IgA vasculitis nephritis – outcomes in adult-onset disease.

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Abstract

Objectives

IgA vasculitis (IgAV) in adults has been relatively under-investigated. Since outcomes are worse in other forms of vasculitis with increasing age, we investigated the outcomes of IgAV comparing younger adults (18-34), middle aged adults (35-64) and elderly patients (≥64 years) focusing on kidney outcomes.

Methods

We identified patients with renal biopsy confirmed IgAV nephritis and collected data regarding clinical features and progression to end stage kidney disease (ESKD). The relationship between patient factors and ESKD was analysed by regression.

Results

We identified 202 cases, 34% aged 18-34, 43% aged 35-64 and 23% were elderly (>64 years). Median follow up was 44 months. Elderly patients were more likely to present with ESKD (23.9%) compared with middle aged (13.7%) and younger adults (2.9%)(χ^2 11.6, p=0.002). In patients with independent kidney function at biopsy, there was no difference in outcomes between age groups. Male gender, Black ethnicity, diabetes, histological evidence of chronic renal damage and eGFR<30mls/min were risk factors for development of ESKD. In this observational study 68.3% of patients received glucocorticoids and 56.9% additional immunosuppression.

Conclusions

Elderly patients with IgAV are more likely to have ESKD at presentation, but there is no difference in renal survival between age groups, among those presenting with independent renal function. Renal impairment at biopsy is an independent risk factor for subsequent development of ESKD. There is significant variability in the timing of kidney biopsy and management of these patients among specialist centres. Young adults have outcomes more in keeping with childhood IgAV.

Key words:
IgA vasculitis; Henoch-Schonlein purpura; end stage renal disease (ESKD); elderly, adult

Key messages:

IgA vasculitis is an important cause of kidney dysfunction in all age groups.
IgA vasculitis in older patients is more frequently associated with ESKD

Introduction:

Henoch-Schonlein Purpura (HSP) or IgA vasculitis (IgAV) is rare in adults with an estimated annual incidence of only 0.8–1.8/100 000 compared with 3–26.7/100 000 for children and infants[1]. While end stage kidney disease (ESKD) occurs in up to 15% of high-risk children with IgAV [2], it represents an important cause of kidney failure in the adult and elderly populations. By contrast, ANCA associated vasculitis is rare in children, but increasing age is associated with poorer outcomes [3-6]. Adult IgAV has been described in a small number of European studies, which have generally found that adults have a higher incidence and more severe course of renal involvement when compared to children[7, 8]. The largest study so far has come from a French cohort in 2002, in which they retrospectively analysed 250 cases of biopsy proven adult IgAV nephritis and found that age over 50 was associated with a higher rate of severe renal impairment (eGFR below 30mls/min). Proteinuria at presentation and histological features were also important prognostic factors[9]. In contrast, a smaller UK study from 2006 of 37 patients with biopsy proven IgAV nephritis found that age under 30, as well as hypertension and renal impairment at presentation were risk factors for progression to end stage renal failure[10]. The prognostic significance of proteinuria, hypertension and severe histological appearances have been further validated in a single center study of 74 IgAV patients where the risk of dialysis or death correlated with the presence of the above factors[11]. More recently, using a UK primary care database, investigation of IgAV patients' outcomes demonstrated an increased risk of hypertension and CKD compared to healthy controls[12].

IgAV in elderly patients was specifically investigated using data from the Japan renal biopsy register [13]. Outcomes in 150 patients over the age of 18 with biopsy confirmed disease were analysed and demonstrated no difference in renal survival in two age groups (19-64 and ≥65). However, the older group were significantly more likely to sustain a 50% rise in serum creatinine during a mean follow-up of 3.9 years. Multivariate analysis also highlighted the use of corticosteroid as a protective factor and hypoalbuminaemia as a negative prognostic marker.

The aim of this study was to investigate renal outcomes in adults with IgAV according to age at presentation.

Methods:

This was a retrospective audit study for which we did not require ethical approval under National Health Service guidelines and only anonymized data was analysed centrally. Cases were identified by searching the hospital biopsy registries for patients over the age of 18 years with an IgA mediated glomerulonephritis. Patients were included if they also had evidence of concurrent vasculitis, either vasculitic changes on the renal biopsy, skin biopsy proven leukocytoclastic vasculitis or a purpuric rash on clinical examination. Data was collected from six UK sites: Royal Free Hospital London (RFH), Manchester Royal Infirmary (MRI), Queen Elizabeth Hospital Birmingham (QE), Addenbrookes Hospital Cambridge (AH), Salford Royal Foundation Trust (SRFT), Royal Preston Hospital (RPH), Imperial College Hospitals (ICH) and one Swedish site: Linköping University

Hospital (LUH). Some of the Cambridge dataset have already been published in a separate manuscript.

