The association of serum free light chains with mortality and progression to end-stage renal disease in chronic kidney disease: systematic review and individual patient data meta-analysis

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Abstract

Objective

To clarify the associations between polyclonal serum free light chains (sFLC) and adverse outcomes in patients with chronic kidney disease (CKD) by conducting a systematic review and individual patient data meta-analyses**.**

Patients and Methods

On December 28, 2016, we searched four databases (MEDLINE, Embase, CINAHL, PubMed) and conference proceedings, for studies presenting independent analysis of associations between sFLC and mortality or progression to end-stage renal disease (ESRD) in patients with CKD. Study quality was assessed in five domains: sample selection, measurement, attrition, reporting, and funding. Study registered a priori with PROSPERO.

Results

Five prospective cohort studies were included, judged moderate to good quality, involving 3921 participants in total. In multivariable meta-analyses, sFLC (kappa+lambda) levels were independently associated with mortality (5 studies, 3680 participants; hazard ratio (HR) 1.04 (95% CI 1.03 to 1.06) per 10 mg/L increase in sFLC), and progression to ESRD (3 studies, 1848 participants; HR 1.01 (95% CI 1.00 to 1.03) per 10 mg/L increase in sFLC). sFLC values above upper limit of normal (43.3mg/L) were independently associated with mortality and ESRD (HR 1.45 (95% CI 1.14 to 1.85)) and 3.25 (1.32 to 7.99) respectively).

Conclusion

Higher levels of sFLC are independently associated with higher risk of mortality and ESRD in patients with CKD. Future work is needed to explore the biological role of sFLC in adverse outcomes in CKD, and their use in risk stratification.

Abbreviations

CKD	Chronic Kidney Disease
ESRD	End-stage Renal Disease
sFLC	Polyclonal serum free light chains
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
uACR	Urine albumin to creatinine ratio
DM	Diabetes
SBP	Systolic blood pressure
MGUS	Monoclonal gammopathy of uncertain significance
RAASi	Renin angiotensin aldosterone system inhibitors
RRT	Renal replacement therapy

Introduction

Chronic kidney disease (CKD) is common, with an estimated prevalence of 3-17% in Europe and 15% in the US.[1,2] It is associated with adverse health outcomes including acute kidney injury, progression to end-stage renal disease (ESRD), cardiovascular disease (CVD), and mortality.[3-6] Estimated glomerular filtration rate (eGFR) and albuminuria are well-established prognostic factors in CKD that are measured routinely in clinical practice and used for risk stratification. However, there is significant interest in the study of novel prognostic factors and biomarkers that could potentially improve current risk stratification methods, and may provide insights into the underlying mechanisms of adverse outcomes associated with CKD and thereby identify potential therapeutic targets.[7]

Polyclonal serum free light chains (sFLC) are produced by cells of the B cell lineage and undergo renal metabolism. Thus sFLC are increased in CKD and there are plausible mechanisms by which they may be directly implicated in the associated risks of mortality and ESRD.[8] However, studies published to date have reported results that are inconsistent, with variable adjustment for confounding factors, and so there remains uncertainty whether sFLC are independently associated with adverse outcomes in CKD.

To address this, we performed a systematic review and meta-analysis of individual patient data to summarize and synthesize published data on the association between sFLC and mortality as well as progression to ESRD in patients with CKD.

Materials and methods

This study was conducted in accordance with published guidelines for systematic review, analysis, and reporting of meta-analyses of observational studies.[9] It was registered a priori with PROSPERO, an international database of prospectively registered systematic reviews, accessible at: www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015025195.

Studies meeting the following criteria were included:

- *Types of studies:* Quantitative studies presenting an independent analysis of the association between sFLCs and mortality and/or ESRD in humans with CKD. Case reports and qualitative studies were not included. No restrictions on language, publication date, or publication status were imposed.
- *Participants:* Individuals with CKD. Participants were excluded if they were on dialysis, or if they had monoclonal gammopathy (MGUS or multiple myeloma).
- *Exposure:* Polyclonal sFLC concentration.
- *Outcomes:* 1: All-cause mortality; 2: ESRD, defined as initiation of renal replacement therapy (RRT).

