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Introduction:

Lupus nephritis (LN) is one of the most severe organ manifestations of systemic lupus erythematosus and despite great progress in the treatment of LN in past decades, it remains a significant cause of morbidity and mortality¹. The aim of this retrospective study was to evaluate different types of initial treatment in terms of long-term outcome, to assess short term response after initial therapy and to evaluate possible risk factors associated with unfavourable prognosis.

Methods:

Patients with most severe forms of lupus nephritis (class III, IV and combined forms III+V and IV+V) were enrolled into the study (n=157; median age 32.6 years; M/F 25/132). Patients were divided into 3 groups based on administered initial treatment: cyclophosphamide (CYC, 70.1 %), cyclosporine A (CsA, 15.9 %) and mycophenolate mophetil (MMF, 13.4 %). We assessed overall survival comparing class 3 and 4S against 4G using Kaplan-Meier statistic model. Possible risk factors (age, creatinine at baseline and presence of renal relapse any time during follow up) were evaluated using two groups divided by its median value. Renal response (using criteria as defined by EULAR/ERA-EDTA recommendation 2012²) after one year of treatment was assessed in a sub study counting a total of 102 patients with biopsy proven LN diagnosed between 2007 and 2013 in our centre.

Baseline characteristics of patients:

Gender	Age (median)	Ethnicity	Class of LN	IV S/G	Initial Therapy	Creatinine (median)	PU (median)
132 women 25 men	32 years	153 Caucasians 3 Asians 1 Afro-American	35 class III 11 III+V 91 class IV 14 IV+V	28 S 49 G	106 CYC 28 Cy A 22 MMF 1 Other	82 umol/l	2 g /day

Results:

Analysis of 157 patients:

Median time of follow-up was 7.2 years (range 3 – 16 years). At baseline, the CYC group had significantly higher proteinuria (median 2.3 g/day) compared to MMF (median 0.8 g/day) (p = 0.0436) while it did not differ from CsA group. There were no statistically significant differences in renal function among the groups at baseline (Figure 1). At the end of follow-up, nor renal function neither proteinuria differed in the three groups. During the follow up, 11/110 (10 %) patients from CYC group, 4/25 (16 %) in the CsA group and 1/21 (4.7 %) in the MMF group died. There was no difference in the overall survival (p=0.395). Renal replacement therapy was needed in 7/110 (6.4 %) in CYC group, 4/25 (16 %) in CsA group and 1/21 (4.7 %) in MMF group, and the renal survival did not significantly differ between groups.

Overall five year survival differed in group of patients with either LN class 3 or 4S (95,3 %) from LN class 4G that showed 89,2 % five year survival (Figure 2).

In patients with creatinine higher than 82 umol/l (median baseline value) renal survival was significantly worse than in patients with levels of creatinine lower than median at baseline (p-value 0,0011), see Fig. 4. Significant difference in renal survival was found also in patients with age higher than 32 years (median at baseline) compared with opposite group (p-value 0,0036), see Fig. 3.

Patients with documented renal relaps had the same outcomes as patients without known renal relaps (data not shown).

Figure 1. Baseline creatinine levels according therapeutic regime.

