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The value of IgG-uria in predicting renal failure in idiopathic glomerular diseases. A long-term follow-up study

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Running title: Urine IgG predict renal survival

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Abstract

Background. Proteinuria is the hallmark of glomerular disease and non-selective proteinuria often associated with progression to renal failure. The predictive value of urine IgG excretion was studied comprehensively in patients with nephrotic syndrome. In the present follow-up study, we examine the predictive value of IgG-uria in patients with idiopathic glomerular diseases with a wide range of proteinuia.

Methods. 189 (113 males and 76 females) patients with idiopathic glomerulonephritis and serum creatinine of less than 150 μmol/l diagnosed between 1993 and 2004 were followed up to last visit year 2009. Measurement of urine excretion of albumin, IgG, and protein HC were performed in the early morning of spot urine samples collected at the time of the diagnostic renal biopsy. Patients were stratified according to urine protein concentrations and the progression rate to end-stage renal disease (ESRD) calculated using Kaplan–Meier survival analysis . ESRD was defined as start of renal replacement therapy.

Results. During the study follow-up time of 1429 person-years; 26 (13.8%) patients reached ESRD. The overall mean kidney survival time of studied patients with serum creatinine less than 150 were 13.4 years. The incidence rate of ESRD was ~18 per 1000 person-years. Stratified analysis identified urinary excretion of IgG, but not albuminuria, as predictor of ESRD. The progression rate to ESRD was 36 per 1000 person-years in patients with urine IgG concentration exceeding 5 mg/mmol urine creatinine, compared to a progression rate of 6 /1000 person-years for patients with lower levels of urine IgG.

***Conclusion*.** The findings of the study suggest that at early stages, the level of IgG-uria is useful to be used in risk stratification of patients with proteinuric glomerular diseases.

Key Words

Albuminuria

Glomerulonephritis

End-stage renal disease

IgG

Protein HC

Introduction.

Glomerular disease is an important cause of chronic kidney disease worldwide [1]. Glomerular diseases are characterised by an increased glomerular filtration and urine excretion of plasma proteins of the size of albumin and larger, i.e. glomerular proteinuria [2-4]. Glomerular proteinuria is associated with the development of progressive tubulo-interstitial fibrosis [5]. Tubulo-interstitial fibrosis and tubular damage cause impaired tubular reabsorption of plasma proteins, such as Protein HC, (α1-microglobulin), which are normally nearly freely filtered and almost completely reabsorbed in the proximal tubules [6].

It has been observed that patients with increased glomerular filtration of high molecular weight plasma proteins like IgG, IgM, have a greater risk of progressing to end-stage renal disease (ESRD) than patients with pure albuminuria [6-8]. However, the predictive value of increased urine IgG excretion was evaluated mostly in short term studies of patients with nephrotic syndrome [9-11]. In the present cohort, we studied the long term impact of IgG-uria in patients with glomerular diseases presenting with a wide range of proteinuria. Our objective was to determine cut-off levels for urinary IgG-uria that can be clinically useful for predicting the risk of progression to ESRD in patients with chronic glomerular disease.

Methods.

Patients

The patients in this study were recruited between August 1993 and February 2004. All the patients (113 males and 76 females) were participants of a large investigation of glomerular diseases being conducted at the Nephrology department, University Hospital of Lund, Sweden. The inclusion criteria were biopsy-verified diagnosis of mesangial proliferative glomerulonephritis, IgA nephropathy, membranous glomerulonephritis, minimal change nephropathy, focal segmental glomerulosclerosis, or nephrosclerosis. Patients with diabetic nephropathy, systemic diseases, or with severe renal failure on admission (serum creatinine > 150 μmol/l) were excluded. The study was approved by the local ethical committee. The morphological diagnoses were in all cases established by evaluation using light microscopy and immunofluorescence staining of representative percutanous renal biopsy specimens.