Literature review

We searched four databases (MEDLINE 1946-present, Embase 1947-present, CINAHL, and PubMed) using terms for CKD and immunoglobulin light chains using both MeSH and related terms as free text, and also included a term to exclude studies with 'myeloma' in the title. Our full search strategy for MEDLINE is shown in the Supplementary material. We also searched the Cochrane library and the Centre for Reviews and Dissemination (York). Grey literature searching included conference proceedings and abstracts for three major Nephrology conferences from 2012-2015

(UK Renal Association, European Renal Association/European Dialysis and Transplant Association and the American Society of Nephrology Kidney Week). Authors of abstracts were contacted if relevant. We conducted reference follow up of full text papers. We also searched trial registers – Clinical Trials.gov. The last search was performed on December 28, 2016. Searches and study selection processes were performed independently by two investigators (SF, AF) using titles and abstracts. Decision regarding inclusion was based on pre-specified eligibility criteria, with differences resolved by discussion.

Data collection

Two reviewers (SF, AF) extracted data for each study using a standardized form (based on the STROBE Statement checklist), including study date, location, primary aim, participant characteristics (number, CKD stage), setting (e.g. primary or secondary care), main outcome, sampling method and potential sampling bias, potential confounders, presence of sample size calculation, main results (measure and magnitude of effect), method of sFLC analysis, missing data, loss to follow up, and evidence of reporting bias including funding source.[10] A risk of bias tool similar to that recommended in the Cochrane Handbook was used to judge study quality, attributing low, moderate or high risk of bias status based on sample selection (including risk of residual confounding), measurement, attrition, reporting and funding (SF and AF independently, with final study quality status agreed by discussion, (Supplementary Table 1)).[11]

Outcome measures

Primary outcome measures were the adjusted hazard ratio for all-cause mortality and progression to ESRD.

Statistical analysis

Individual patient data were obtained from all included studies. All had included the following baseline variables: age, sex, diabetes (DM), CVD, systolic blood pressure (SBP), MDRD eGFR, serum albumin, calcium and phosphate, renin angiotensin aldosterone system inhibitors (RAASi), and sFLC (defined for these analyses as combined sFLC: κ plus λ). Descriptive statistics were used to show the characteristics of individuals in the combined study population.

A meta-analysis of individual patient data was conducted using two distinct methods in view of the different way in which individual studies had analysed sFLC, the differing covariates used in the individual analyses, and the limited number of people in two studies with sFLC ≤43.3 mg/L (95th percentile of the normal range) threshold (only 5 [6%] and 10 [3%] people in the Desjardins and Haynes studies respectively). Individual datasets from each study were combined for common variables and Kaplan-Meier analysis and univariate and multivariable Cox regression models were conducted on combined data to explore relationships between sFLC >43.3 mg/L and all-cause mortality and ESRD. Study of origin was included as a fixed-effect co-variable to account for study heterogeneity. A high proportion of participants in the studies by Ritchie et al (39%) and Desjardins et al (100%) were missing values for urine ACR (uACR). uACR was therefore not included in the main analyses. A sensitivity analysis was conducted for survival analysis in those with complete uACR data (n= 3103) (see Supplementary data). To address the potential for effect modification of survival and progression by comorbidity and age, interaction terms were tested between DM and RAASi, DM and CVD and age and CVD. We also tested interactions between ethnicity and DM and RAASi and DM for ESRD

analyses. The individual patient data meta-analyses were conducted in IBM® SPSS® version 22.