Data:

Clinical information was collected by reviewing the available clinical notes and retrieving relevant biochemistry and histopathology results from hospital pathology databases. Data collected included age at biopsy; gender; ethnicity; presence of crescents and chronic damage on biopsy; estimated glomerular filtration rate (eGFR) at biopsy; eGFR one year post biopsy; most recent eGFR, progression to end stage kidney disease (ESKD); treatment with steroids or immunosuppression; diabetic status. The biopsies were classified according to the local report provided by each site. The presence of glomerular crescents was recorded, however, assessment of the proportion of crescentic changes could not be made due to variations in biopsy reporting. Tubular atrophy was recorded if it was present and used as a histological marker of chronicity. The degree of tubular atrophy categorized as none-minimal, mild to moderate or severe. Estimated GFR was calculated using the Modified Diet in Renal Disease method (MDRD). ESKD was defined as the use of renal replacement therapy (dialysis or transplant) or eGFR below 15mls/min/1.73m^2.

Analysis:

Statistical analysis was carried out using R studio. Sex distribution was compared using binomial test. Medians were compared using Wilcoxon test for two group comparison and Kruskal-Wallis test for multi group comparisons. Non-time dependent categorical variables were compared using chi squared test and

logistic regression displayed as (odds ratio (95%CI), p). Univariate and multivariate survival analysis was carried out to compare progression to ESKD after diagnosis. Renal survival between age groups was compared using the log-rank test, displayed as chisq(p). The effect of sex, ethnicity, diabetic status and site of presentation were compared using multivariate cox regression displayed as (hazard ratio (95%CI), p), the proportional hazards assumption was checked.

Results:

Demographic and clinical details:

Results are summarised in Table 1. Two hundred and two patients were identified with a median follow up of 43.5 months (IQR 12-78.5). Younger adults (18-34) made up 34% of the cohort (median age 25, IQR 22-29); older adults (>64) made up 23% (71, 68-75), and the remainder were aged 35-64 (49, 41-57). There was a 2:1 male to female ratio. The majority (79%) of patients were of white ethnicity. Clinical data were missing for some of the cohort, of 145 patients with available data, 126 (86.9%) had a rash in keeping with vasculitis, this was consistent between age groups. For some patients (88), data were available regarding the time elapsed between first presentation of IgAV and the renal biopsy. Whilst not varying significantly, a shorter time to renal biopsy was observed in the elderly group compared to the young and middle ages groups (1.1, 2.4 and 1.4 months, respectively).

Renal biopsy features

Crescents were present in 45.3% of biopsies, with no significant difference between age groups. Data regarding chronicity was unavailable for 48 patients.

Of those remaining, 48.8% had evidence of some degree of chronic damage (table 1). There was significant variation according to age group (Chi Sq=15.1, p=0.005), older patients were more likely to have some degree of chronic damage on biopsy.

Renal Failure

Overall, 43 patients (21%) reached ESKD in our cohort with the higher rates in the older age groups. Twenty-five of the patients reaching ESKD did so at time of biopsy and 18 did so during follow up. Risk factors for ESKD at either time were investigated by regression analysis.

Renal failure: At biopsy

At biopsy, 25 patients (12.4%) had ESKD. The older groups had higher rates of ESKD at biopsy; 2.9%, 13.7% and 23.9% of 18-34, 35-64 and over 64-year olds respectively (Chi-Sq = 11.6, p=0.002)(Figure 1). Univariate logistic regression showed that the younger group were significantly less likely than the middle age group to present in ESKD (OR 0.2, 0.03-0.7, p=0.04). The older were more likely to have ESKD at the time of biopsy (OR 2.0, 0.8-5.0, p=0.14), but this did not reach the level of statistical significance. Gender and diabetic status were not significantly associated with increased odds of ESKD at the time of biopsy by univariate analysis. The effect of age, gender, and diabetic status were analysed by multivariate logistic regression (Table 2). The younger group had lower (OR 0.24, 0.04-1.0, p=0.07) and the elder group higher (OR 2.4, 0.9-6.3, p=0.08) odds of presenting in ESKD, though the threshold for statistical significance was not met.

Male patients fared worse compared to females (OR 3.8, 1.2-17.0, p=0.04), whilst diabetic status had no significant impact.

