Urinary neutrophil gelatinase-associated lipocalin (NGAL) is associated with mortality in a community-based cohort of older Swedish men

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ABSTRACT

Objective: Neutrophil gelatinase-associated lipocalin (NGAL) indicates tubular kidney damage, neutrophil activation and possibly atherogenesis, however the prospective association between urinary NGAL (u-NGAL) and cardiovascular death in the community is not known.

Methods: This study evaluates the association between urinary and serum NGAL and mortality in a Swedish population of 597 men aged 78 years. During the study (median follow-up 8.1 years) 261 men died, 90 of cardiovascular causes.

Results: U-NGAL was associated with increased all-cause and cardiovascular mortality (HR 2.0 for quartile 4 vs. quartile 1, 95% CI 1.0-4.0, $p<0.05$) in Cox regression models independently of cardiovascular risk factors, CRP and cystatin C estimated glomerular filtration rate ($eGFR_{CysC}$) but not urinary Albumin (u-Alb). A combination of low $eGFR_{CysC}$ (≤60 mL/min), high u-Alb (≥ 3 mg/mmol Cr) and high u-NGAL (≥1.19 µg/mmol Cr) was associated with a 9-fold increased cardiovascular mortality ($P<0.001$) and a 3-fold increased all-cause mortality ($P<0.001$). Serum NGAL was associated with increased all-cause mortality risk independent of other cardiovascular risk factors (HR 1.4 for quartile 4 vs.1, 95% CI 1.0-1.9, $p<0.05$) but not after adjustment with CRP, $eGFR_{CysC}$ or u-Alb.

Conclusion: This community study is the first to show that the tubular kidney biomarker u-NGAL associated with increased cardiovascular and all-cause mortality independent of cardiovascular risk factors and glomerular filtration. Additional research is needed to evaluate the utility of NGAL in clinical practice.

Keywords: chronic kidney disease, epidemiology, inflammation, mortality, NGAL, risk factors

1. Introduction

Neutrophil gelatinase-associated lipocalin (NGAL) [1], also known as human neutrophil lipocalin (HNL) [2] and lipocalin-2, is a member of the lipocalin family of binding proteins. Activated neutrophils are the main cellular source of NGAL in the circulation and the most important biological function of the protein is to mediate inflammatory response and inhibit bacterial growth [3, 4]. However, other tissues may also release NGAL as a signal of acute-tissue injury in conditions that are not primarily associated with bacterial infections. For example, NGAL mRNA and the NGAL protein are upregulated in mouse, rat and human kidney tubular cells shortly after ischemic damage [5]. Subsequently, NGAL has been shown to be an excellent indicator of acute kidney injury (AKI) in several human clinical studies and may signal kidney injury earlier than creatinine concentrations do [6, 7]. Urinary NGAL (u-NGAL) may be a more robust indicator of AKI than plasma or serum NGAL (s-NGAL) in critically ill patients with systemic inflammation since circulating NGAL primarily reflects NGAL released from activated neutrophils while u-NGAL primarily represent tubular epithelial-derived NGAL [8]. Recent data also suggest that elevated u-NGAL may reflect kidney injury of chronic nature [4, 9]. Plasma and u-NGAL may be useful predictors of chronic kidney disease progression independently of other indicators of kidney injury such as creatinine-estimated glomerular filtration rate (GFR) [9-12].

Furthermore, the dual role of NGAL as an inflammatory mediator together with the properties of being a prognostic biomarker of kidney damage suggests that NGAL may be related to the development of cardiovascular disease and some of its complications [13]. Increased concentrations of s-NGAL and u-NGAL are found in patients with chronic heart failure [14, 15] and with acute ischemic events [16, 17] and increased plasma NGAL concentrations are also associated with a higher risk of mortality in these patient groups [18-20] and in the

community [21]. However, the prospective association between the tubular kidney damage biomarker u-NGAL and cardiovascular death in the community is not known.

Based on previous studies supporting a link between NGAL and the development of cardiovascular disease our hypothesis was that increased NGAL concentrations may relate to mortality. Consequently, we aimed to explore the associations between urinary and serum concentrations of NGAL and the risk of death of cardiovascular causes and all causes in a community-based cohort of elderly men with up to 10 years of follow-up.