A second, more traditional, meta-analysis of individual studies was conducted to demonstrate the association of a 10 mg/L rise in sFLC with all-cause mortality and ESRD (for those studies that included progression to RRT as an outcome) using inverse-variance-weighted fixed effects models. These analyses controlled for age, sex, MDRD eGFR, CVD, DM, and serum albumin. A 10 mg/L increase was chosen as it was perceived to reflect a clinically meaningful change in sFLC while allowing broader interpretation than the binary 43.3 mg/L threshold. Fixed effects models were used in view of the small number of studies. I^2 statistics were calculated as a measure of study heterogeneity. Forest plots were used to combine and display the results. The traditional meta-analyses were conducted in STATA® SE version 14.

Results

We identified 1554 citations meeting our search criteria. Title and abstract review led to exclusion of 1542 articles. Full texts were obtained and reviewed for the remaining 12, from which seven were excluded, leaving five studies for inclusion (Figure 1).[12-16] Table 1 shows the individual study characteristics and results. All five were prospective cohort studies with a total of 3912 participants. The study by Haynes et al included 35 participants with monoclonal gammopathy of undetermined significance (MGUS), and that conducted by Desjardins et al included 44 participants on dialysis. After excluding these, 3833 participants remained, with all CKD stages represented (except for patients on dialysis or with a kidney transplant). Four were conducted in the UK, and one in France. Four recruited participants from secondary care nephrology clinics, and one from primary care. All studies had used the

Freelite™ assay to measure sFLCs. Statistical analysis methods varied between studies: three studies assessed sFLC as a categorical variable (using median, quartiles, or upper limit of the reference range as cut-offs) and two studies analysed sFLC as a continuous variable. Four studies combined kappa (κ) and lambda (λ) sFLC for survival analyses and one study analysed κ and λ FLC separately. All studies evaluated associations between sFLC and all-cause mortality; two also evaluated progression to ESRD (Table 1). One study defined ESRD as initiation of RRT, and one as initiation of RRT or reaching an eGFR ≤9.

The overall risk of bias was judged to be low for the study by Ritchie et al, and moderate for the other four studies. Assessments of the risk of bias in the domains of sample selection (including risk of residual confounding), measurement, attrition (drop-out), reporting, and funding, are presented individually for each study in Supplementary Table 1.

Findings of individual studies

All-cause mortality:

Assi et al (n=1695) assessed sFLC as a categorical variable, using the upper limit of the reference range for sFLC in the healthy population (>43.3 mg/L) as a cut-off. sFLC >43.3 mg/L was associated with three-fold increase in mortality risk in univariate Cox regression analysis and this increased risk remained significant, though attenuated, in their fully adjusted model. Desjardins et al (n=133) analysed κ and λ FLC separately, using their respective medians as cut-off values. κ FLC above median was associated with an increased risk of mortality on univariate analysis but this association did not remain after adjusting for age and eGFR. λ FLC above median was not associated with an increased risk of mortality on either univariate or

multivariable analysis. Haynes et al (n=364) analysed sFLC on a log scale (both combined, and κ and λ FLCs separately), and showed weak evidence of an association between λ FLC and mortality risk, with no significant effect of sFLC after full adjustment. Hutchison et al (n=848) assessed sFLC both as a categorical (in quintiles) and continuous variable. On univariate analysis, a 1-unit increase in sFLC on a log scale was associated with three-fold increased risk of death. This risk remained significant after full adjustment. Ritchie et al (n=872) analysed sFLC by quartiles, and on univariate analysis those in the third and fourth quartiles had a significantly increased mortality risk compared to the lowest quartile. This association remained in their multivariable model (Table 1).

Progression to end-stage renal failure

Haynes et al reported an increased risk of ESRD in a model adjusted for age and sex, but the statistical significance no longer remained after further adjustment for eGFR. Ritchie et al identified an increased risk of ESRD among those in the highest two quartiles of sFLC in both univariate and multivariable models (Table 1).