Renal failure: During follow up

Survival analysis was performed to characterise clinical risk factors associated with the development of ESKD during follow up for the 177 patients with independent renal function (eGFR >15 mls/min) at diagnosis. A similar proportion of patients in each group progressed during follow up, 12.1%, 7.9% and 11.4% of each group in age ascending order. The effects of age, gender, ethnicity, diabetes, biopsy features and eGFR at biopsy were examined by univariate cox-regression; renal survival curves are shown in figures 2a-f. There was no effect of age group on progression to ESKD (log rank test 1.08, p=0.58). Black ethnicity (HR 10.2, 2.2-46.3, p=0.003); severe features of chronic renal disease (HR 8.8, 2.3-33.7, p=0.001) and eGFR < 30mls/min (HR 9.6, 3.8-24.3, p=<0.001) were associated with a significantly increased risk of progression to ESKD. Next, multivariate cox-regression was performed (table 2). Again, no significant effect of age was observed, though a non-significant trend towards higher rates of progression to ESKD was noted in the younger compared to middle age groups (HR 5.5, 0.94-32.6, p=0.06). Black ethnicity and an eGFR <30mls/min were again associated with progression to ESKD. Male gender (HR 5.2, 1.1-25.5, p=0.04) and diabetes (HR 5.2, 1.2-23.4, p=0.03) were also significantly associated with progression to ESKD by multivariate analysis. Features of severe chronic damage were found to be associated with progression to ESKD by univariate analysis (HR 8.8, 2.3-33.7, p<0.001, figure 2f) but not by multivariate analysis,

suggesting this may simply reflect reduced eGFR, which was identified as an independent risk factor.

Estimated glomerular filtration rate at time of biopsy.

Median eGFR at the time of biopsy was 67.9mls/min and varied significantly according to age group. Estimated GFR in the 18-34 group was 101.2mls/min compared to 60.6mls/min and 34.0mls/min in the 35-64 and >64 groups respectively, ($p<0.001$). There was also variation in the median eGFR at the time of biopsy between sites reflecting to some extent biopsy protocols ($p<0.001$).

Change in renal function in patients who did not progress to end stage renal disease:

In those patients who did not develop ESKD, we compared the renal function at one-year post biopsy and at the last clinic visit. Whilst the renal function differed significantly between the age groups at both time points, neither groups' renal function changed significantly over the follow up period.

Patients with Vasculitic Rash

We analysed the subgroup of patients with vasculitic rash. As with the whole cohort, ESKD at biopsy was significantly different according to age, with the >64 year cohort having the highest rates compared to 35-64 and 18-34 year old cohorts (17.2% , 7.3% and 0% respectively, Chi-sq =0.02). In addition, univariate and multivariate regression analysis demonstrated similar effects of male sex, eGFR at biopsy and ethnicity on developing ESKD during follow up as the whole cohort.

Treatment:

Use of glucocorticoids or immunosuppression for treatment was recorded; glucocorticoids were administered to 68.3% of patients and additional immunosuppression was given to 56.9% patients across all age groups. This consisted of varied protocols most commonly using mycophenolate mofetil, followed by cyclophosphamide, azathioprine and rituximab. Rarely other therapies with alemtuzumab, plasmapheresis, methotrexate and tacrolimus were used. In 34% of those treated with immunosuppressants, multiple agents were used. Treatment varied significantly by age with the two older age groups receiving both categories of treatment more frequently than the younger adults. There was also significant variation between sites regarding the treatments administered to each age group.

Discussion:

The aim of this study was to evaluate the renal outcomes in adults with IgAV according to age at presentation. We classified 34% as young adults and 23% of our cohort as elderly. Two thirds of our cohort were men, in keeping with previous data showing a higher incidence of IgAV in male children and a similar 2:1 male to female predominance in adults with IgAN, in European and north American cohorts[14]. Interestingly, this gender discrepancy is not observed in east Asian populations where this disease is most prevalent[15]. Our results suggest that male gender may be an independent risk factor for progression to ESKD following diagnosis of IgAV nephritis.

Regarding ethnicity, the majority of the cohort were white (79%), 15.1% Asian and 1.5% Black. Though there were fewer black and slightly more Asian patients than would be expected according to England and Wales demography, these

numbers are too small for statistical conclusions to be drawn, furthermore, our study includes one non-UK site. It is not clear to what extent the numbers reflect the local populations, though previous work has indicated a lower incidence of IgAV amongst Black children in keeping with our ethnic variation [16]. Similarly, IgAN is particularly common amongst Asian and less frequent among African populations, this ethnic variation has been linked to the prevalence of single nucleotide polymorphism (SNPs) in the HLA-DQB1/DRB1 locus[17]. Beyond IgAV, ANCA associated vasculitis has also been shown to be less common amongst patients of black ethnicity in epidemiological studies and PR3-ANCA vasculitis has been linked to possession of HLA-DRB1*15 alleles[18, 19].