2. Methods

2.1 Study population

The Swedish cohort Uppsala Longitudinal Study of Adult Men (ULSAM) initiated in 1970 when all 50-year-old men living in Uppsala county (N =2841) were invited to participate in a health survey (participation rate 82%) [22]. Participants from the third reinvestigation of the cohort, performed 1997-2001 at 77-78 years of age, were included in this study. Of the 839 participants, 208 were excluded because of absent urinary collection and 34 because of missing data on covariates, thus 597 men constituted the study population. This study complies with the Declaration of Helsinki. The Ethics Committee at Uppsala University approved to the study, and all participants gave their informed consent.

2.2 Baseline investigations

24-Hour urine and serum were collected, aliquoted and stored at -70° until analysis. Urinary and serum NGAL were analyzed with a commercial sandwich ELISA kit, (DY1757, R&D Systems, Minneapolis, MN). The total CV of the assay was approximately 6%. U-NGAL concentrations were adjusted for urinary creatinine (IL Test creatinine 181672-00, Monarch 2000 analyser, Instrumental Laboratories, Lexington, MA). Urinary Albumin (u-Alb) was measured by nephelometry (Urine albumin, Dade Behring, Deerfield IL) and high-sensitive CRP measurements were performed by latex-enhanced reagent (Dade Behring, Deerfield, IL) using a Behring BN ProSpec® analyzer (Dade Behring). Blood sampling, anthropometrical and blood pressure measurement, questionnaires regarding medication and smoking habits and diabetes definition were performed using the same standardized methods as described previously [22, 23]. Serum cystatin C and cholesterol and fasting plasma glucose were measured as previously described [24]. GFR in mL/min/1.73m^2 ($eGFR_{cysC}$) was calculated from serum cystatin C results in mg/L by the formula y = 77.24x-1.2623 [25]. Information of

previous ischemic heart disease or cerebrovascular disease was obtained from the Swedish Hospital Discharge Registry using the International Statistical Classification of Diseases ICD-9 codes 410-413, 428, 433-436 and ICD-10 codes I20-I25, I50, I63-I66.

2.3 End point definitions

The Swedish Cause of Death register was used to define the endpoints all-cause mortality and cardiovascular mortality (ICD-10 I00-99).

2.4 Statistics

The linear association between u-NGAL and s-NGAL at baseline was tested with Pearson´s correlation. The associations of u-NGAL and s-NGAL with cardiovascular mortality and all-cause mortality were analysed with Cox proportional hazard regression in a univariable and in three multivariable models (A , B and C). Model A was adjusted for established cardiovascular risk factors including age, systolic blood pressure, BMI, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering, anti-hypertensive and low-dose aspirin medication, smoking status, diabetes and prevalent cardiovascular disease. Model B was adjusted for the above mentioned established cardiovascular risk factors and additionally for $eGFR_{cysC}$. Model C was adjusted for the above mentioned established cardiovascular risk factors and additionally for u-Alb. In our primary analyses u-NGAL and s-NGAL were entered into the models as a continous variables (expressed as 1-unit increase). We also performed multicategory models (quartile 1 vs quartile 2, quartile 3 and quartile 4). The participants were also divided into four groups according to; all three kidney biomarkers normal (normal u-NGAL were defined here as <1.19 µg/mmol Cr, which is the lowest quartile in this study cohort, normal $eGFR_{CysC}$ >60 mL/min and normal u-Alb <3 mg/mmol Cr); 1 pathological biomarker; 2 pathological biomarkers; all 3 biomarkers pathological.

Additionally the study participants were divided into four groups according to; u-NGAL above and below 1.19 μg/mmol Cr and u-Alb above and below <3 mg/mmol Cr or $eGFR_{cysC}$ below and above 60 mL/min, respectively.

We did tests for effect modification by prevalent cardiovascular disease and eGFR by including multiplicative interaction terms of these variables and u-NGAL. Stratified analysis were performed with subgroups of the cohort with and without prevalent cardiovascular disease at baseline. P-values <0.05 were regarded as statistically significant. Calculations were performed with Stata/IC 11.0 (College Station, TX).