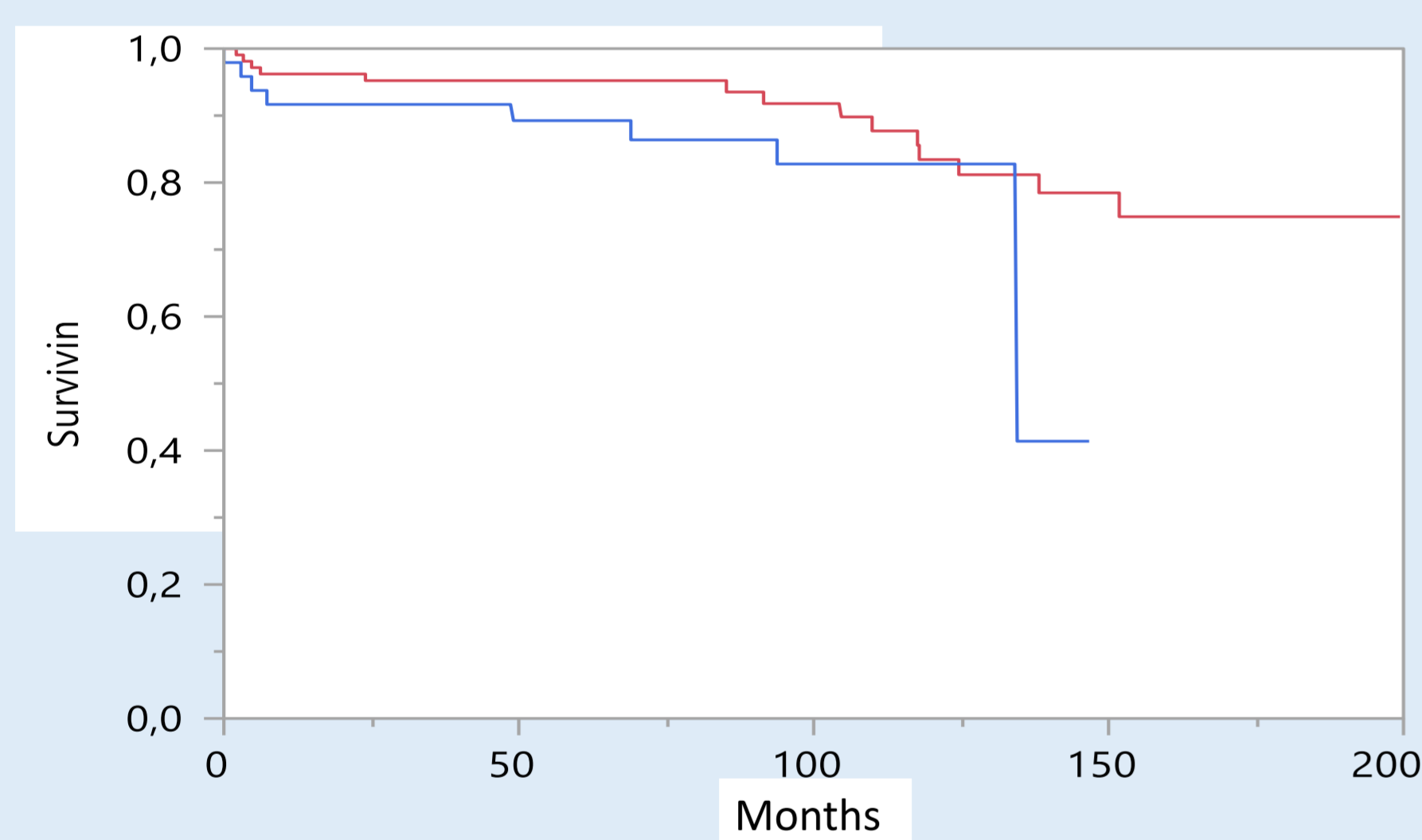