The definition of IgA vasculitis in adults remains to some extent contentious and is complicated by its potential relationship with IgA nephropathy (IgAN). There have been numerous classification criteria including definitions by the American College of Rheumatology (ACR) in 1990, the Chapel Hill Consensus Conferences for Nomenclature in Vasculitis (CHCC) in 1994 and 2012 and the European League Against Rheumatism (EULAR) in 2010. Some definitions stipulate that a rash must be present, however this prerequisite is no longer supported by the recent CHCC criteria[20]; indeed other forms of systemic vasculitis are diagnosed frequently in the absence of purpura, although purpura can be a common feature. Although the exact relationship between IgAN and IgAV is not fully understood, they are clearly related and may represent different presentations of the same underlying process. There does appear to be subset of patients with a vasculitic process occurring in the kidney (evidenced by focal necrosis, endocapillary proliferation and crescent formation) which can be classified as IgA vasculitis, according to the latest CHCC. Supporting this notion, subgroup analysis of our data, including all patients or just

those presenting with a purpuric rash (126 of 202 cases; 62%) produced similar outcomes with regard to age and risk of presenting with ESKD as well as male sex, eGFR at biopsy, and ethnicity on progression to ESKD during follow up.

On renal biopsy, elderly patients were more likely to show signs of mild-moderate chronic damage than the younger age groups and although no elderly patients had severe chronic changes, fewer in this group had no signs of chronic damage. Elderly patients tended to present with ESKD whereas the middle aged and younger adults showed a more gradual progression over the follow up period. A number of factors could account for these findings. It may be that elderly patients are biopsied later during the disease process, possibly because they present to medical services later than their younger counterparts do. Alternatively, with IgAV usually considered a disease of childhood, treating physicians may have a lower index of suspicion for IgAV in elderly patients, delaying referral to the appropriate specialist. The more frequent presence of chronic changes on the renal biopsy would fit with these explanations, though a certain degree of tubular atrophy is expected with advancing age. Timing of the biopsy depends not only on patient factors but varied according to site. However, this is an observational retrospective study and although an early biopsy may lead to an earlier diagnosis, and possibly a better prognosis, there are multifactorial reasons that may explain the delay. Another explanation for our results is that adult and elderly patients are biopsied at a similar time after the initiation of the disease process but elderly patients have a shorter time between this point and the development of ESKD, either due to a poorer physiological reserve or a more aggressive disease process. However, in those patients with independent renal function at the time of biopsy,

there was no difference between the age groups in subsequent progression to ESKD or change in GFR.

Early diagnosis and treatment is likely to be beneficial in this disease, especially in the elderly population, allowing for initiation of disease modifying treatment such as systemic immunosuppression and now including SGLT2 inhibitors, and the use of supportive treatments (eg: anti-hypertensives) or earlier planning of renal replacement [21, 22]. The continued progression to ESKD of some patients during follow up highlights the need for ongoing renal follow up, with a particular emphasis on those with impaired renal function at biopsy.

In contrast to ANCA associated vasculitis where there have been trials investigating the efficacy of glucocorticoids, immunosuppression and biological therapies in both induction and maintenance therapy, there are few studies on the treatment of IgAV nephritis and fewer specifically regarding adults. Glucocorticoids and immunosuppression are commonly employed as treatment options but there are few rigorous data and no consensus on the best management strategy[23]. The data on the treatment of IgAV in adults is largely limited to case reports and case series, though one small randomized control trial of 54 adults demonstrated no clinical benefit of cyclophosphamide in addition to glucocorticoid treatment[24]. A number of case reports indicate a role for plasma exchange in refractory disease, if immunosuppression is contraindicated or in the case of rapidly progressive disease [25-27]. Furthermore, a case series from 2016 showed positive results for the use of rituximab in disease resistant to glucocorticoids and conventional immunosuppression[28]. In our cohort 68.3% received glucocorticoids, and 56.9% received immunosuppression of one form.

There was a significant difference between sites when comparing which therapies were given, this could reflect both differences in local practice as well as the severity of cases presenting at each site. Although cox regression showed no significant effect of glucocorticoid or other immunosuppressive therapy, this is not a randomized control and conclusions cannot be drawn regarding the efficacy of these treatments. Further investigation is warranted to determine the benefit of current treatment regimes in randomized trials. It is important to note that following diagnosis, immunomodulation is not the only treatment modality and other therapeutic strategies, such as those employed for IgA nephropathy, including improved management of hypertension and use of SGLT2 inhibitors may also impact upon the disease course.

Limitations

The retrospective nature of this study meant that the definition of IgA vasculitis could not be aligned with the ACR definition, due to the limited availability of clinical information for some subjects. Other limitations included the variability in biopsy reporting and treatments received therefore restricting meaningful guidance on the best management for this condition.