3. Results

3.1 Baseline characteristics of the study population (n= 579)

The study participants had a median (interquartile interval) age of 77.6 (77.0-78.1) years, $eGFR_{CysC}$ 73.5 (62.7-84.3) mL/min/1.73 m^2, u-Alb 0.7 (0.3-21) mg/mmol Cr, u-NGAL 1.9 (1.2-3.4) µg/mmol Cr, s-NGAL 224 (176-292) µg/L, systolic blood pressure 150 (136-164) mmHg, BMI 26 (24-28) kg/m^2, s-Cholesterol 5.4 (4.7.6.0) mmol/L, HDL-Cholesterol 1.3 (1.1-1.5) mmol/L. Twenty-six percent of the study population had previous history of cardiovascular disease, 7 % smoked, 14 % had diabetes mellitus, 48 % had antihypertensive medication, 19 % statins and 28 % low-dose aspirin. The participants were followed up for a median of 8.1 years (interval 0.3-10.8 years). The mortality incidence rates for u-NGAL and s-NGAL are shown in Table 1 and supplmentary Table 1, respectively. U-NGAL and s-NGAL did not show a significant linear correlation (R = 0.07, P = 0.07).

3.2 Cox regression models for associations between u-NGAL and cardiovascular and all-cause mortality risk

A 1-unit increase of u-NGAL was associated with a 1.23 hazard ratio (HR) of cardiovascular mortality and 1.15 HR for all-cause mortality in the univariable models. Participants in u-NGAL quartile 2, quartile 3 or quartile 4 were, compared to quartile 1, also significantly associated with a higher risk of cardiovascular mortality and all-cause mortality in the univariable models, see Table 1. These associations remained significant after adjustment for age and established cardiovascular risk factors (model A) and $eGFR_{CysC}$ (model B) but not after adjustment for u-Alb (model C). None of the models were substantially affected when CRP was added as a covariate (multivariate HR 1.1 for 1-unit increase of u-NGAL, 95% CI 1.0-1.3, $p<0.05$). Regression splines indicate a linear increase in hazard for u-NGAL levels up to 5 µg/mmol Cr, however above this level there appears to be no major increase in risk

(Figure 1). The cumulative incidence of cardiovascular mortality in participants above vs. below u-NGAL 1.19 μg/mmol Cr is shown in Figure 1.

A significant effect modification of prevalent cardiovascular disease was observed (P<0.01). Accordingly, we performed analyses stratified for prevalent cardiovascular disease. In these analysis the increased cardiovascular mortality risk appeared greater in the subgroup with established cardiovascular disease at baseline (no. of events/no. at risk 41/157; multivariate [model B] HR 5.2 for u-NGAL quartile 4 vs. quartile 1, 95% CI 1.1-25, P <0.05) than in the subgroup without cardiovascular disease at baseline (no. of events/no. at risk 49/440; multivariate [model B] HR 1.6 for u-NGAL quartile 4 vs. quartile 1, 95 % CI, 0.7-3.6, P = 0.22).

3.3 Cox regression models for associations of u-NGAL, $eGFR_{CysC}$ and u-Alb combined and cardiovascular and all-cause mortality risk

The group of participants with high u-NGAL (≥1.19 μg/mmol Cr), low $eGFR_{CysC}$ (≤60 mL/min) and high u-Alb (≥ 3 mg/mmol Cr) had a 9-fold increased risk in cardiovascular mortality and a 3-fold increased risk of all-cause mortality compared to participants with all three biomarkers normal (Table 2). Participants with only one pathological biomarker (high u-NGAL, low $eGFR_{CysC}$ or high u-Alb) were at no increased mortality risk. These associations did not substantially change when adjusting for cardiovascular risk factors or CRP. When analysing the additive cardiovascular mortality risk of u-NGAL on u-Alb, separately, a significant additive mortality risk by high u-NGAL (≥1.19 μg/mmol Cr) was seen in the group of participants without albuminuria (u-Alb < 3 mg/mmol Cr), HR 2.1, 95 % CI 1.1-4.2, P <0.05), Fig 3a. High u-NGAL (≥1.19 μg/mmol Cr) was not associated with cardiovascular mortality in participants with normal eGFR, but the combination of low $eGFR_{CysC}$ and high u-

NGAL (≥1.19 μg/mmol Cr) was significantly associated with cardiovascular mortality compared to the reference group with both low u-NGAL and normal eGFR, HR 4.8, 95 % CI 2.4-9.5, P <0.001, Fig 3b.

