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Differences in clinical presentation, treatment and medium-term outcome in children with different biopsy classes of lupus nephritis

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Abstract

Background

Lupus nephritis is an uncommon severe glomerulonephritis which on kidney biopsy is classified into class I-V. The aim of this study was to describe differences in presentation, treatment and outcome between children with the different biopsy classes.

Methods

We compared, in a cohort of 428 children, clinical and laboratory data at onset, two-year and last follow-up (median of four years and four month) between children with the different biopsy classes.

Results

The number of children with the biopsy classes III, IV, V and mixed V and III or IV, were 132, 191, 43 and 62 respectively. At onset did children with a biopsy pattern of class III and IV show lower haemoglobin levels, 99 and 96 g/L, vs 104 and 112.5 g/L, respectively and lower complement C3 levels 0.37 and 0.35 g/L vs 0.44 and 0.59. Levels of double stranded DNA antibodies (dsDNA) and ESR showed no statistically significant differences between the groups. Reduced eGFR was found significantly more often in children with class IV compared to the other groups of children. Children with mixed class V and III or IV had the highest levels of proteinuria and lowest serum albumin levels.

Treatment of the children in the different groups was mainly similar with the exceptions of less frequent use of initial methylprednisolone and cyclophosphamide in children with pure class V.

At two years and last follow up no differences in neither inflammatory parameters nor complement and dsDNA levels were found. eGFR was also not significantly different at follow-up while between 9.6 and 31.9 percent of the children still showed impaired kidney function. Children with class V combined with III or IV did most often show continuing proteinuria.

Discussion

At onset children in the biopsy classes with proliferative glomerulonephritis showed more haematological signs of inflammation while those with class V, membranous nephritis, had higher levels of proteinuria. Children with mixed biopsy phenotypes showed a combination of these findings. Treatment and outcome were however surprisingly similar in children from all biopsy groups.

Introduction

A kidney biopsy is regarded as essential in children with suspected lupus nephritis. This is to confirm, or not, the suspected diagnosis but also to classify the degree of changes found on the biopsy. The most recent recommendations on grading of the biopsy are based on the International Society of Nephrology/Royal Pathology Society (ISN/RPS) classification. [1]

The biopsy classes I and II are regarded as too mild to warrant treatment on their own, many of those children will however need treatment due to other lupus manifestations. Class III and class IV are proliferative forms with the need for immunosuppressive treatment and corticosteroids to reduce the risk of progressive kidney damage.

Class V is a membranous lupus nephritis and is characterised of less inflammatory disease activity. In some children the biopsy findings show a mixture of both inflammatory and membranous nephritis (class V mixed with III or IV).

The aim of the present study was to describe a large multiethnic international cohort of 428 children with lupus nephritis to evaluate to which degree the biopsy class could be predicted by clinical findings. Were children with different biopsy findings treated differently? Was the outcome dependant on the biopsy class?

Material and methods

Four hundred and twenty-eight patients (≤ 18 years old) were studied. All patients had a biopsy proven LN class ≥ III (International Society of nephrology/Royal Pathology Society; ISN/RPS) at diagnosis [1] and were treated in 25 international centres from January 2009 up to last available follow-up. Centres involved were in USA, India, China, Thailand, Singapore, Japan, Brazil, France,

Italy, Turkey, Hong Kong and UK. Data are reported at diagnosis, 24 months and at last available follow-up. It was a retrospective observational anonymized study. It has been registered at Great Ormond Street NHS Foundation Trust as a Clinical Audit (Registration Number: 2347). Approval from the local research ethics committee was given according to local policies. No written informed consent was required due to the use of anonymized patient data.

We studied the different biopsy classes in terms of patient characteristics, laboratory parameters, treatment received and medium-term outcome.

The biopsies are classified into five main groups with some children having a dual classification class V with class III or IV [1]. Class I and II show only mesangial involvement and are regarded as relatively mild and that no specific treatment is needed for the nephritis. The findings seen in class III and IV are worsening degrees of a proliferative glomerulonephritis with active and sclerotic lesions. Membranous nephritis is the main finding on biopsies with a class V LN. Children with mixed class V and III or IV show both inflammatory lesion and membranous changes.

Nephrotic range proteinuria was defined as UPCR > 2 mg/mg (200 mg/mmoL) in spot urine or timed urine sample, while sub-nephrotic range proteinuria was defined as UPCR between 0.2 and 2 mg/mg. Microscopic haematuria was defined as more than 5 x 10^6 red cells/L or more than 15 /µl. Nephrotic syndrome was defined as nephrotic range proteinuria and hypoalbuminemia (serum albumin < 3 g/dl) [2].