Meta-analysis

Of the 3912 participants included in the five studies, 3815 (97.5%) had a value for sFLC and 3680 (94.1%) had complete data for exposure and mortality outcome variables and hence were included in the survival analyses (Table 2).

All-cause mortality

On univariate Cox regression analysis, increasing age, male sex, White ethnicity, DM, CVD, higher systolic blood pressure (SBP), higher albuminuria, lower eGFR,

lower albumin, lower calcium, higher phosphate and sFLC >43.3 mg/L were all positively associated with all-cause mortality. Use of renin angiotensin aldosterone system inhibitors (RAASi) was associated with a lower risk of all-cause mortality (Table 3). The results of the unadjusted Kaplan-Meier analysis are shown in Figure 2 and demonstrate the difference in cumulative survival by sFLC status above and below the 43.3 mg/L threshold. In the final multivariable model, after adjustment for age, sex, DM, CVD, eGFR, albumin, calcium, taking RAASi, and sFLC with original study as a fixed effect, the associations with age, sex, DM, CVD, eGFR, albumin and sFLC remained (Table 3). A sFLC concentration > 43.3 mg/L was associated with a hazard ratio of 1.45 (95% CI 1.14-1.85, *P*<.001). The sensitivity analysis in those with urinary albumin to creatinine ratio (uACR) values found no difference in the association between sFLC and all-cause mortality (Supplementary Table 2). No interactions were identified. A 10 mg/L rise in sFLC was associated with an overall increased risk of 4% (95% CI 3 to 6%) for all-cause mortality on meta-analysis of the five individual studies (Figure 3), although we detected significant heterogeneity (I^2 = 62.6%, *P*=.03).

Progression to End Stage Renal Disease

Although only two studies had reported progression to ESRD as an outcome, three studies had collected data on this (combined n=2152).[13-15] We conducted combined analyses on the 1848 participants with complete data for exposure and ESRD as an outcome.

On univariate Cox regression analysis, younger age, non-White ethnicity, DM, higher SBP, increased albuminuria, lower eGFR, lower albumin, lower calcium, taking RAASi and sFLC >43.3 mg/L were all positively associated with progression to ESRD. In the final multivariable model, after adjustment for age, sex, ethnicity, DM,

SBP, eGFR, albumin, calcium, taking RAASi, and sFLC with original study as a fixed effect, the associations with age, SBP, eGFR, albumin, calcium and sFLC remained (Table 4). A sFLC concentration > 43.3 mg/L was associated with a hazard ratio of 3.25 (95% CI 1.32-7.99, *P*=.01). No interactions were identified. A 10 mg/L increase in sFLC was associated with an overall increased risk of progression to ESRD of 1% (95%CI 0 to 3%) (Figure 3). There was evidence of considerable heterogeneity across studies (I^2 = 58.8%, *P*=.09).

Discussion

This is the first systematic review and meta-analysis examining the association between polyclonal sFLC and adverse outcomes in patients with CKD. We believe it includes the totality of data published to date. We included five moderate to good quality prospective cohort studies that included people across the full spectrum of pre-dialysis CKD.[12-16] We found an independent association between sFLC and both mortality and progression to ESRD in an analysis that included conventional risk factors for these outcomes. Moreover, the hazard ratio for mortality observed in participants with sFLC above the upper limit of normal was similar in magnitude to that associated with diabetes or previous cardiovascular disease.

Mortality

In a meta-analysis incorporating individual patient data from all five studies, we found an independent association between elevated levels of sFLC and all-cause mortality, which supported the findings of three of the individual studies.[14-16] Although we had only 17 (0.4%) participants with CKD category G1 in the meta-analysis, the results

indicate that sFLC may have a role in all stages of pre-dialysis CKD. This is consistent with general population studies identifying an association between elevated sFLC and mortality in individuals without CKD.[17,18]