Treatment and follow-up

All patients were followed regularly at nephrology outpatient clinics and were on a normal protein diet. Most of the patients (n=139) were treated with ACE inhibitors during follow-up time. Sixty one patients with heavy proteinuria or rapidly deteriorating kidney function were treated with immunosuppressive therapy. Patients with advanced nephrosclerotic changes were not given immunosuppressive treatment. Patients with minimal change nephropathy were treated by corticosteroids (n=13) alone or in combination with calcineurin inhibitors (n=5). Patients with proliferative glomerulonephritis were treated by corticosteroids (n=5) alone or in combination with cyclophosphamide (n=9) or calcineurin inhibitors (n=5). Patients with IgA nephropathy received corticosteroids alone (n=5) or in combination with cyclophosphamide (n=2). Patients with membranous nephropathy were treated with corticosteroids alone (n=12) or in combination with calcinuerin inhibitors (n=2). Patients with

focal segmental glomerulosclerosis were treated with corticosteroids alone (n=2) or in combination with cyclophosphamide (n=1).

The patients were followed up to the last planned follow-up visit in 2009. The number of patients, age, gender, and baseline data are presented in table I. Blood pressure was measured using a mercury sphygmomanometer with the patients in supine position. The diastolic blood pressure was measured at Korotkoff phase V. Mean blood pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic blood pressure. The primary end point was start of renal replacement therapy at ESRD. For renal survival analysis, the patients were divided into quartiles according to the presentation levels of urinary proteins: albumin, IgG, and protein HC. Survival time was calculated from the date of diagnosis.

Laboratory analysis

Blood samples and the first voided urine specimens were obtained in the morning of the day of the kidney biopsy. Urinary albumin-to-creatinine ratio measured in a spot morning urine sample was used as a reliable estimate of the degree of proteinuria [12]. ACI (mg/mmol) designates the ratio of urine albumin (mg/L) to urine creatinine (mmol/L), IgGCI (mg/mmol) the ratio of urine IgG (mg/L) to urine creatinine (mmol/L), and HCCI (mg/mmol) the ratio of urine protein HC (mg/L) to urine creatinine (mmol/L).

Serum and urine creatinine were determined enzymatically using a Kodak Ektachem 700 XR-C system. Serum and urine albumin, IgG, and urine protein HC were determined by immunoturbidimetry using a Cobas Mira S system (Roche Inc.) and monospecific rabbit antisera obtained from Dako (Copenhagen, Denmark) [13-15]. GFR was estimated using the Lund-Malmö formula [16, 17]: eGFR for patients with plasma creatinine (pCr) <150 μmol/L $= e^{4.62-0.0112*pCr-0.0124*age+0.339*ln(age)-0.2226(if\ female)}$.

Statistical methods

The data in the tables are expressed as medians and interquartile ranges. Statistical comparison of baseline characteristics of patients with glomerular histological diagnoses was performed with non-parametric Kruskal Wallis Test, (table I). Cox proportional hazards regression analysis was performed to examine the association of the baseline characteristic with the progression to ESRD. The baseline characteristics examined are age, gender, type of glomerular disease, GFR, blood pressure, and quartiles of urine concentration of proteins: albumin, IgG, and protein HC. Patients with missing data were excluded. ESRD was defined as start of renal replacement therapy. Renal survival analysis was performed using the Kaplan–Meier method. Patients were censured at the time of death or at end of follow-up. Log rank test was used to assess the difference in survival. All statistics were performed using Episheeth and SPSS software, version 17.0 (Chicago, IL, USA). P <0.05 was selected as level of significance. For urinary concentrations below the detection limit we used 0.1 mg/mmol for both HCCI and IgGCI.

Results

Out of the 189 patients included in the cohort, 26 (16 males & 10 females) patients reached ESRD, 16 (10 & 6) died and 5 (2 & 3) patients were lost from follow-up. All other patients were followed up to the last planned visit in 2009. The number, age, gender, and baseline data of patients are presented in Table I.

The cohort follow-up time was 1429 person-years (median 8 years, and maximum 15.3 years). The overall mean kidney survival time of studied patients with serum creatinine < 150 μmol/L were 13.4 years (95% CI 12.7–14.1). The incidence of renal failure was estimated to be 18.2 per 1000 person year (95% CI = 12.4–26.5).

Univariate Cox regression analysis showed albuminuria, IgG-uria, and HC-uria, as well as mean arterial blood pressure, and GFR to be predictors of ESRD, (table II). Age, gender, glomerular diagnosis, and treatment with immunosuppressive drugs did not correlate with the risk of ESRD, (table II). Stepwise multivariate Cox regression analysis showed that IgG-uria was the strongest independent predictor of ESRD (HR =1.03; 95% CI, 1.015-1.046; $p<0.001$).