Definitions of remission

Complete remission was considered as urine-protein-creatinine ratio (UPCR) or urine-albumin/urine-creatinine (UACR) ≤ 0.2 mg/mg (≤ 20mg/mmol) and eGFR ≥90 ml/min/1.73m2 or serum creatinine increased less than 15% compared to the upper limit of reference value for age.

Partial remission was defined as UPCR or UACR < 2 mg/mg (<230 mg/mmol), or a 50% reduction if UPCR ≥ 2 at baseline; and eGFR ≥ 90 ml/min/1.73m^2, or serum creatinine increased less than 25% compared to the upper limit of reference value for age. [3;4]

Statistics

Data are presented as percentages or medians with interquartile ranges (25°-75°). Line graphs show medians. Kruskal Wallis and Chi-square tests were used for comparisons. We used Statistics Package for Social Sciences (SPSS; IBM Corp., Armonk, NY) and GraphPad Prism for graphical illustrations. P< 0.05 was considered statistically significant.

Results

Patient characteristics

We studied 428 patients who underwent a kidney biopsy at diagnosis (Table 1). The median age at diagnosis was between 12 and 13.9 years in the different classes and between 70.5% and 79.1% of the patients were girls (P>0.05). East Asian children were the largest ethnic group, followed by Caucasian and children from South Asia. Other ethnic groups were Hispanic (7.5%), unknown (6.5%), Subsaharan African/African American (5.6%), heterogenous (3.3%) and Semitic-Arabic (2.3%).

Children of different ethnicities showed significant differences in the proportion of the different biopsy classes (P<0.001). Class IV was the most represented biopsy class, except for Subsaharan African/African American who had more patients with class III. Children from East and South Asia more often had a biopsy pattern of class III than the other groups while class IV was most commonly seen in children of Caucasian background (Table 1).

Laboratory parameters

At diagnosis, the haemoglobin levels were lower in children with biopsy class III and IV compared to class V mixed and pure (P= 0.0002), while ESR was raised to similar levels in all biopsy groups. The complement C3 levels were significantly lower in class III and IV compared to the other two classes (P<0.0001). This was also seen in the numeric double stranded DNA (dsDNA) levels, but this did not reach statistical significance (Table 2, figure 1).

More than half of the patients with class IV had reduced eGFR at diagnosis, while it was impaired in about one-third of the patients in the other biopsy classes (P= 0.004) (Table 2). Proteinuria was present in more than 85% of children in all biopsy classes, with the highest median level of 3.36 mg/mg in class V mixed with III or IV (P<0.0001). These children did also show the lowest serum albumin levels, 24.5 g/L compared to the other children (P<0.0001). About 40% of patients with class IV and V mixed with III and IV had nephrotic syndrome at onset, compared to patients with class III and V pure, 31% and 24.2%, respectively (P 0.15). The degree of haematuria was most pronounced in patients with class IV, 40 RBC/µl, and lowest in patients with pure class V, 8 RBC/µl (P<0.0001) (Table 2).

Induction treatment

Patients with pure class V were significantly less often treated with iv Methylprednisolone during the induction phase compared to the other classes (P 0.00004) (Table 3). The vast majority, but not all, of the patients in all biopsy groups were treated with oral prednisolone with an initial median dose of 1 mg/kg/day in all the classes. Fifty patients (20% class III, 52% class IV, 4% class V mixed with III and IV, 24% class V pure) didn't received either oral or IV corticosteroids. No differences were found considering the median dose of prednisolone at diagnosis among biopsy

classes: class III 0.10 (0.05-0.17) mg/kg, class IV 0.09 (0.03-0.23) mg/kg, class V mixed with III and IV 0.07 (0-0.1) mg/kg, class V 0.07 (0-0.17) mg/kg (P 0.16).

The initial immunosuppressive medication was rather similar in all biopsy groups except in pure class V where iv cyclophosphamide was used significantly less and azathioprine significantly more often (Table 3). All other studied immunosuppressive drugs were used in similar proportions of the children in all biopsy groups. The most commonly used drugs were Mycophenolate mofetil (MMF) and Hydroxychloroquine. Rituximab was administered in 12.9% to 19.9% of all patients. Cyclosporine A, Tacrolimus and Methotrexate was only used in a small proportion, less than 5%, of the children. About half of the patients in all biopsy classes were treated with an ACE inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB) (Table 3).