It is not known if sFLC are causally linked to increased mortality in patients with CKD, but there are plausible explanatory mechanisms including through their association with immune dysfunction. sFLC isolated from patients with kidney disease abrogate essential functions of neutrophils, including chemotaxis.[19,20] sFLC also inhibit neutrophil apoptosis, and so by interfering with the resolution of inflammation may perpetuate a chronic inflammatory state, which has been showed to be associated with adverse outcomes in patients with CKD.[19-21] In addition, sFLC activate mast cells which may accelerate both atherosclerosis and myocardial fibrosis, and can contribute to the development of interstitial fibrosis in the kidney through a range of mechanisms.[22] However, a specific cell receptor for sFLC has not been identified to date.[23]

Contrary to our findings in pre-dialysis CKD, a study of haemodialysis patients found an inverse relationship between sFLC and mortality, i.e. those with higher sFLC levels had lower mortality risk.[24] The authors speculated that higher sFLC levels may reflect less uraemia-related bone marrow dysfunction and that increased sFLC levels are associated with improved defence against infection. Further work is needed in the haemodialysis population to validate this study's findings.[24]

Progression to ESRD

Two studies, with inconsistent results, previously reported the relationship between sFLC level and progression to ESRD and were included in this meta-analysis.[13,15]

We incorporated additional data from a third study and identified a positive independent association between sFLC level and risk of ESRD.[14]

High levels of sFLC may directly cause additional kidney damage in those who already have CKD, and thus increase progression risk. Whilst it is known that monoclonal sFLC can cause various forms of kidney injury and, in the proximal tubule, can induce pathways linked with inflammation, apoptosis, and fibroblastic differentiation, outside the evidence we summarise above on the effect of polyclonal FLC on leukocytes subsets, there are no published studies reporting a direct mechanism for kidney injury to date.[25-28]

Although it is possible that the associations between sFLC and adverse outcomes reflect residual confounding due to the association between sFLC and GFR, there is good supportive evidence for a true independent association of sFLC with adverse outcomes. First, the significant association between sFLC and adverse outcomes remained after adjustment for creatinine-based eGFR. In contrast, a recent patient-level meta-analysis showed limited additional prognostic value for other alternative markers of glomerular filtration such as cystatin C, beta-trace protein (BTP), and beta-2-microglobulin (B2M) in analyses that included creatinine-based eGFR .[29] Second, in the studies included in this meta-analysis, the correlation between eGFR and sFLC (where reported) is moderate (*r* values of -0.56 and -0.49).[15,16] This indicates that whilst sFLC is in part associated with eGFR, a substantial contribution to differences in sFLC levels is independent of kidney function. For example, FLC undergo significant non-renal clearance through the reticulo-endothelial system, which accounts for a greater portion of clearance in CKD as kidney function declines.[30]

Third, the association between sFLC and mortality has been reported in studies of a general population with normal kidney function and non-renal disease, supporting the theory that sFLC have adverse effects via mechanisms other than through an association with kidney disease, although it remains possible that even in this group the sFLC level partially reflects the spectrum of kidney function.[17,18,31-33]
Finally, there are biologically plausible mechanisms for a relationship between sFLC and adverse outcomes, for example through their association with inflammation and reticulo-endothelial system health, properties which other renally-cleared small molecules such as BTP and B2M do not possess.

The strengths of this study include a broad search strategy, the use of robust methods for study selection and quality assessment, and inclusion of individual patient data from all included studies. Limitations include a limited search of grey literature, which means that we may have missed some studies that had only been reported as conference abstracts, and our inability to conduct a traditional meta-analysis using the 43.3 mg/L cut-off due to the small numbers of patients with values below this level in two of the studies. There may also have been undetected variation in the methods used to collect data in the original studies. Our inclusion of at least one collaborator from each of the original studies aimed to mitigate this. There were also some important missing variables in some included studies (for example, those with missing uACR data in Desjardins and Ritchie), though we were able to conduct sensitivity analyses in the subgroup who had uACR data.