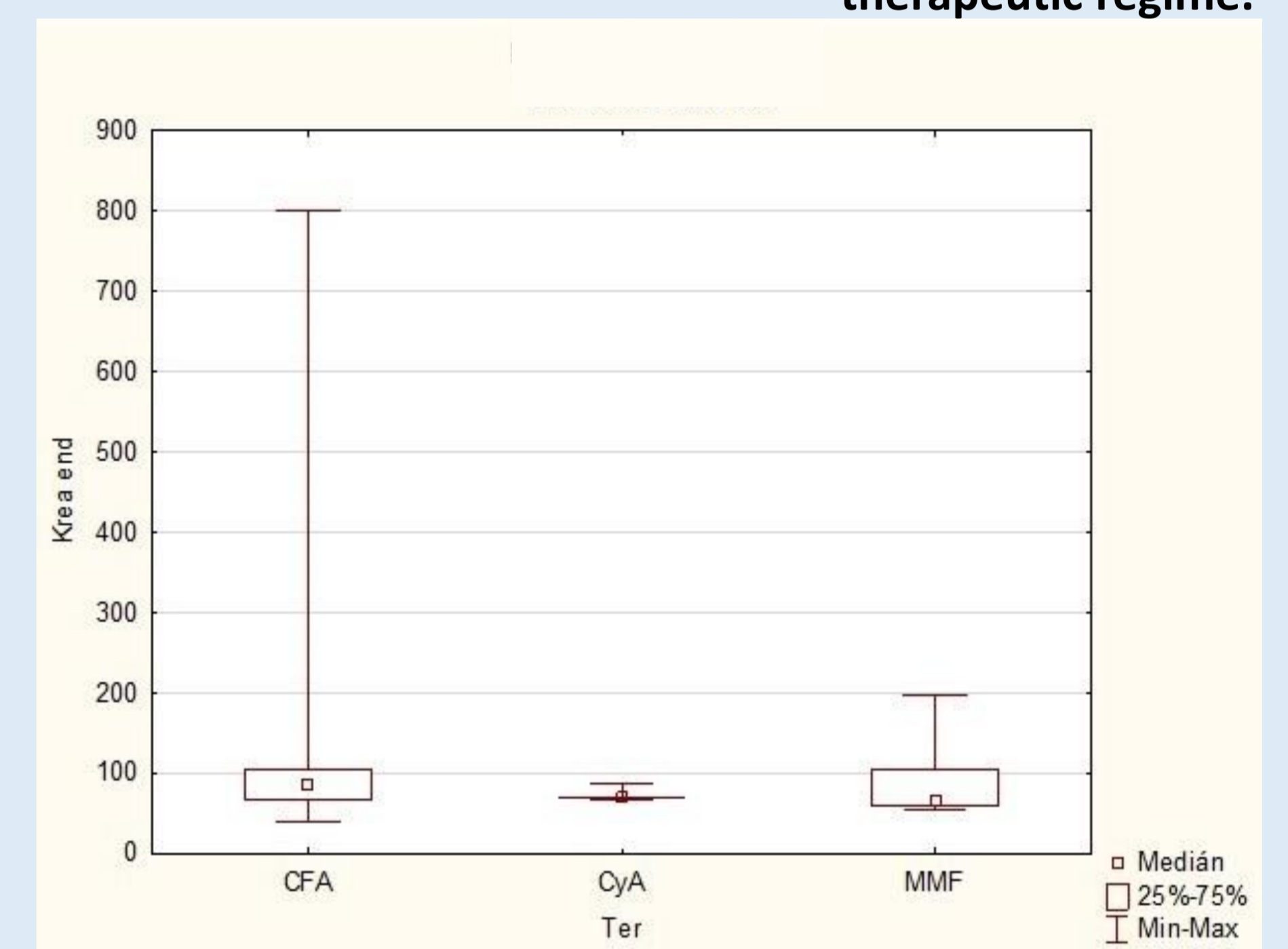