Stratified analysis identified that patients in 3rd and 4th quartiles of IgG-uria were at high risk for progression to ESRD (Fig 1, table III). The risk of ESRD was ~36/1000 person-years in patients with urine IgG concentration > 5 mg/mmol, compared to patients with lower levels, 6/1000 person-years, RR= 5.94 (95% CI: 2.0-17.3) . Also patients with urine protein HC concentration in the 4th quartiles (> 2.8 mg/mmol) were at high risk for ESRD (43/ 1000 person-years) compared to the risk of 14.5/1000 person-years in patients with lower HC levels, RR= 2.9 (95% CI: 1.4- 6.5), (Fig 2, table III). There was no significant difference in the renal survivals between patients in different quartiles of albuminuria (Fig 3, table III).

Discussion

This consecutive cohort of ~~all~~ adult patients investigated ~~for~~ primary proteinuric glomerular diseases at a single Swedish regional centre confirms the finding of previous studies, suggesting that progression to ESRD varies substantially based on urinary excretions of proteins larger than albumin. Although the observations of this study did not directly address the benefit of treatment, they do suggest that the risk of stratification in terms of albuminuria alone appeared relatively insensitive for predicting renal prognosis. This study confirms that baseline IgG-uria is a powerful independent predictor of progression to ESRD in patients with proteinuric glomerular diseases.

In healthy conditions, only small amounts of albumin (molecular radius 3.6 nm) and IgG (molecular radius 5.5 nm) pass through the glomerular filter, because the glomerular filtration barrier has only a very scant number of "large pores" of radius 11–12 nm and hardly any "large shunt pathways." With loss of size selectivity, large amounts of albumin and other high molecular weight proteins escape into the urinary space [18]. Theoretically, pure albuminuria may occur if only charge selectivity is lost, as is proposed to be the case in minimal change nephropathy. This condition is not associated with this progressive renal damage [19]. However, ~~an~~ increased urinary excretion of larger proteins, like IgG, imply a worse kidney outcome [7, 8, 20].

The finding in this study is important, because current recommendations for management of patients with glomerular disease are based on the degree of albuminuria (albumin/creatinine ratio) without consideration of the urine IgG excretion. This may be partly due to the difficulty in daily clinical practice of using "proteinuria selectivity index," which requires simultaneous measurement of two proteins in serum and urine. Also, serum and urine creatinine concentrations are needed for calculation of fractional protein clearance [21, 22].

We find that in clinical practice, the urine IgG/creatinine ratio is easily measured and simpler to use than selectivity index and fractional clearance.

Previous studies on patients with the nephrotic syndrome have used higher cut-off levels for IgG-uria (12 mg/mmol)as an indicator of bad prognosis [11]. Because many of the patients we studied (74%) had non-nephrotic range proteinuria, and due to longer follow-up times in this study, we believe that the cut-off level of 5 mg/mmol for urine IgG is more suitable for characterising the type of proteinuria in patients with a wide range of proteinuria. The number of patients is too small to run a survival regression analysis for each individual glomerular diagnosis. However, the cross-table analysis suggests that the cut off level of 5 mg/mmol is useful irrespective of the individual histological glomerular diagnosis, (table IV).

In addition to IgG-uria, it is useful to include urine HC concentration in the workup of patients with glomerular diseases [6]. Patients with protein HC/creatinine ratio > 2.8 mg/mmol are at high risk of renal failure. Biopsies from patients with IgG-uria > 5 mg/mmol had more severe interstitial fibrosis than patients with low IgG-uria (37.5% and 24.0%, respectively, $p = 0.07$). Increased HC- uria may reflect the development of tubulo-interstitial damage secondary to unselective proteinuria. However, at early stages of kidney diseases, IgG-uria is a more powerful predictor of progression to renal failure than HC-uria.