Further research is needed to identify the biological basis for the associations between sFLC and adverse outcomes in CKD, and to examine the utility of sFLC as a biomarker for enhanced risk stratification. Whether sFLC have a role in routine risk

stratification in CKD could be addressed by a multi-centre validation study with an a priori design that includes a statistical model for incorporating sFLC with routine laboratory variables that represent the standard of care.[34] This would allow elucidation of any additional sensitivity and specificity of sFLC for risk stratification and the impact of this on clinical and health economic outcomes. Future study designs should take into account the measurement uncertainty (inter-assay variability) of the Freelite assay.[35]

Conclusion

This meta-analysis has demonstrated independent associations between sFLC and progression to ESRD and mortality in patients with CKD. It provides the basis for further work to explore the biological basis for these associations, and to assess whether sFLC provides incremental value when added to current risk stratification models.

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This manuscript is not under consideration for publication elsewhere, though an abstract was included in the American Society of Nephrology conference material, Nov 2016, and it was presented as a poster at the UK Kidney Week Conference, June 2017

Authors' contributions

SF, AF, MT and PC conceived and designed the study.
SF and AF conducted the literature searches.
SF and AF drafted the article, which was then critically reviewed by all authors.
SF and SH conducted statistical analyses with input from JE.
SL, ZM, AB, CH, ML, JE, PK, JR, PC and MT were all involved in providing original study data for the individual patient data metaanalysis.

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Figure legends

Figure 1. Flow chart of study selection

Figure 2. Kaplan Meier plot showing cumulative survival by sFLC status above and below the 43.3 mg/L threshold

Footnote to figure 2: This figure shows the unadjusted survival curves. Continuous line = sFLC>43.3mg/L, dotted line = sFLC⩽43.3mg/L

Figure 3. Forest plots showing the associations between a 10 mg/L rise in sFLC and all cause mortality and ESRD

Footnote to figure 3: numbers reaching each end point may differ from those reported by the individual studies because people on dialysis or with monoclonal gammopathy were excluded for these analyses. Shaded boxes reflect study weight.

Table 1. Characteristics of included studies, including outcomes in each study[a,b]

First author, year of publication	Patient no	Years of enrolment	Mean age (y)	Male (%)	CKD stages	Follow up period (months)	FLC analyses	All-cause mortality[c]			ESRD[c,d]		
								Univariate HR (95%CI)	Multivariable HR (95%CI)	Model covariates	Univariate HR (95%CI)	Multivariable HR (95%CI)	Model covariates
Assi et al,[16] 2015	1695	2008-2010	74	39	3	114.5 (median)	Categorical: above/below 43.3mg/L	**3.20 (2.34-4.36)**	**1.50 (1.04-2.16)**	Age, sex, CVD, diabetes, hypertension, smoking, eGFR, albuminuria, hsCRP, central obesity, PWV, serum albumin			
Desjardins et al,[12] 2013	133 (89 non-dialysis)	2006-2007	67	62	2-5	88.2 (median)	Categorical: above/below median for κ and λ separately	**κ: 3.05 (1.20-7.75)** λ: 1.35 (0.54-3.40)	κ: 1.22 (0.38-3.95) λ: 0.65 (0.22-1.92)	Age, eGFR			
Haynes et al,[13] 2011	364 (329 non-MGUS)	1997-1999	61	65	3-5	72 (mean) for death 49.2 (mean) for ESRD	Continuous: per 1SD increase in log sFLC and κ and λ	Not reported	κ: 1.04 (0.83-1.31) **λ: 1.33 (1.05-1.67)** sFLC: 1.15	Age, sex, eGFR, NT-proBNP, troponin, smoking	Not reported	κ: 1.05 (0.88-1.26) λ: 0.99 (0.83-1.19) sFLC: 1.05 (0.87-1.26)	Age, sex, eGFR