3.4 Cox regression models for the associations of s-NGAL and cardiovascular and all-cause mortality risk

S-NGAL was not significantly associated with cardiovascular mortality risk in any models (Supplementary Table 1). S-NGAL was linearly associated with an increased all-cause mortality risk (HR for 1 SD increase 1.1, 95 % CI 1.0 -1.3, P <0.05) also when adjusting for established cardiovascular risk factors (Supplementary Table 1). However, adding $eGFR_{CysC}$, u-albumin or CRP to the models as covariates abolished the significant linear association. Likewise, participants in the highest s-NGAL quartiles had significantly higher mortality risk than participants in the lowest s-NGAL quartile (HR 1.4, 95 % CI 1.1-2.0, P<0.05) but the associations were abolished when adjusting for $eGFR_{CysC}$, u-Alb or CRP.

4. Discussion

This is the first community-based longitudinal study to show that higher u-NGAL concentrations are associated with increased mortality risk, predominantly increased cardiovascular mortality risk. These associations could not primarily be explained by confounding by established cardiovascular risk factors or glomerular filtration (eGFR), however may in part be mediated by u-Alb. S-NGAL was associated with increased all-cause mortality risk independently of established cardiovascular risk factors, however these associations were abolished after further adjustment for eGFR, u-Alb or CRP. No association was seen between s-NGAL and cardiovascular mortality.

Impaired kidney function is a risk factor for development of cardiovascular diseases [26, 27]. Even mild impaired glomerular filtration, estimated by serum creatinine or serum cystatin C [28], or high u-Alb predicts cardiovascular and all-cause mortality [27, 29-31], thus chronic kidney dysfunction is now considered a significant fatal cardiovascular risk factor. U-NGAL is a new promising renal tubular damage indicator that has been identified as an early biomarker of acute renal damage [6, 7, 32, 33] but also chronic renal damage [9-12] in clinical studies. NGAL is upregulated in injured tubular cells and secreted into the urine, thus can be used as an early indicator of tubulointerstitial damage [5, 34]. The results presented in this study indicate that u-NGAL may carry risk information beyond impaired glomerular filtration estimated by plasma cystatin C, but speculatively some of the risk information may in part be reflected by u-Alb. U-Alb is considered as a biomarker of glomerular barrier damage [35] and tubular dysfunction [36]. Based on the results of the present study, we speculate that u-NGAL in this population may reflect early chronic tubular damage that may be indicative of an increased mortality risk. The additive mortality risk effect seen by combining u-NGAL, $eGFR_{CysC}$ and u-Alb indicate that u-NGAL, $eGFR_{CysC}$ and u-Alb may reflect partly different

pathological mechanisms. The clinical usefulness of measuring u-NGAL for risk prediction purposes in patients and in the community needs to be evaluated in further large scale studies.

Moreover, NGAL has other functions in non-renal cells which may theoretically be related to the associations seen in this study. A biologically important role of NGAL is that of an acute phase protein being released from circulating, activated neutrophils in response to bacterial infections [3, 4]. Mild chronic inflammation reflected by other acute phase proteins (CRP, interleukin-6) are previously known to predict the risk of cardiovascular morbidity and mortality in some populations [37]. Circulating NGAL may also indicate chronic inflammation which may contribute to atherogenesis and subsequent progression of cardiovascular diseases [13] and a recent study showed that plasma NGAL may predict all-cause and cardiovascular mortality [21]. NGAL from circulating activated neutrophils are primarily reflected in plasma or serum but it can not be ruled out that NGAL from activated neutrophils also contributes to u-NGAL concentrations. During AKI both infiltration of neutrophils in the kidney [38] or glomerular filtration of circulating NGAL may contribute to urinary concentrations of NGAL [39]. The origin of u-NGAL in this setting of elderly but relatively healthy humans is not fully known, however we speculate that a major part of the measured u-NGAL derives from tubular endothelial cells rather than from circulating neutrophils. The lack of linear correlation between NGAL in serum and urine in this study further supports the kidney origin of u-NGAL. Further studies using an NGAL assay that discriminates between the monomeric tubular epithelium-derived and the dimeric neutrophil-derived forms may clarify the origin of u-NGAL [39]. However, we find it unlikely that systemic inflammation would primarily explain the associations between u-NGAL and mortality since CRP as a covariate did not seem to confound the risk estimation models.

This study showed apparent associations between u-NGAL and mortality while the associations between s-NGAL and mortality were relatively weak. There are several possible explanations for this observation. Firstly, u-NGAL is more likely to primarily reflect NGAL derived from the tubular epithelium and s-NGAL reflects mainly NGAL derived from neutrophils as discussed above. Thus, urinary and serum NGAL mirror two different aspects; tubular damage and activated neutrophils, respectively, which may explain the different associations to mortality risk. Secondly, the s-NGAL concentrations in this study may show a larger variability than usually expected since the time from sample collection until separation of blood cells from serum was not strictly standardized. Activated neutrophils may have released NGAL ex vivo during the time from sample collection to centrifugation and thus contributed to this variability [40] which may have resulted in overall weaker associations between s-NGAL and mortality risk than expected.

