum creatinine, a low glomerular filtration rate (GFR) and heavy proteinuria at diagnosis on renal biopsy. The results of the study highlight the role of close medical monitoring of patients, which presents with fatigue, edema, hypotension and nephrotic syndrome. These clinical features are strongly associated with renal amyloidosis. Moreover, Patients with such features should have a renal biopsy as soon as possible thus to minimize risk of irreversible kidney damage that adversely affect the renal outcomes.

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