Figure 2. Kaplan-Meier overall survival curve depending on Lupus nephritis class. Patients with class 3 and 4S (red line), separately class 4G (blue line).

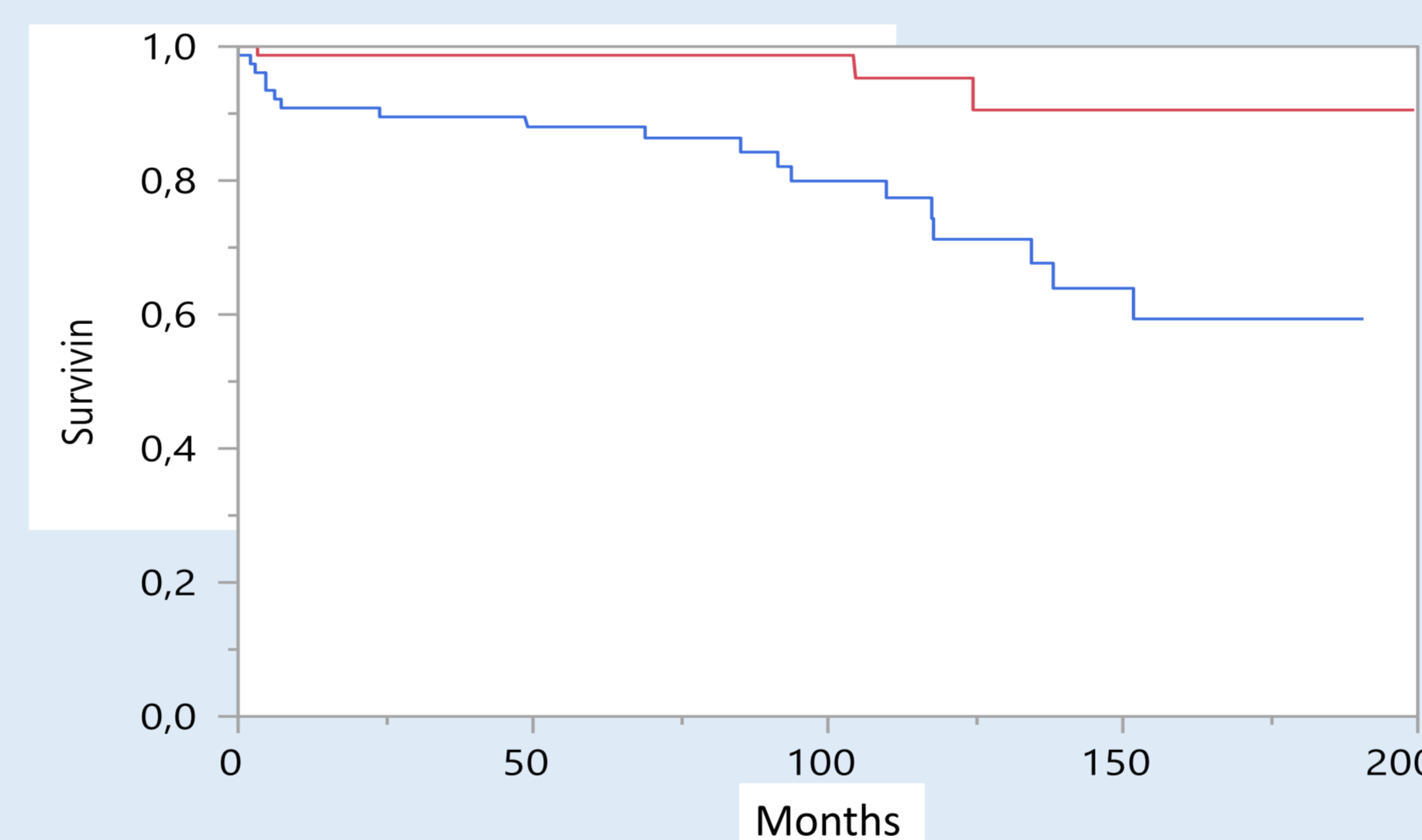


Figure 3. Kaplan-Meier renal survival curve depending on the age at the time of manifestation. Red line represents group younger than 32 years, blue line the opposite group.