Conclusions:

IgA vasculitis causes kidney failure in adults and the elderly as well as children. Patients aged 64 and over had poorer renal function at presentation and were more likely to present with end stage disease, whereas a higher proportion of adults reaching ESKD did so during follow up. Age group was not associated with progression to end stage disease in all patients with an eGFR >15 mls/min at

presentation, though an eGFR below 30mls/min was found to be a factor, as was Black ethnicity, diabetes and male sex. These risk factors were consistent for those with or without a vasculitic rash. The treatment offered varied between sites, as did renal function at the time of biopsy. These findings suggest that earlier diagnosis in the elderly would be required to prevent ESKD and that formal multicenter trials of therapy are warranted in patients of all ages so that we can better understand how to manage this condition. It also shows that young adults have a more similar disease course to children with regards to ESKD.

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Table 1. Patient demographics and outcomes

Variable		*Total*	*18-34*	*35-64*	*>64*	*p*
N(%)		202	68(33.7)	88(43.6)	46(22.8)	
Median Age(IQR)		44(29-64)	25(22-29)	49(41-57)	71(68-75)	<0.001
Sex	Male	133(65.9)	40	62	31	<0.001
	Female	69(33.7)	28	26	15	
Ethnicity	White	159(78.7)	53	69	37	0.9
	Asian	31(15.3)	11	14	6	
	Black	3(1.5)	1	2	0	
	Other	9(4.5)	3	3	3	
Diabetes*	Diabetic	29(14.4)	6	14	9	0.6
	Non-diabetic	165(81.7)	62	67	36	<0.001
Rash**	Vasculitis rash present	126(62.3)	42(61.7)	55(62.5)	29(63.0)	0.8
Biopsy***	Crescents	91(45.0)	32(47.1)	35(39.8)	24(52.2)	0.3
	Chronic damage: none/min	100(64.5)	42(79.2)	40(58.9)	18(50.0)	<0.01
	Mild-mod	47(29.9)	8(15.1)	21(30.9)	17(50.0)	
	Severe	10(6.4)	3(5.7)	7(10.3)	0	
	Time between first presentation of IgAV and biopsy (months, IQR)****	1.4(0.2-4.8)	2.4(0.3-12.2)	1.4(0.1-3.8)	1.1(0.4-3.1)	0.4
ESKD	Total	43(21.3)	10(14.7)	18(20.5)	15(32.7)	
	At biopsy (% of total)	25(12.4)	2(2.9)	12(13.7)	11(23.9)	<0.01
	In follow up (as % of those with independent renal function at biopsy)	18(10.2)	8(9.1)	6(7.9)	4(11.4)	
	Time to ESKD in follow up (Months,IQR)	*9(4.3-32.0)*	*18(6.3-32.0)*	*29(7.0-47)*	*3(0.8-6.8)*	*0.2*
eGFR mls/min, (IQR)	At Biopsy	67.9(31.9-95.4)	101.2(78.7-115.5)	60.6(30.9-83.3)	34.0(16.8-56.6)	<0.001
	At biopsy +1 yr	69.9(51.5-92.7)	93.3(71.6-108.5)	66.8(51.5-84.2)	50.8(36.6-62.1)	<0.001
	Latest	74.2(44.8-98.6)	91.0(75.7-110.3)	71.3(47.8-94.4)	44.9(28.0-68.5)	<0.001
Follow up	Total	43.5(12.0-78.5)	44.5(21.0-79.5)	53.5(17.3-82.5)	28.0(0.4-64.3)	<0.05
Treatment***	Glucocorticoids	138(68.3)	38(55.9)	65(73.9)	35(76.1)	<0.05
	Immunosuppression	115(56.9)	29(42.6)	58(65.1)	28(60.9)	<0.01

Categorical variables are displayed as *total (percentage)*. Continuous variables are displayed as *median(IQR)* where data is missing medians have been calculated from results available. Figures in the treatment by site section represent the percentage of patients in each age group at each site receiving the respective treatment. P values for between site comparisons compare overall figures for each site.

*4 cases missing data
** 57 cases missing data
***46 cases missing data
**** 114 cases missing data
*****3 cases missing data

Table 2: Multivariate regression analysis comparing factors associated with ESKD at the time of biopsy (logistic regression) and during following up (Cox regression).