Our study has limitations due to its observational nature. The cohort is limited to patients investigated with kidney biopsy and therefore does not include individuals who have not been biopsied. However, our clinical guidelines in the Region recommend kidney biopsy of all patients with albuminuria with signs of glomerulonephritis, such as hematuria and renal casts, and we therefore believe that most of the patients with clinically significant glomerular disease were investigated. Although, we did not find any significant effect of treatment on the progression of kidney disease, the limited number of patients with specific glomerular diagnosis hindered us from studying the effect of the treatment for each histological

diagnosis. The treatment with ACE inhibitors and the immunosuppressive therapy might minimise the progression rate to ESRD. The other limitation is that urine proteins were measured only once, and this may misclassify the degree of proteinuria because of its variability. We used the urine protein/creatinine ratio to minimise this variability. Also, the variability in urine protein measurement is unlikely to negate the observed association, because the effect of IgG-uria on the risk of progression to ESRD observed in this study was very large (six-fold higher) and consistent with the previous studies.

In conclusion, the urine IgG/creatinine ratio was found a useful non-invasive test for early identification of patients at risk of progression to ESRD and should be included in the investigational program of all patients with glomerular disease. We suggest that future therapeutic studies should incorporate information about the treatment effect on the urinary excretion of large proteins, such as IgG.

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Table I. The baseline characteristics of 189 patients with biopsy-verified glomerular disease divided according to the type of glomerular disease. Data are presented as median and inter-quartile range (in parentheses).

Variables	Minimal change	IgA-N	Membra-nous	Nephro-sclerosis	Mesangio-proliferative	FSGS	All patients
Number (M/F)	32 (13/19)	31 (20/11)	21 (12/9)	24 (17/7)	75 (48/27)	6 (3/3)	189 (113/76)
*Age years	41.0 (35.0)	33.0 (29.5)	63.0 (25.0)	53.0 (18.3)	52.0 (18.5)	31.0 (21.0)	48.5 (26.0)
Follow-up years	7.9 (5.8)	8.3 (5.5)	9.4 (3.4)	8.1 (4.9)	8.9 (4.8)	8.1 (3.8)	8.8 (4.6)
*MAP mm Hg	98.3 (14.7)	93.4 (19.3)	100.0 (23.3)	109.0 (18.0)	106.7 (16.6)	115.0 (25.0)	103.3 (20.0)
*S. crea µmol/L	75 (33)	83 (27)	93 (54)	124 (31)	96 (40)	104 (30)	92 (40)
*GFR ml/min/L 73	(29.1)	(29.6)	(28.9)	(26.0)	(32.2)	(31.2)	(31.4)
*S. alb g/L	23.6 (19.7)	32.1 (9.0)	19.6 (6.5)	35.7 (5.0)	31.3 (11.0)	30.0 (27.0)	29.3 (14.0)
IgG-uria mg/mmol	7.3 (19.1)	4.9 (5.6)	8.0 (15.6)	4.2 (13.5)	4.2 (10.6)	2.1 (9.0)	5.1 (10.6)
HC-uria mg/mmol	1.3 (2.9)	0.9 (1.4)	2.8 (5.6)	1.3 (1.2)	0.8 (2.3)	0.8 (4.6)	1.2 (2.3)
Albuminuria mg/mmol	165 (621)	98 (110)	225 (406)	86 (234)	99 (153)	309 (287)	107 (266)

* The difference between the types of glomerular diagnosis is statistically significant. IgA-N = IgA nephropathy, FSGS= focal segmental glomerulosclerosis, S. alb= serum albumin.

Table II: Univariate Cox regression analysis for end-stage renal disease (ESRD) in 189 patients with biopsy-verified glomerular disease.

Variables	Beta	SE	P-value	HR	95% CI
Albuminuria	0.39	0.19	0.04	1.47	1.02–2.14
IgG-uria	0.56	0.20	0.005	1.76	1.18–2.62
HC-uria	0.49	0.20	0.013	1.63	1.11–2.40
MAP mm Hg	0.06	0.02	<0.001	1.06	1.03–1.09
GFR ml/min/1.73	-0.068	0.014	<0.001	0.93	0.91–0.96
S.albumin g/l	0.17	0.022	0.43	1.017	0.97–1.06
Age years	0.019	0.01	0.11	1.02	0.99–1.04
Gender F/M	-0.08	0.40	0.84	0.92	0.42– 2.03
Diagnosis	0.02	0.11	0.85	1.02	0.83–1.26
IM yes/no	-0.09	0.43	0.82	0.91	0.40 – 2.1

Beta= regression coefficient, SE = standard error, HR= hazard ratio, CI= confidence interval,

MAP = mean arterial blood pressure. Diagnosis= type of glomerular disease. IM = immunosuppressive therapy (yes/no)

Table III. Progression rate to end-stage renal disease (ESRD) in 189 patients with biopsy-verified glomerular disease with serum creatinine < 150 μmol/L, according to quartiles of urine concentrations of proteins: albumin, IgG and protein HC.