Maintenance treatment at 24 months and at last visit

Oral prednisolone was continued at two years after the diagnosis in most children, 72.6% to 84.3% and at last follow-up in 27.4 to 55.3% of the children (Figure 2A). No differences were found in the median dose of prednisolone at 24 months: class III 0.14 (0.08-0.24) mg/kg, class IV 0.12 (0.07-0.30) mg/kg, class V mixed with III and IV 0.09 (0.05-0.24) mg/kg, class V 0.14 (0.05-0.27) mg/kg (P 0.40). Only one patient with class III (0.8%), two patients with class IV (1.09%), one with class V mixed (2.6%), and none with pure class V received prednisolone ≥5mg/day at 24 months.

At last follow-up significantly more children with biopsy class III and fewer with class V pure were given prednisolone. The median dose of prednisolone was 0.10 (0.04-0.17) mg/kg for class III, 0.09 (0.03-0.21) mg/kg for class IV, 0.07 (0-0.1) mg/kg for class V mixed, 0.07 (0-0.17) mg/kg for class V pure (P 0.19). One patient with class IV (0.57%) and one with class V (2.63%) had prednisolone ≥5mg/day at last follow-up.

No significant differences were found between the groups in the usage of MMF two years after the diagnosis (Figure 2B) while at last follow-up fewer children with class III at biopsy were given MMF and some of these children had been switched to azathioprine (Figure 2B and C) (P=0.01). The use hydroxychloroquine was similar from diagnosis until last follow-up (data not shown). The use of ACEi and ARBs remained stable over the whole study period with 45% to 65% of the children receiving one of those drugs.

Outcome

At 24 months follow-up and at last visit haemoglobin and ESR improved in similar ways with no significant differences found in the median values of the children in the different biopsy groups (Table 4 and 5). The complement levels did also improve in a similar way in the different groups. The median levels of dsDNA showed a somewhat smaller improvement in children with biopsy class III and V mixed with III or IV (Figure 1).

Despite eGFR being significantly lower at onset in children with biopsy class IV the kidney function had improved both at 24 months and at last visit and no significant differences were found between the groups neither in the median eGFR level nor in the proportion of children with impaired kidney function (Figure 1, Table 4 and 5) at those time points. Proteinuria improved significantly in all biopsy groups but children with class V mixed with III or IV continued to have both higher median levels of proteinuria and a higher proportion of children with abnormal levels (Figure 1, Table 4 and 5).

At 24 months follow-up complete remission was reached by 64.2% of patients with class III, 47.2% of patients with class IV, 50% of patients with class V mixed and 62.2% with pure class V (P 0.06). At the end of the follow-up 54.7%, 47.7%, 44.1% and 50% of patients class III, IV, V mixed and V

pure respectively, were in complete remission (P 0.91) (Figure 3A). At 24 months follow-up partial remission was achieved by 8.6%, 22.8%, 10% and 10.8% and at last follow-up by 10.5%, 15.6%, 17.6% and 12.5% of patients class III, IV, V mixed and V pure respectively (Figure 3B).

End-stage renal disease occurred in three patients (one patient with biopsy class V and two with biopsy class IV) at 24 months and in four patients (one with class V, one with class IV and two with class II) at the end of the follow up.

Discussion

We have in our very large cohort of 428 children with lupus nephritis (LN) shown that children with LN biopsy class IV compared to the children with the other biopsy classes had significantly worse eGFR at onset. The eGFR improved markedly with treatment and at 2 year and last follow-up no statistically significant differences in kidney function were found between children with different biopsy classes.

At onset, all groups of children had significant proteinuria with the highest values being seen in children with LN class V mixed with III or IV. At last follow-up the proteinuria had normalised in more than half of the children, even so, V mixed group had still the highest percentages of patients with proteinuria.

A kidney biopsy is regarded as an important tool to decide the treatment of a child with LN. The proportion of children in our study with the different classes is consistent with that of previous studies with children with class IV being the largest group, 45% of cases [5;6;7].

The laboratory markers found at onset in our study were different in the different groups. Markers of inflammation were found most often in children with proliferative LN.

The group with proliferative lesions had more pronounced anaemia, but the levels of ESR showed no differences between the groups. Children with proliferative LN showed the lowest levels of complement C3 compared to the other groups. No differences were found in the C4 levels. In contrast a recent study in children found both low C3 and C4 in patients with proliferative lesions [8] Low complement C3 within the first 6 months has been associated with increased risk of developing CKD in adult patients [9].