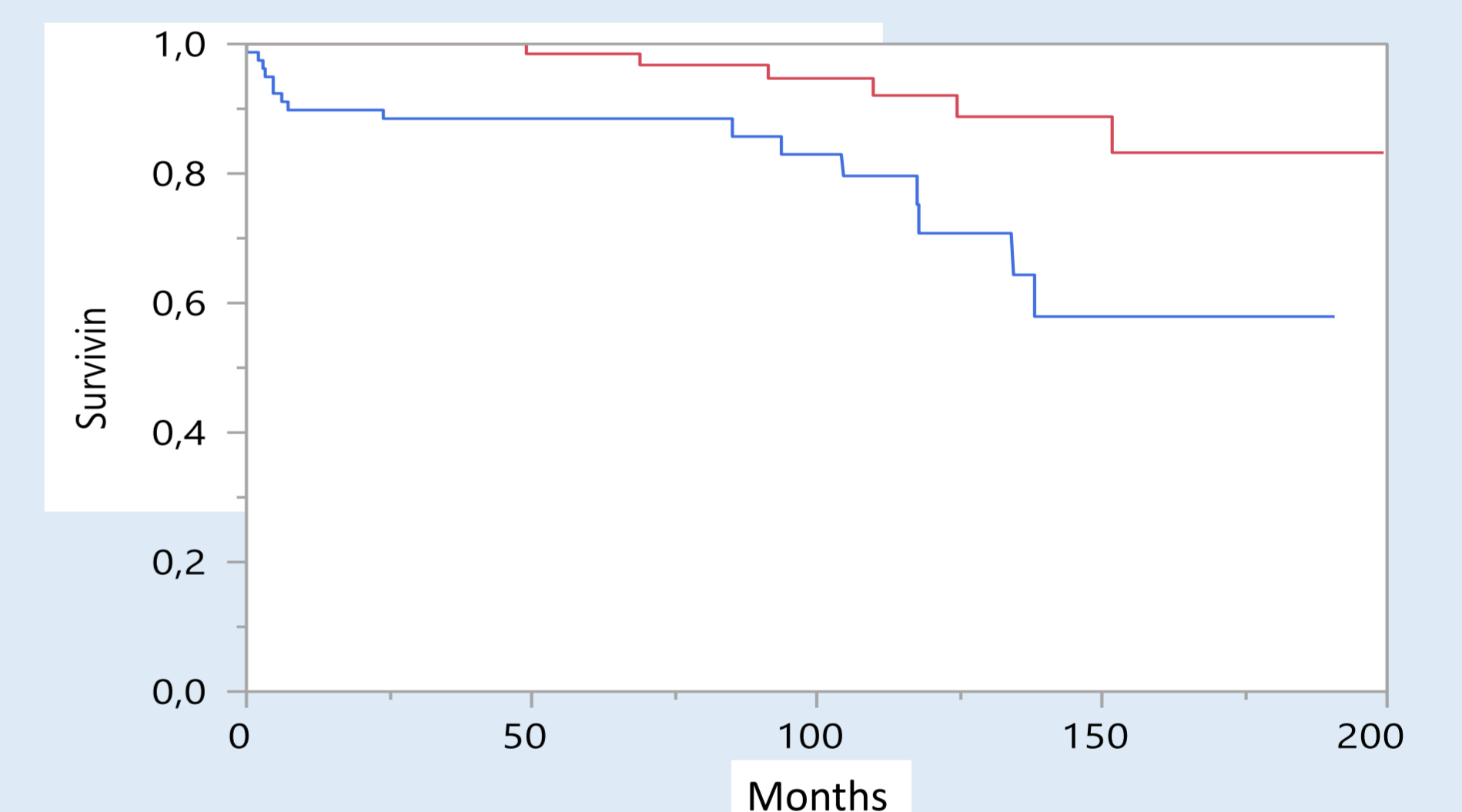


Figure 4. Kaplan-Meier renal survival curve depending on the baseline creatinine. Red line showing outcome of group with creatinine less than 82 umol/l at baseline, blue line represents the rest.