Variable	Person-years	Number of ESRD	Rate/1000 person-years (95% CI)	P-value
IgG-uria (mg/mmol)				
Q1 (<1.8)	323.6	3	9.3 (3.2–26.9)	
Q2 (1.8–5)	337.2	1	3.0 (0.5–16.6)	
Q 3 (5–14)	317	12	37.9 (21.8–65)	
Q4 (>14)	271.8	9	33.1 (17.5–61.7)	0.004
HC-uria (mg/mmol)				
Q1 (<0.6)	279.2	3	10.7 (3.7–31.1)	
Q2 (0.6–1.2)	357.3	5	14.0 (6.0–32.3)	
Q3 (1.2–2.8)	260.6	5	19.2 (8.2–44.1)	
Q4 (>2.8)	277.3	12	43.3 (24.9–74.1)	0.045
Albuminuria (mg/mmol)				
Q1 (<20)	344.8	3	8.7 (3.0–25.3)	
Q2 (20–109)	411.3	6	14.6 (6.7–31.5)	
Q3 (110–279)	322.0	7	21.7 (10.6–44.2)	
Q4 (>280)	321.2	10	31.1 (17.0–56.4)	0.2 (Ns)

Ns= non statistically significant

Table IV. Cross-table analysis of risk of progression to end-stage renal disease (ESRD) according to a cut-off level of IgG-uria of 5 mg/mmol in patients with different histological diagnoses of glomerular diseases.

IgG-uria mg/mmol	< 5	>5 mg/mmol	
Diagnosis	% ESRD	% ESRD	P-value
Proliferative	9.4%	34.5%	0.02
IgA-nephropathy	0%	20%	0.08
MCN	0%	0%	
FSGS	0%	100%	0.03
Membranous	0%	8.3%	0.5
Nephrosclerosis	10%	54.5%	0.03. .

Caption for the figures

Fig.1: Cumulative risk of end-stage renal disease (ESRD) according to a cut off-level of IgG-uria (less than *vs* greater than 5 mg/mmol) in 189 patients with glomerular disease with serum creatinine < 150 µmol/L. Log-rank test P value < 0.001

Fig 2: Cumulative risk of end-stage renal disease (ESRD) according to a cut-off level of HC-uria (less than *vs* greater than 2.8 mg/mmol) in 189 patients with glomerular disease with serum creatinine < 150 µmol/L. Log-rank test p value = 0.006

Fig 3: Cumulative risk for end-stage renal disease (ESRD) according to cut-off level of albuminuria (less than *vs* greater than 110 mg/mmol) in 189 patients with glomerular disease with serum creatinine <150 µmol/L. Log-rank test P value = 0.07, not significant