It can not be excluded that the results of this study to some extent are related to reverse causation, that is high u-NGAL is a consequence of prevalent cardiovascular disease possibly because of atherosclerotic lesions in the renal vasculature. This is supported by the stratified analysis results where the associations between u-NGAL and mortality risk were more distinct among the subgroup of study participants with pre-existing cardiovascular disease. The results from subgroups analysis however, must be interpreted with caution considering the limited number of participants in the different strata. This is to some extent supported by other studies reporting that plasma NGAL predicts mortality in patients with pre-existing acute cerebral ischemia [18] or chronic heart failure [19, 20], although u-NGAL was not evaluated in these studies. The more distinct associations in individuals with pre-existing cardiovascular diseases could also indicate that u-NGAL is an indicator of faster progression of atherosclerosis and chronic heart failure resulting in an increased mortality risk of

cardiovascular causes. The fact that the association between u-NGAL appeared stronger in participants with prevalent cardiovascular disease suggest that u-NGAL is a less suitable candidate for risk prediction in the primary preventive setting.

The strengths of this study include the community-based study design which to our knowledge is one of the largest studies with u-NGAL and detailed clinical characterization. The study is longitudinal with a relatively long follow-up time and in addition a very low loss to follow-up due to the high quality Swedish registry data. Limitations include the limited generalizability to women, and to other age- and ethnic groups.

Data from the regression spline graph indicate that there appeared to be no major increase in risk above u-NGAL levels > 5 μg/mmol Cr. The reason for this is unclear and a potential threshold effect should be interpreted with caution given the low number of participants with u-NGAL above this level. Further studies are needed to validate our findings and to investigate the underlying pathophysiology of the present associations.

5. Conclusions

In conclusion, the new tubular damage biomarker u-NGAL was associated with increased mortality, predominantly cardiovascular mortality, independent of cardiovascular risk factors and glomerular filtration. However, the pathophysiological role of u-NGAL in the development of cardiovascular diseases and the clinical utility of measuring u-NGAL for risk prediction purposes remain to be evaluated in future studies.

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Tables

Table 1. The associations between u-NGAL (μg/mmol Cr) and cardiovascular mortality and all-cause mortality, respectively, in Cox regression models.

	Cardiovascular mortality					**All-cause mortality**				
	N of events/ N at risk: Incidence rate (95%CI)	**Univariate**	**Model A**	**Model B**	**Model C**	**N of events/ N at risk: Incidence rate (95%CI)**	**Univariate**	**Model A**	**Model B**	**Model C**
		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95% CI)		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Continuous models										
Per unit increase of NGAL	90/597: 2.0 (1.7-2.5)	1.23* (1.02-1.49)	1.19 (0.98-1.43)	1.12 (0.92-1.36)	1.02 (0.82-1.25)	261/597: 5.9 (5.2-6.7)	1.15* (1.03-1.29)	1.12* (1.00-1.26)	1.08 (0.96-1.22)	1.03 (0.91-1.16)

Category										
models										
Quartile 1	13/150:	referent	referent	referent	referent	55/150:	referent	referent	referent	referent
(<1.19)	1.1 (0.6-1.9)					4.6 (3.5-6.0)				
Quartile 2	22/149:	1.88	1.84	1.69	1.69	73/149:	1.48*	1.47*	1.43*	1.38
(1.19-1.93)	2.0 (1.3-3.1)	(0.95-3.74)	(0.97-3.80)	(0.85-3.37)	(0.85-3.37)	6.7 (5.3-8.4)	(1.04-2.10)	(1.04-2.10)	(1.00-2.04)	(0.97-1.97)
Quartile 3	28/149:	2.46**	2.34*	2.23*	1.98*	67/149:	1.57*	1.55*	1.51*	1.41
(1.94-3.40)	2.6 (1.8-3.8)	(1.27-4.76)	(1.21-4.54)	(1.15-4.33)	(1.01-3.86)	6.3 (5.0-8.0)	(1.09-2.24)	(1.08-2.23)	(1.05-2.17)	(0.98-2.03)
Quartile 4	27/149:	2.49**	2.37*	2.01*	1.57	66/149:	1.61*	1.56*	1.45	1.22
(>3.40)	2.6 (1.8-3.8)	(1.28-4.84)	(1.21-4.64)	(1.02-3.98)	(0.77-3.22)	6.4 (5.0-8.2)	(1.12-2.30)	(1.08-2.25)	(1.00-2.10)	(0.82-1.82)

HR, Hazard Ratio; * P<0.05, **P<0.01, Incidence rates are given per 100 person-years.