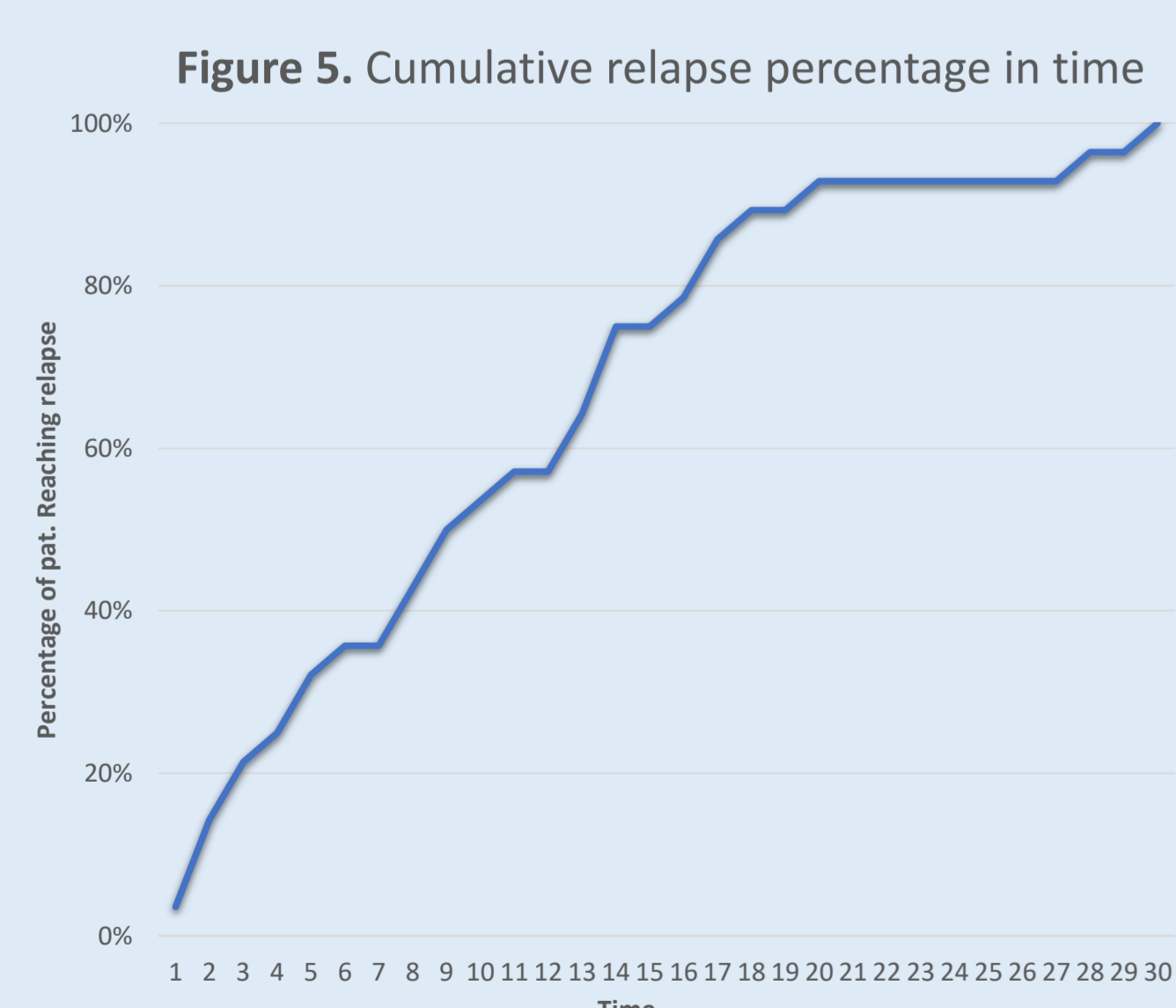
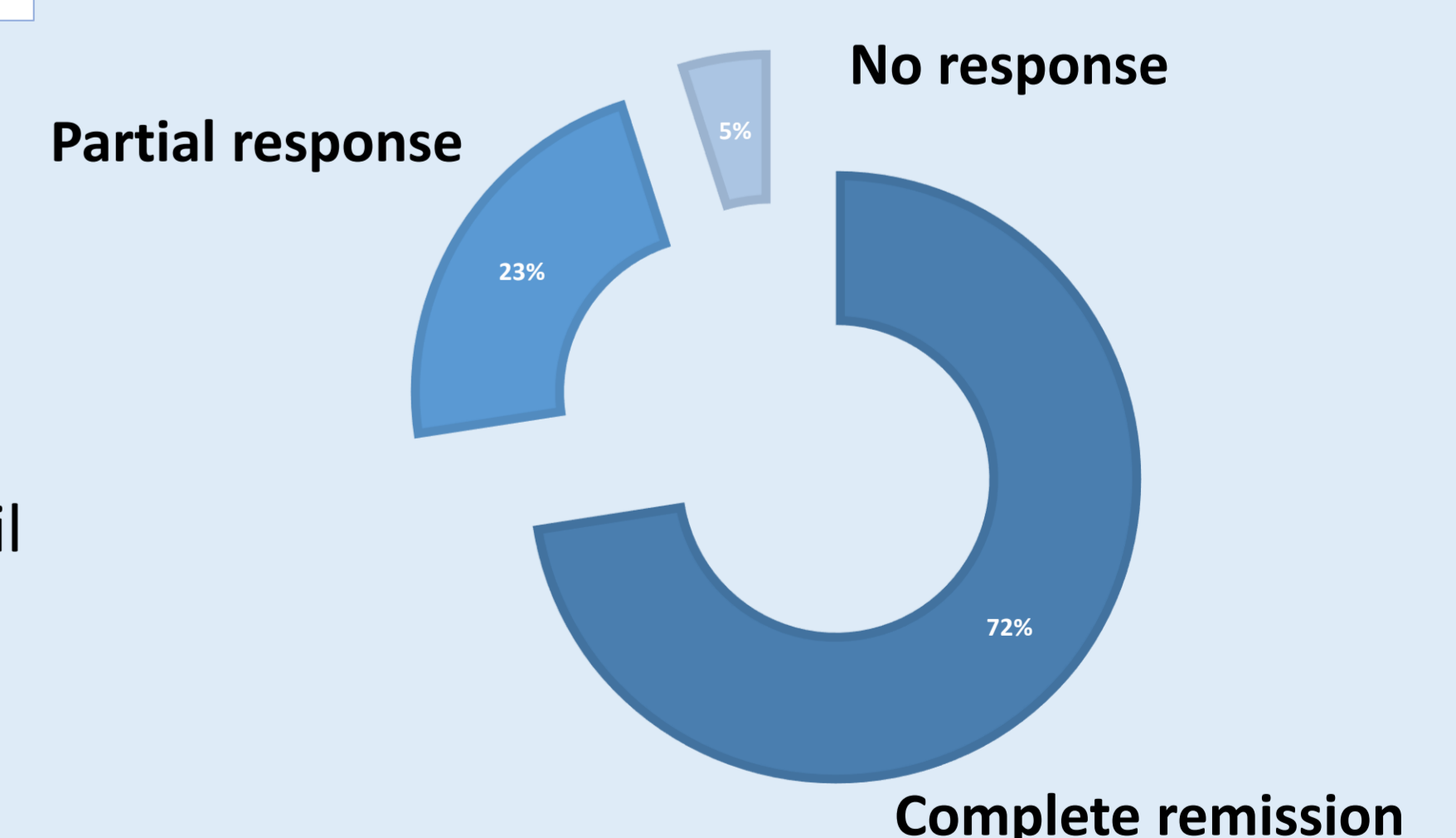