Fig 1

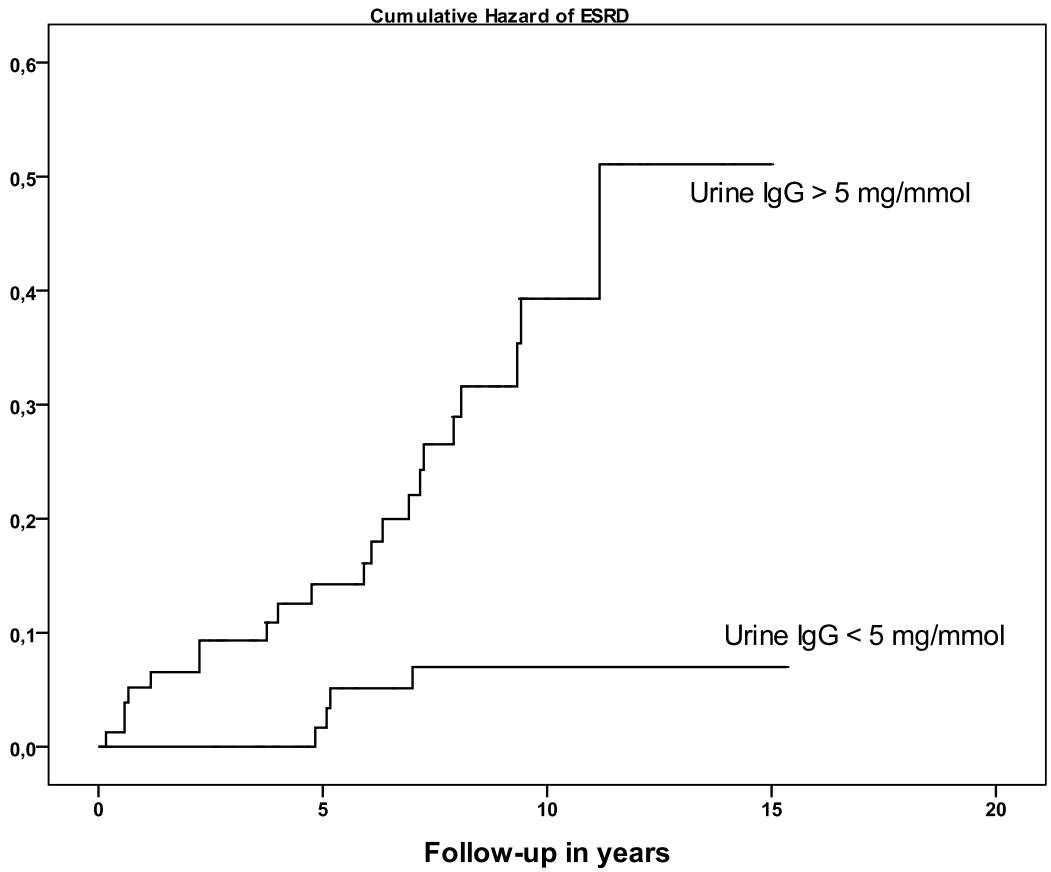

Cumulative Hazard of ESRD
0,6
0,5
0,4
0,3
0,2
0,1
0,0
Urine IgG > 5 mg/mmol
Urine IgG < 5 mg/mmol
0
5
10
15
20
Follow-up in years