Model A. Adjusted for age and established cardiovascular risk factors including systolic blood pressure, BMI, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering, hypertensive and low-dose aspirin medication, smoking status, diabetes and prevalent cardiovascular disease

Model B. Adjusted for the covariates in model A and in addition $eGFR_{CysC}$

Model C. Adjusted for the covariates in model A and in addition u-Alb

Table 2. The combined effects of u-NGAL, $eGFR_{CysC}$ and u-Alb for cardiovascular and all-cause mortality risk estimated by Cox regression models.

	Cardiovascular mortality			**All-cause mortality**		
	N of events/ N at risk	**Univariate** HR (95%CI)	**Model A** HR (95%CI)	**N of events/ N at risk**	**Univariate** HR (95%CI)	**Model A** HR (95%CI)
All biomarkers normal	8/115	referent	referent	42/115	referent	referent
1 pathological biomarker	35/288	1.89 (0.87-4.07)	2.06 (0.95-4.49)	101/288	1.15 (0.80-1.64)	1.17 (0.81-1.68)
2 pathological biomarkers	30/153	3.38** (1.55-7.37)	2.67* (1.21-5.93)	89/153	2.11*** (1.46-3.04)	1.91** (1.31-2.78)
All 3 biomarkers pathological	17/41	9.21*** (3.97-21.4)	8.63*** (3.58-20.8)	29/41	3.33*** (2.07-5.36)	3.34*** (2.03-5.50)

HR, Hazard Ratio; * P<0.05, **P<0.01, ***P<0.001

Normal u-NGAL is in this table defined as <1.19 µg/mmol Cr (lowest quartile in this study cohort); pathological u-NGAL ≥1.19 µg/mmol Cr

Normal $eGFR_{CysC}$ >60 mL/min, pathological $eGFR_{CysC} \leq 60$ mL/min.

Normal u-Alb <3 mg/mmol Cr., pathological u-Alb ≥ 3 mg/mmol Cr.

Figure legends

Figure 1 Regression spline curve for the relation between u-NGAL and the risk for cardiovascular mortality. The reference was set at u-NGAL 1.19 µg/mmol Cr.

Figure 2. Nelson-Aalen plot of cumulative incidence of cardiovascular mortality by participants above vs. below u-NGAL 1.19 µg/mmol Cr

Figure 3. Cardiovascular mortality risk in participants with u-NGAL below and above 1.19 µg/mmol Cr and a) u-Alb below and above 3 mg/mmol Cr (N of events/N at risk: 30/102 for u-NGAL ≥1.19 and u-Alb ≥ 3; 3/12 for u-NGAL <1.19 and u-Alb ≥ 3; 47/339 for u-NGAL ≥1.19 and u-Alb < 3; 10/138 for u-NGAL <1.19 and u-Alb < 3) and b) eGFR above and below 60 ml/min (N of events/N at risk: 32/102 for u-NGAL ≥1.19 and eGFR <60; 2/26 for u-NGAL ≥1.19 and eGFR <60; 45/339 for u-NGAL ≥1.19 and eGFR >60; 11/124 for u-NGAL <1.19 and eGFR >60). * P<0.05, ***P<0.001 compared to the reference groups with u-NGAL <1.19 and u-Alb < 3 and eGFR >60, respectively.