Renal failure at biopsy

Factor(comparator group)	*Group*	*OR*	*95% CI*	*p*
Age (35-64)	18-34	0.2	0.04-1.0	0.07
	>64	2.4	0.9-6.3	0.08
Gender (Female)	Male	3.8	1.2-17.0	0.04
Diabetic (No)	Yes	1.2	0.3-3.8	0.8
Renal failure in follow up				
Factor(comparator group)	*Group*	*HR*	*95% CI*	*p*
Age (35-64)	18-34	5.5	0.9-32.5	0.06
	>64	1.8	0.2-13.5	0.6
Gender (Female)	Male	5.2	1.1-25.5	0.04
Ethnicity (White)	Asian	1.8	0.4-8.7	0.4
	Black	58.9	6.3-554	0.0004
	Other	1.7	0.1-23.7	0.7
Diabetic (No)	Yes	5.2	1.2-23.4	0.03
eGFR<30 at biopsy (No)	Yes	10.1	2.7-36.9	0.0005
Crescents (None)	Any present	1.1	0.8-4.1	0.9
Chronic changes (None/minimal)	Mild/moderate	2.3	0.5-11.2	0.3
	Severe	5.6	0.7-43.8	0.1

Figure Legends

Figure 1: Overall renal survival in the cohort according to age group
Figure 2: Kaplan-Meier plots comparing progression to ESKD in those with independent function at biopsy according to a) age groups, b) gender, c) ethnic groups, d) diabetic status, e) those with impaired renal function and f) those with chronic features on biopsy.