A study in adult patients reported higher dsDNA values in those with proliferative LN [10]. Those findings are similar to ours where we found a tendency towards higher dsDNA antibody titres in the children with proliferative nephritis, but this did not reach statistical significance. Overall, we haven't found any clinical, laboratory or histological features among children who failed to achieve normalization of kidney function or sufficient reduction of proteinuria. None of the blood and clinical parameters could replace kidney biopsy at predicting LN class.

Very interestingly the treatments given were, with a few exceptions, similar between the different biopsy classes. Oral steroids were given to most children from all biopsy groups while those with a pure membranous nephritis were given initial treatment with intravenous methylprednisolone significantly less often than the other children. In all groups of children, the most commonly used immunosuppressive drugs for induction were MMF and iv cyclophosphamide except for those with pure membranous nephritis where cyclophosphamide, very understandably, was used much less often. A retrospective study of 33 children with class IV LN compared oral MMF and iv Cyclophosphamide as induction therapy and found similar tolerance and efficacy of MMF [11].

A recent paper analysed the National Institutes of Health (NIH)-modified activity index (AI) and chronicity index (CI) in 60 children with LN and found that use of MMF as maintenance therapy was associated with a reduced risk of CKD as compared to low-dose prednisolone alone or in

combination with cyclophosphamide, or cyclosporine [12]. Unfortunately, AI and CI scores were unavailable for the majority of our study participants.

Methotrexate, which is used in a lot of children with lupus, is not recommended in children with lupus nephritis and in our study only 14 children received methotrexate. Calcineurin inhibitors are increasingly being recommended in lupus nephritis especially in patients with membranous disease but only 16 children had, in our study, been given either cyclosporine A or tacrolimus. Between 15 and 20 percent of all children had been given rituximab.

There was, despite active treatment, a large proportion of children who had not reached the treatment goals of normalised kidney function and of very low levels of protein in the urine with a protein creatinine ration of less than 0.2 mg/mg. At 2-year follow-up did still between 9 and 27 percent of the children have an eGFR lower than 90 ml/min/1.73m^2, and at last visit this had increased to 13 to 32 percent. No statistical differences were found between children from the biopsy groups. Abnormally high levels of proteinuria were found in between 15 and 46 percent and 27 and 49 percent respectively of the children at the two time points. Other paediatric studies showed similar findings. Suhlrie et al. studied 79 children with a proliferative form of LN and reported complete and partial remissions at 1 year of follow-up in 38% and 41% of children, respectively (4). Chibi et al found from 75% to 79% of children with class IV LN with complete remission (UPCR < 30 mg/mmol and eGFR > 60ml/min/1.73 m2) at 3 years of follow-up [11]. There is thus a need for more individualized treatment to further improve the chances of these children for long term kidney health; this could include optimization or prolongation of maintenance therapy, consideration of alternative or add-on agents, or closer monitoring and specific adjustment of treatment rather than uniform escalation.

The most accepted definition of remission of lupus nephritis in children is based on kidney function and proteinuria. The main problem with lowered eGFR and raised protein levels in the urine is that it can signify two different things, and sometimes perhaps both. Firstly, abnormal proteinuria and kidney function implies ongoing lupus activity in the kidneys. Secondly it can be due to scarring of the glomeruli. A kidney biopsy has been regarded as the only way to with certainty define which of those alternatives that are the cause of the abnormal kidney values in a specific patient, but a repeat biopsy is due to its invasiveness not routinely recommended [13;14].

De Vries et al have in a recent paper argued that the level of complement C3 could be used to suggest ongoing renal inflammation [15]. A reduced C3 level could thus indicate a need for further treatment. In our study 15.7% and 15.6% of the children did still have abnormal C3 levels at the two-year and last follow-up, respectively. On the other hand, LLDAS (low level lupus disease activity) has been proposed as a treat to target approach for lupus that allows for ongoing serologic activity in the absence of symptoms [16].

We found significant differences between the different ethnicities and the proportion of children with different biopsy classes. Surprisingly children with Caucasian background showed a class IV nephritis, commonly regarded as the most aggressive form, more often than children of east or south Asian background. This contrasts to the commonly held notion that children of Asian or African background more often have a clinically more aggressive form of lupus [17;18].

The major strength of our study is the large number of included children from many international centres. Our study does however also have several limitations: the observational nature of the analysis may lead to confounding bias and possible influencing factors, such as disease duration, treatment adherence, and comorbidities, were not systematically controlled. Histologic

classification was performed locally by numerous different renal pathologists without central adjudication. It is possible that the low proportion of biopsies in South Asia with mixed proliferative and membranous lesions were due to local pathology preferences. Moreover, activity and chronicity indices were not collected for this cohort study. Participants were enrolled prior to availability of belimumab, obinutuzumab, and voclosporin, so the role of these agents in triple therapy for LN could not be addressed. Nor was our study designed or powered to reliably compare efficacy and safety of different treatments.