							separately		(0.92-1.44)				
Hutchison et al,[14] 2014	848	2006-2007	60	54	1-5	63 (median)	Continuous: per increase of 1 on log sFLC	**3.21 (2.56-4.02)**	**2.71 (1.98-3.70)**	Age, ethnicity, CVD, hsCRP			
Ritchie et al,[15] 2015	872	2004-2010	66	62	3-5	41.4 (median)	Categorical: quartiles vs Q1 for mortality, vs Q1/2 for ESRD	**Q3: 1.87 (1.30-2.69)** **Q4: 2.62 (1.84-3.71)**	**Q3: 1.49 (1.02-2.18)** **Q4: 1.99 (1.34-2.93)**	Age, eGFR, CVD	**Q3: 3.42 (2.20-5.30)** **Q4: 8.74 (5.85-13.06)**	**Q3: 1.72 (1.0-2.97)** **Q4: 3.73 (2.10-6.30)**	eGFR, PCR, Phosphate

[a]Abbreviations: CI = confidence interval; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; FLC = free light chains; HR = hazard ratio; hsCRP = high sensitivity C-reactive protein; κ = kappa; λ = lambda; MGUS = monoclonal gammopathy of uncertain significance; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCR = protein to creatinine ratio; PWV = pulse wave velocity; Q = quartile; SD = standard deviation; sFLC = combined serum free light chains. [b]All studies were conducted in hospital nephrology clinics apart from Assi et al,[16] 2015, which was conducted in primary care. [c]Statistically significant results are in bold. [d]Grey shading indicates the studies for which ESRD was not an included outcome.

Table 2. Characteristics of individuals in the individual patient level meta-analysis at baseline[a]

		Number (or mean for continuous variables)[b]	**% of total (or SD for continuous variables)**[b]
		Total = 3680	
Age	<40	183	5.0
	40-59	706	19.2
	60-79	2201	59.8
	80+	590	16.0
Sex	Male	1852	50.3
	Female	1828	49.7
Ethnicity	White	3325	90.4
	Other	267	7.3
	Missing	88	2.4
Original study	Assi	1636	44.5
	Ritchie	872	23.7
	Hutchison	749	20.4
	Desjardins	79	2.1
	Haynes	344	9.3
Diabetes		810	22.0
Cardiovascular disease		1229	33.4
Blood pressure (mm Hg) (available for 3669 people)	Systolic	139*	21.7*
	Diastolic	75*	12.4*
uACR (available for 3192 people)	(mg/mmol)	38.4*	102.2*
MDRD eGFR	(ml/min/1.73m^2)	41.9*	17.6*
Albumin	(g/L)	41.6*	4.6*
Calcium	(mmol/L)	2.31*	3.9*
Phosphate	(mmol/L)	1.23*	2.6*
CKD stage	G1	13	0.4
	G2	281	7.6
	G3a	1498	40.7
	G3b	877	23.8
	G4	745	20.2
	G5	264	7.2
Taking RAASi		2256	61.3
Free Kappa	(mg/L)	34.4*	28.9*
Free Lambda	(mg/L)	31.1*	24.6*
Combined Kappa+Lambda (sFLC)	(mg/L)	65.6*	51.1*
Haemoglobin (available for 3031 people)		12.8*	1.6*
Died		753	20.5
Progressed to ESRD		474	12.9

[a]Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; MDRD = modification of diet in renal disease formula; RAASi = renin angiotensin aldosterone system inhibitors; SD = standard deviation; sFLC = serum free light chains; uACR = urinary albumin to creatinine ratio. [b]Continuous variables are denoted by *.