Figure 5. Cumulative relapse percentage in time

Subanalysis of 102 patients:

In a sub study of 102 patients complete response at one year after renal biopsy was achieved in 72 % of patients and partial response in 23 %, the remaining 5 % of patients were classified as non-responders (Figure 6). Renal relapse during follow-up occurred in 34 % of patients. Figure 5 shows cumulative percentage of patients reaching relapse in time. More than 90 % reached relapse in five years, so the likelihood of having relapse after five years for group of patients without relapse until then was only 10 %.

Figure 6. Percentage of different response quality



Conclusion:

Our retrospective study of patients with first manifestation of lupus nephritis did not show any difference in long-term survival comparing three common types of initial therapy. Unlike study of Parikh et al.³, we didnt find correlation between patients with relaps and those without, although design of our study was different. We confirmed higher levels of creatinine and age to be negative prognostic factors for patients with LN at baseline. Short term outcomes were comparable with results of other Authors⁴.

References:

- Quintana LF, Jayne D: Sustained remission in lupus nephritis: still a hard road ahead. Nephrol Dial Transplant. 2016 Dec;31(12):2011-2018.
- Bertsias GK et al.: Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012 Nov;71(11):1771-82.
- Parikh SV et al.: Renal flare as a predictor of incident and progressive CKD in patients with lupus nephritis. Clin J Am Soc Nephrol. 2014 Feb;9(2):279-84.
- Dall'Era M et al.: Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. Arthritis Rheumatol. 2015 May;67(5):1305-13.