In summary we found significant differences in kidney function and proteinuria at onset between children with proliferative and membranous lupus nephritis. Despite that the treatment of the children with different biopsy patterns was, with a few exceptions, very similar. Outcome at 2-years and last follow-up, at a median of 4 years and 4 months, was also surprisingly similar with a large proportion of the children having not achieved renal remission.

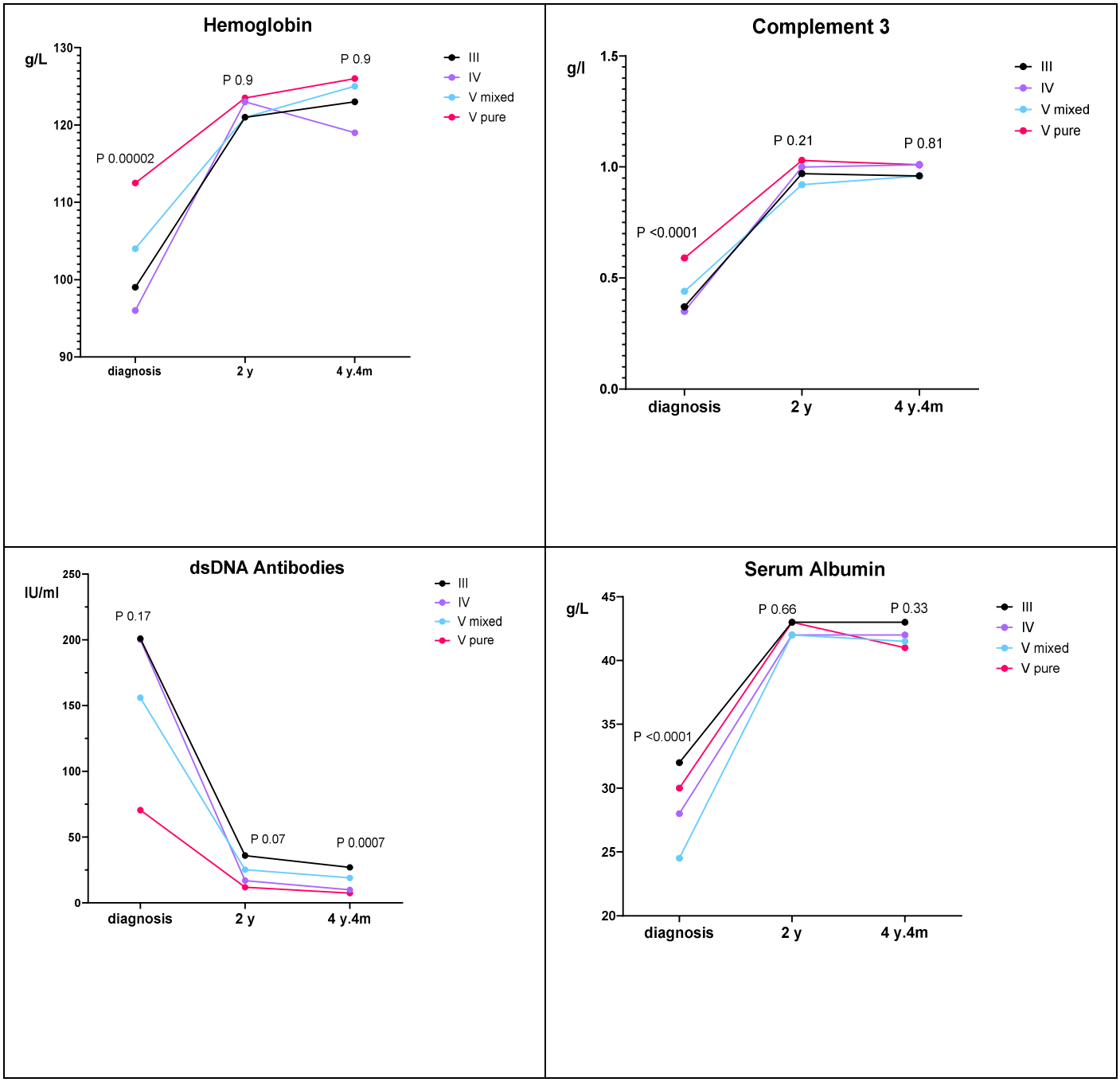
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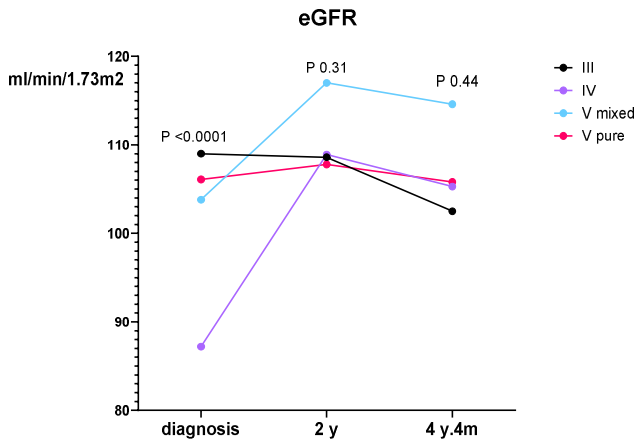
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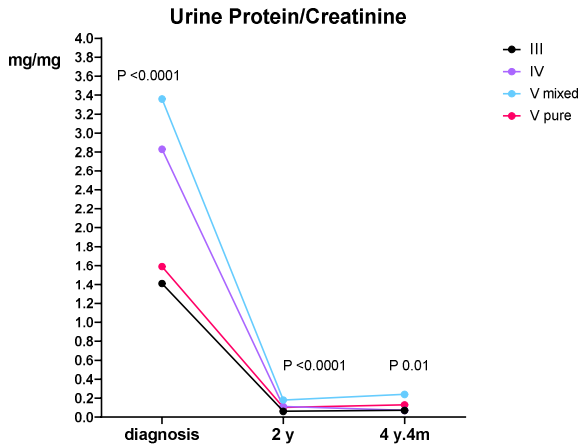
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Figure 1. Development of different haematological and kidney parameters at onset, two years and last follow-up (4 years and 4 months), stratified by lupus nephritis class on initial kidney biopsy