Table 3. Survival analysis (n=3680)[a]

		Adjusted for original study			Final multivariate model[b]		
		HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (continuous)	(Years)	1.07	(1.06-1.08)	<.001	1.06	(1.05-1.06)	<.001
Sex (vs female)	Male	1.52	(1.30-1.76)	<.001	1.29	(1.10-1.50)	.001
Ethnicity (vs. non white)	White	1.64	(1.22-2.21)	.03	-	-	-
Diabetes (vs. not)		1.67	(1.44-1.95)	<.001	1.31	(1.12-1.53)	.001
Cardiovascular disease (vs. not)		2.53	(2.19-2.93)	<.001	1.59	(1.36-1.85)	<.001
Systolic blood pressure (continuous)	(mm Hg)	1.01	(1.00-1.01)	<.001	-	-	-
log uACR (continuous) **	(mg/mmol)	1.24	(1.14-1.35)	<.001	-	-	-
MDRD eGFR (continuous)	(ml/min/1.73m^2)	0.96	(0.96-0.97)	<.001	0.98	(0.97-0.98)	<.001
Albumin (continuous)	(g/L)	0.95	(0.93-0.96)	<.001	0.95	(0.94-0.97)	<.001
Calcium (continuous)	(mmol/L)	0.36	(0.22-0.61)	<.001	0.99	(0.77-1.27)	.94
Phosphate (continuous)	(mmol/L)	1.02	(0.99-1.05)	.21	-	-	-
Taking RAASi (vs. not)		0.82	(0.71-0.95)	.008	1.07	(0.91-1.24)	.42
Combined Kappa+Lambda (sFLC)>43.3mg/L (vs. <=43.3)	sFLC>43.3mg/L	2.94	(2.36-3.65)	<.001	1.45	(1.14-1.85)	<.001

[a]Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MDRD = modification of diet in renal disease formula; RAASi = renin angiotensin aldosterone system inhibitors; sFLC = serum free light chains; uACR = urinary albumin to creatinine ratio. [b]Adjusted for age, sex, diabetes, cardiovascular disease, eGFR, albumin, calcium, taking RAASi, sFLC and original study.

Table 4. Analysis of factors associated with progression to ESRD (n=1848)[a]

		Adjusted for original study			Final multivariate model[b]		
		HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (continuous)	(Years)	0.99	(0.98-0.99)	<.001	0.98	(0.97-0.98)	<.001
Sex (vs female)	Male	0.81	(0.68-0.97)	.02	0.99	(0.82-1.20)	.93
Ethnicity (vs. non white)	White	0.65	(0.51-0.84)	.001	1.18	(0.90-1.54)	.24
Diabetes (vs. not)		1.28	(1.05-1.57)	.02	1.10	(0.88-1.38)	.41
Cardiovascular disease (vs. not)		0.91	(0.75-1.10)	.31	-	-	-
Systolic blood pressure (continuous)	(mm Hg)	1.01	(1.00-1.01)	.002	1.01	(1.01-1.01)	<.001
log uACR, (continuous) **	(mg/mmol)	3.02	(2.57-3.54)	<.001	-	-	-
MDRD eGFR (continuous)	(ml/min/1.73m^2)	0.88	(0.87-0.89)	<.001	0.88	(0.87-0.90)	<.001
Albumin (continuous)	(g/L)	0.95	(0.93-0.96)	<.001	0.97	(0.95-0.99)	.004
Calcium (continuous)	(mmol/L)	0.21	(0.12-0.37)	<.001	0.47	(0.26-0.84)	.01
Phosphate (continuous)	(mmol/L)	1.01	(1.00-1.02)	.22	-	-	-
Taking RAASi (vs. not)		1.23	(1.02-1.49)	.03	0.89	(0.72-1.09)	.25
Combined Kappa+Lambda (sFLC)>43.3mg/L (vs. <=43.3)	sFLC>43.3mg/L	19.35	(9.13-40.98)	<.001	3.25	(1.32-7.99)	.01

[a]Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HR = hazard ratio; MDRD = modification of diet in renal disease formula; RAASi = renin angiotensin aldosterone system inhibitors; sFLC = serum free light chains; uACR = urinary albumin to creatinine ratio. [b]Adjusted for age, sex, ethnicity, diabetes, systolic blood pressure, eGFR, albumin, calcium, taking RAASi, sFLC and original study.