Figure 1

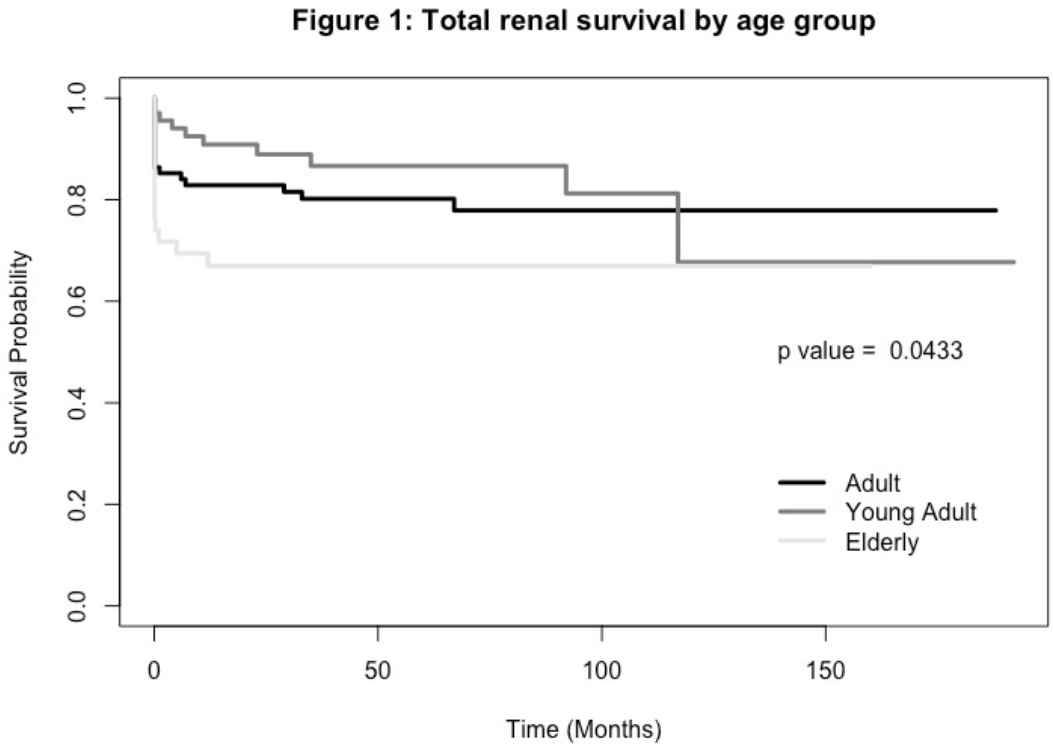

Figure 2

Figure 2a: Renal survival by age group

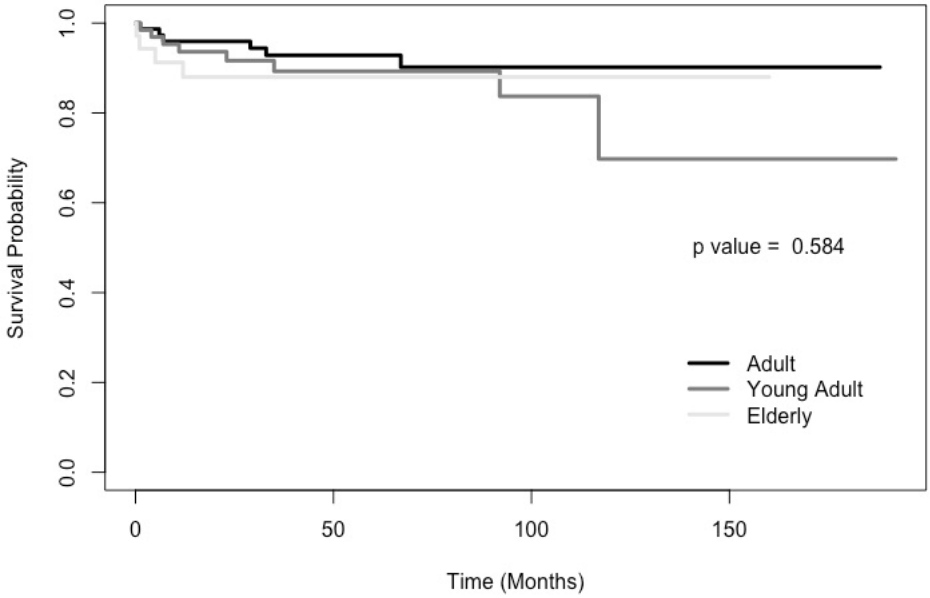

Figure 2b: Renal survival by gender

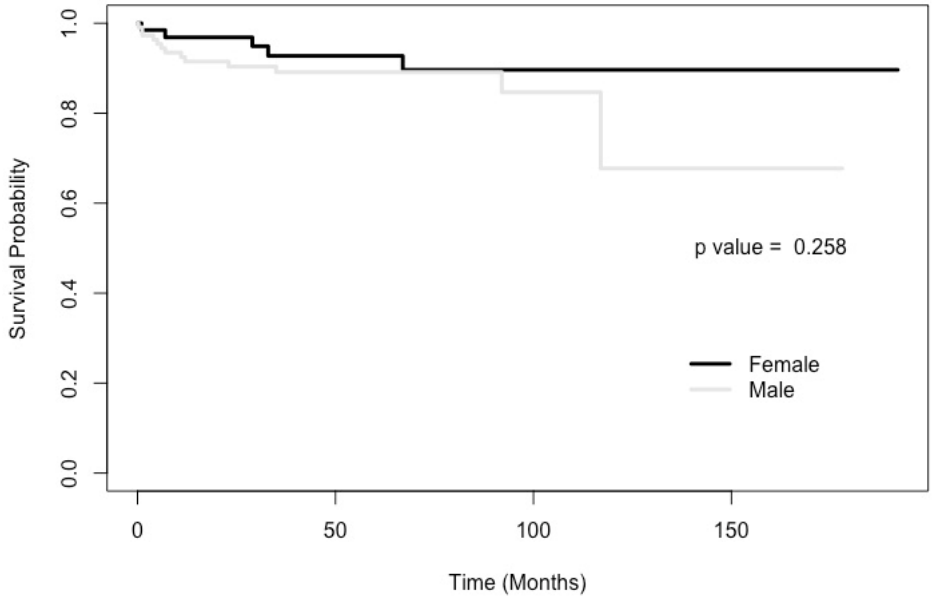

Figure 2c: Renal survival by ethnicity