eGFR
ml/min/1.73m2
120
110
100
90
80
P 0.31
P 0.44
P <0.0001
diagnosis
2 y
4 y.4m
III
IV
V mixed
V pure


Urine Protein/Creatinine
mg/mg
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
P <0.0001
P <0.0001
P 0.01
diagnosis
2 y
4 y.4m
III
IV
V mixed
V pure

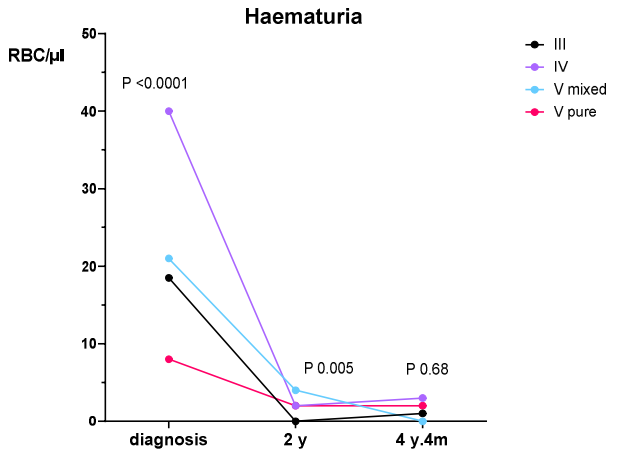
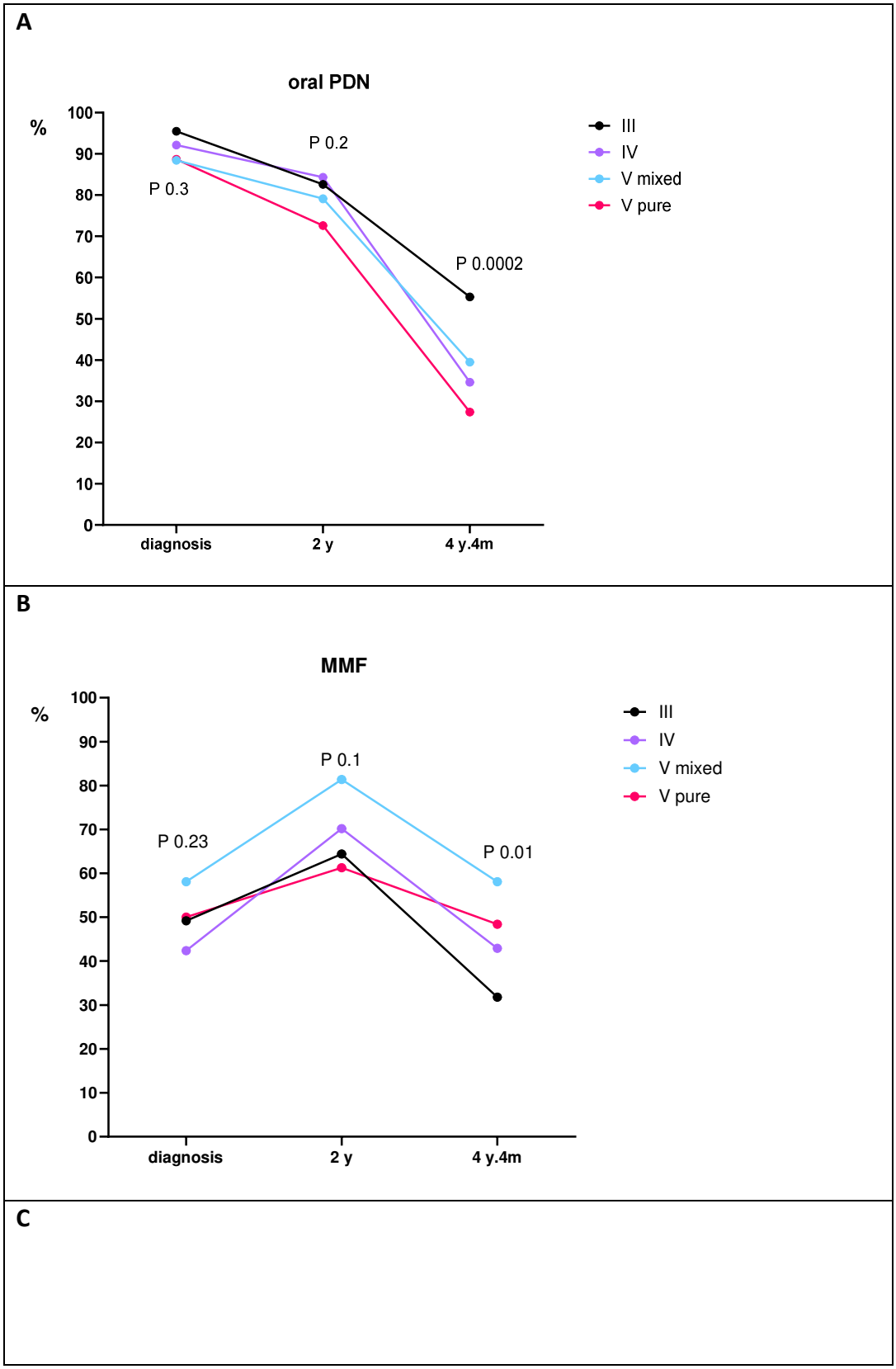

Haematuria
RBC/µl
50
40
30
20
10
0
P <0.0001
P 0.005
P 0.68
diagnosis
2 y
4 y.4m
III
IV
V mixed
V pure

Fig.2 Trends in treatment with oral prednisolone (A), MMF (B) and Azathioprine (C),), stratified by lupus nephritis class on initial kidney biopsy