Figures

Fig 1

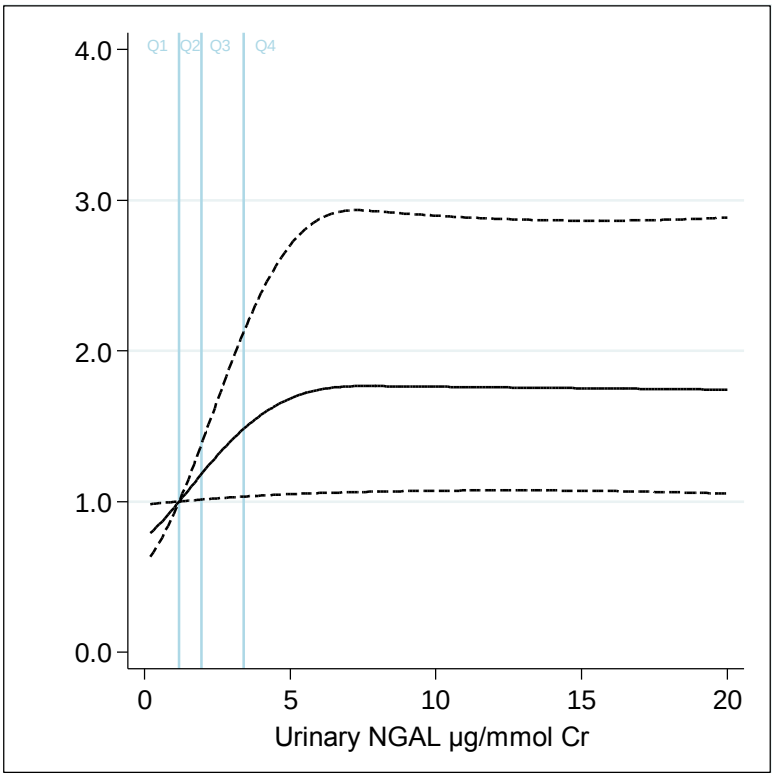


Fig 2

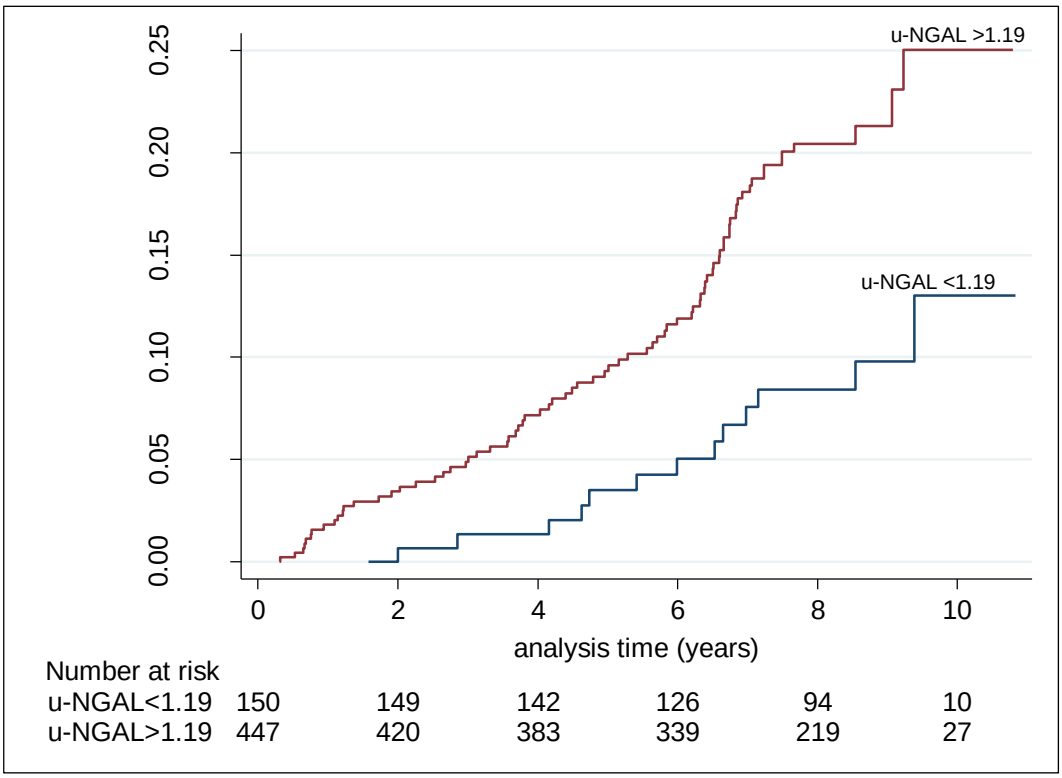
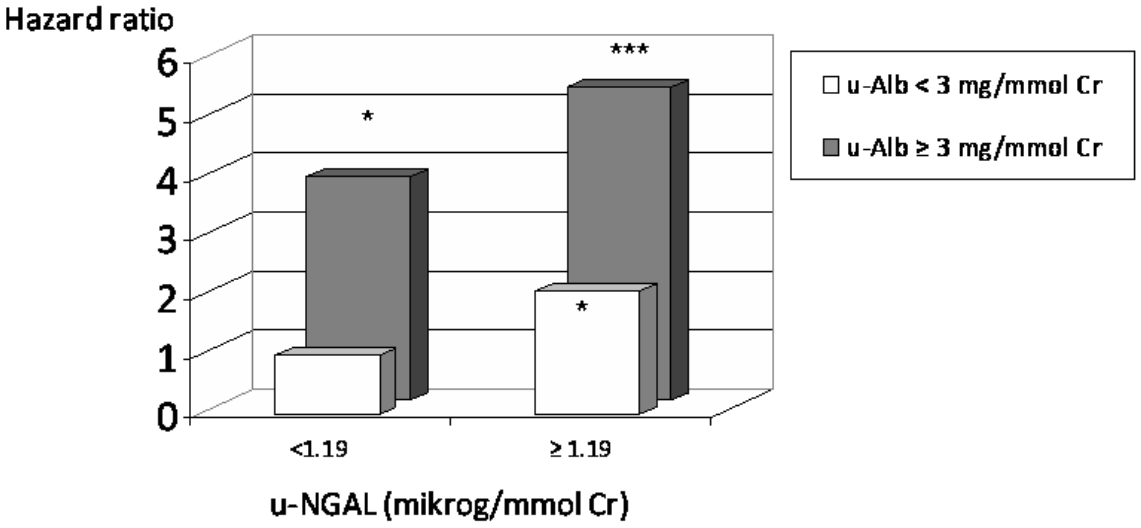
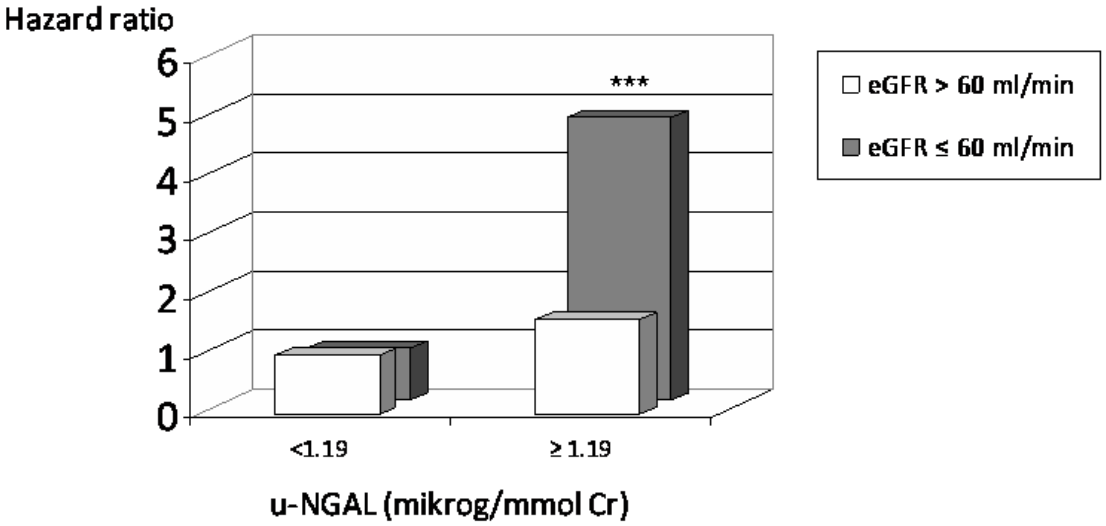

u-NGAL >1.19
u-NGAL <1.19
0.00
0.05
0.10
0.15
0.20
0.25
0
2
4
6
8
10
analysis time (years)
Number at risk
u-NGAL<1.19 150 149 142 126 94 10
u-NGAL>1.19 447 420 383 339 219 27

Fig 3

a)


Hazard ratio
6
5
4
3
2
1
0
*
***
*
<1.19
≥ 1.19
u-NGAL (mikrog/mmol Cr)
u-Alb < 3 mg/mmol Cr
u-Alb ≥ 3 mg/mmol Cr

b)


Hazard ratio
6
5
4
3
2
1
0
***
<1.19
≥ 1.19
u-NGAL (mikrog/mmol Cr)
eGFR > 60 ml/min
eGFR ≤ 60 ml/min