Fig 2

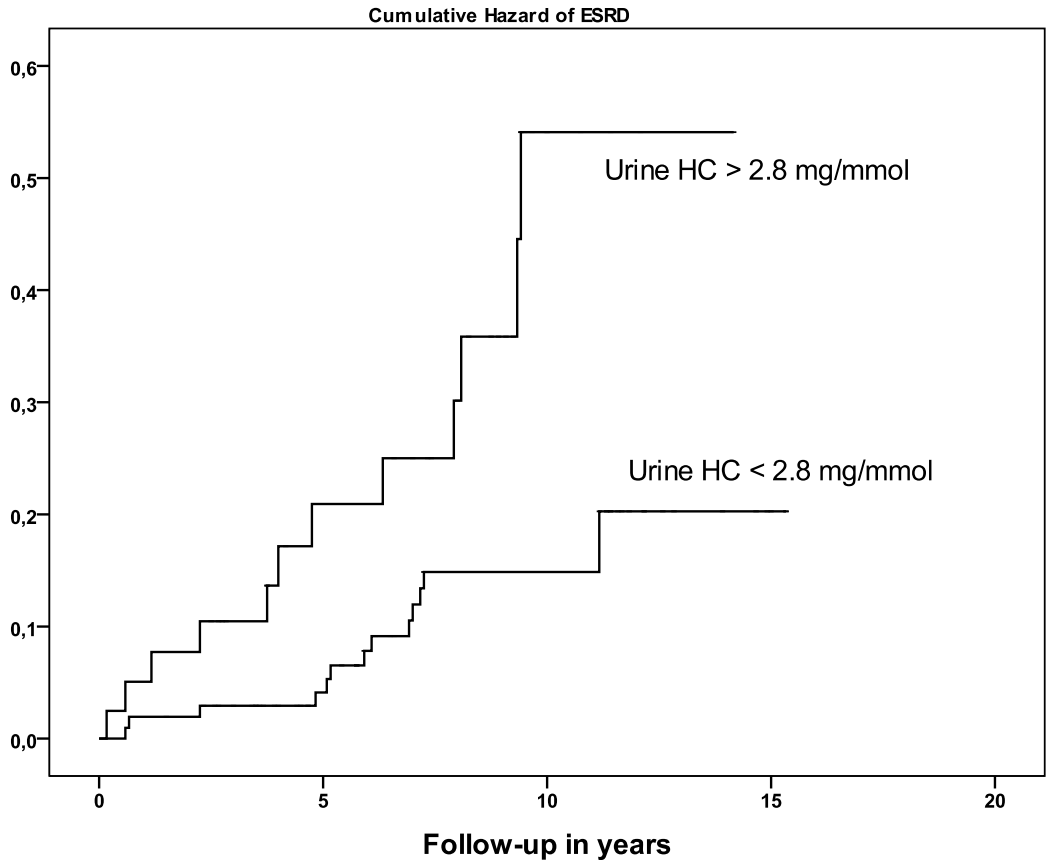
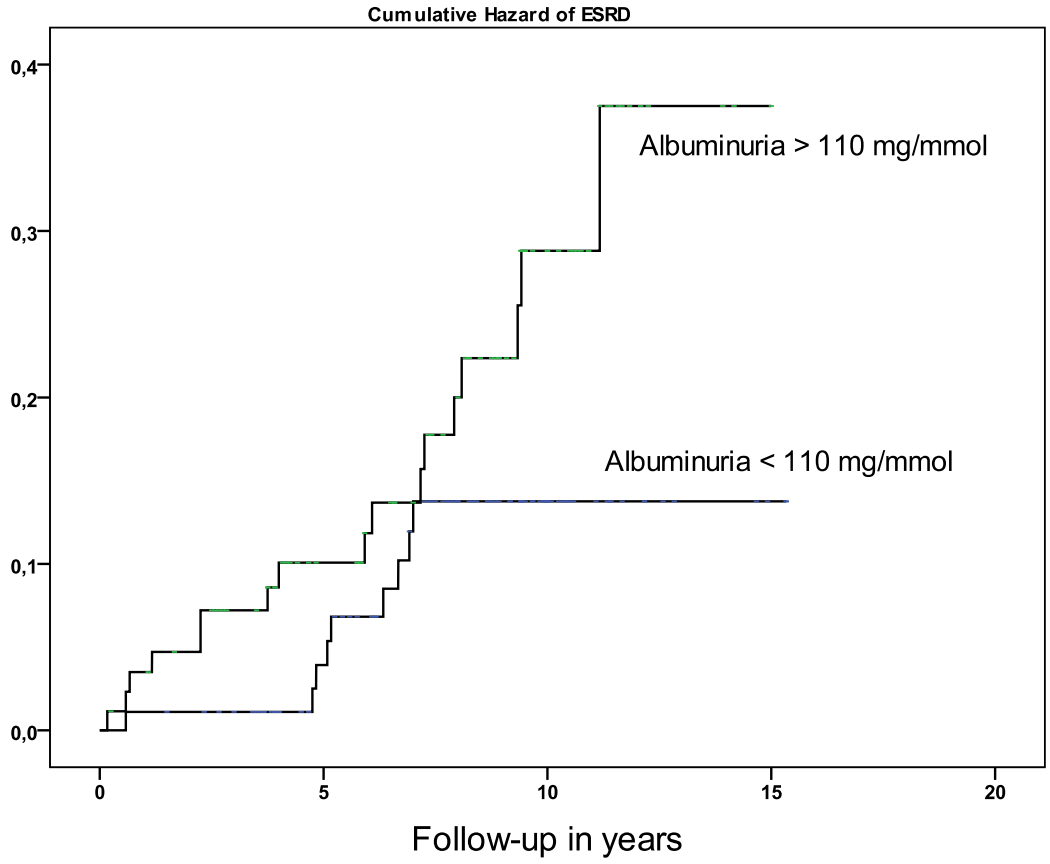

Cumulative Hazard of ESRD
0,6
0,5
0,4
0,3
0,2
0,1
0,0
Urine HC > 2.8 mg/mmol
Urine HC < 2.8 mg/mmol
0
5
10
15
20
Follow-up in years

Fig 3


Cumulative Hazard of ESRD
0,4
0,3
0,2
0,1
0,0
Albuminuria > 110 mg/mmol
Albuminuria < 110 mg/mmol
0
5
10
15
20
Follow-up in years