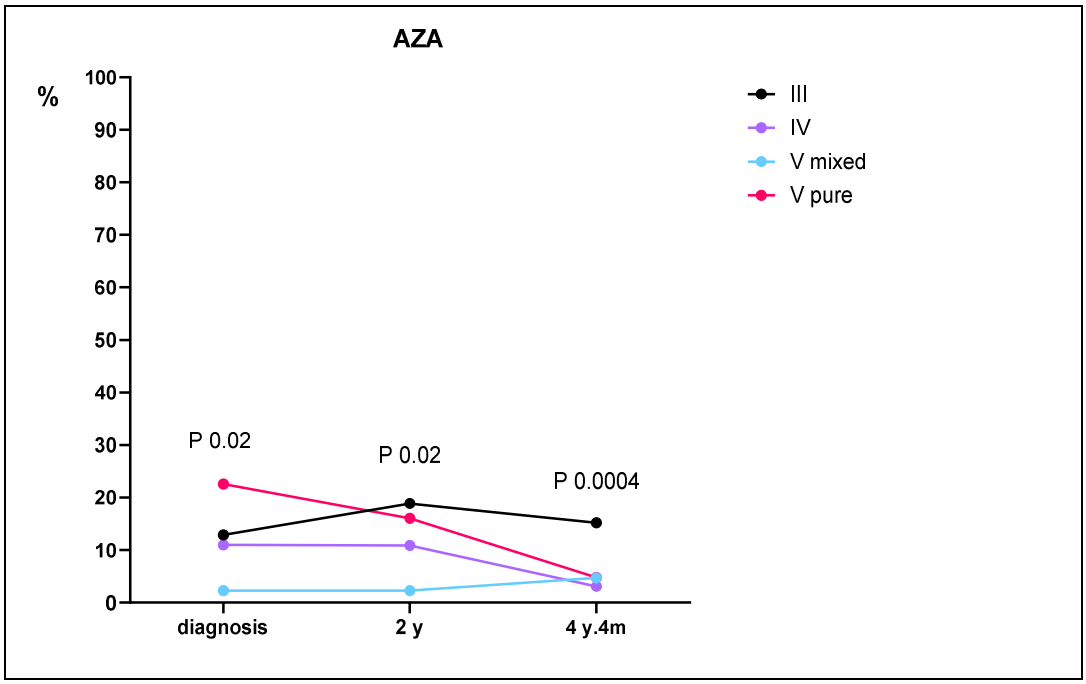
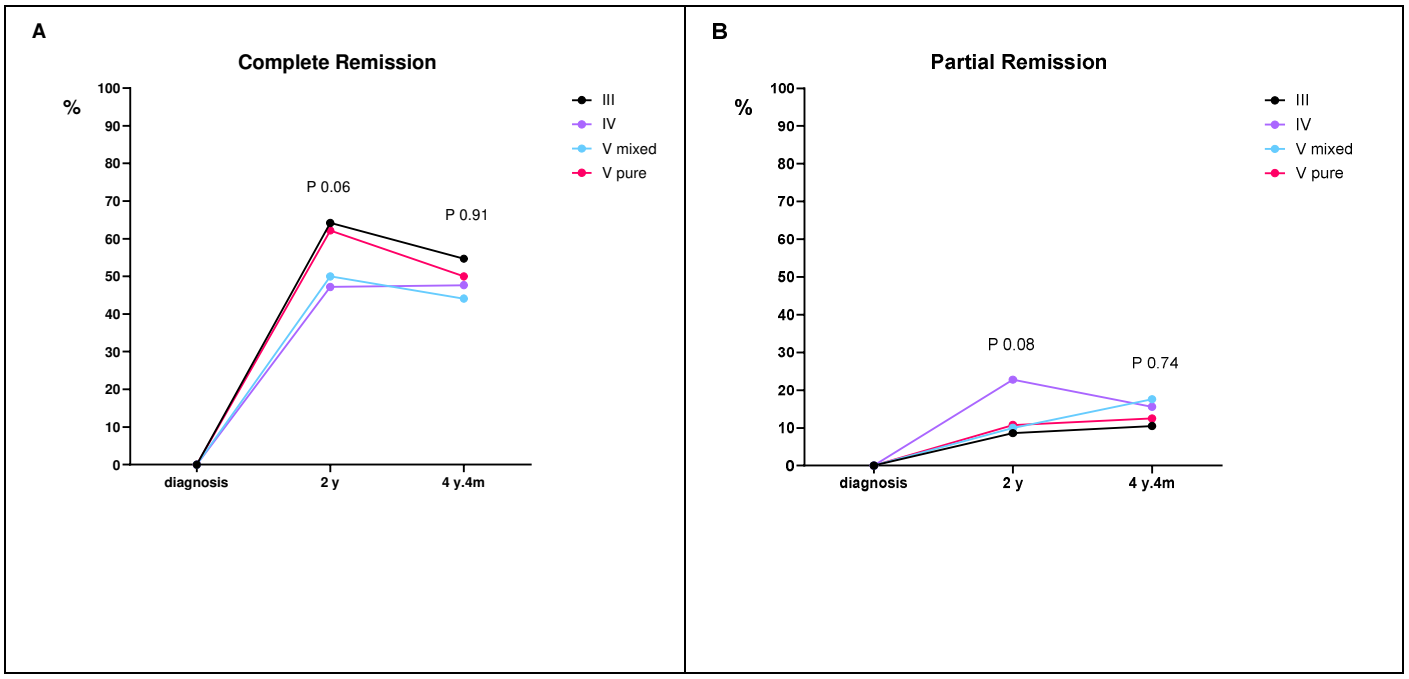

AZA
%
100
90
80
70
60
50
40
30
20
10
0
P 0.02
P 0.02
P 0.0004
diagnosis
2 y
4 y.4m
III
IV
V mixed
V pure

Fig.3 Complete (A) and partial remission (B), stratified by lupus nephritis class on initial kidney biopsy



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