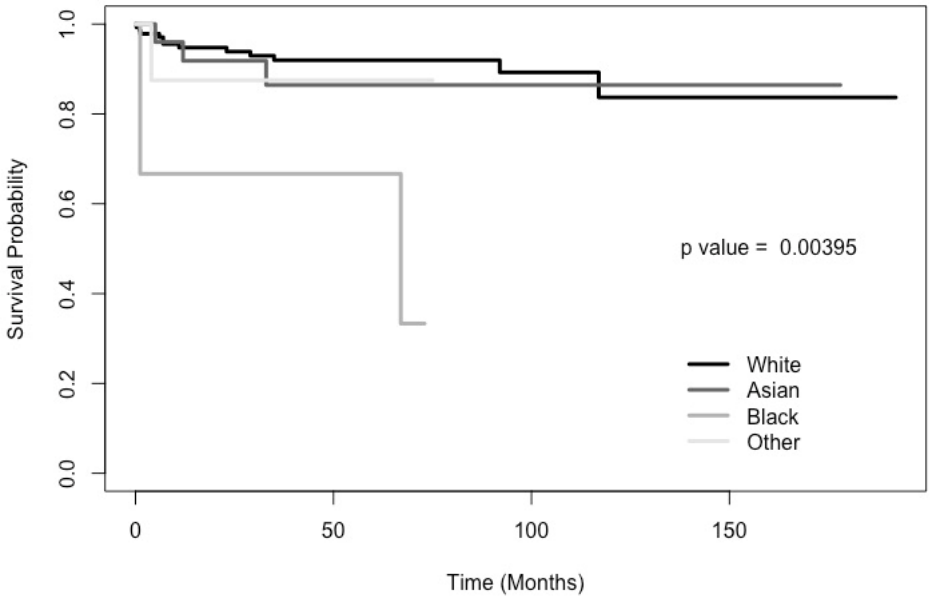

Figure 2d: Renal survival by diabetic status

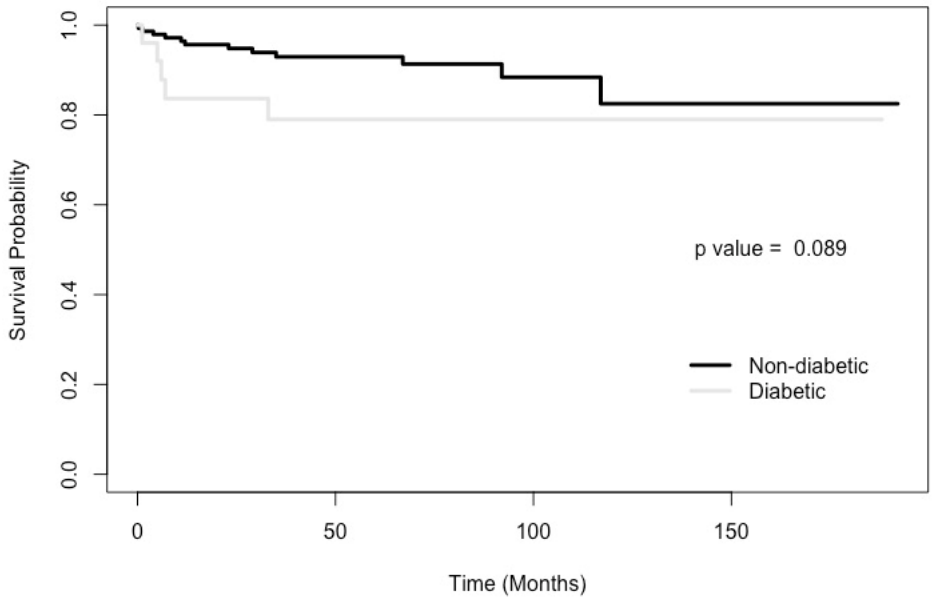

Figure 2e: Renal survival by eGFR at biopsy

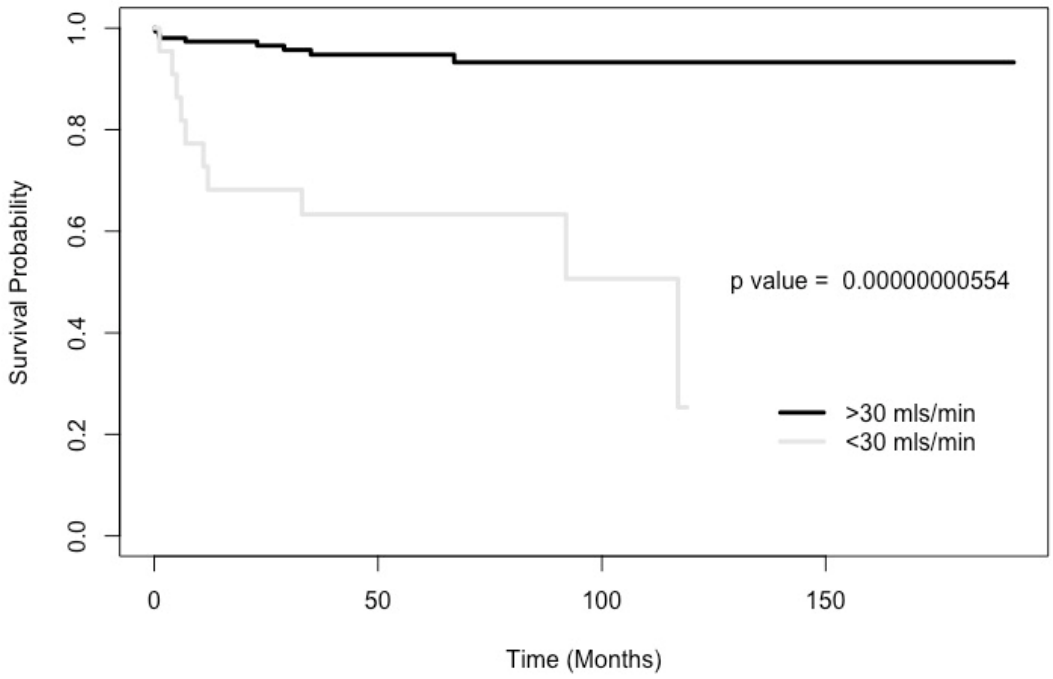

Figure 2f: Renal survival by features of chronicity