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DOI:
10.1016/j.mayocp.2014.01.028

MAYO CLINIC

ORIGINAL ARTICLE

Serum Polyclonal Immunoglobulin Free Light Chain Levels Predict Mortality in People With Chronic Kidney Disease

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Abstract

Objective: To determine whether elevated serum polyclonal free light chain (FLC) levels predict mortality in a population of individuals with chronic kidney disease (CKD).

Patients and Methods: From January 2, 2006, through July 31, 2007, we recruited a cohort of 848 people with CKD who were not receiving renal replacement therapy and did not have monoclonal gammopathy. We measured serum kappa FLC and lambda FLC isotype levels to determine combined FLC (cFLC) levels. The cohort was prospectively followed up for a median of 63 months (interquartile range, 0-93 months). Cox regression analysis was performed to determine variables predictive of mortality.

Results: High cFLC levels were an independent risk factor for death (hazard ratio [HR], 2.71; 95% CI, 1.98-3.70; $P<.001$). Other independent risk factors were age (HR, 1.79; 95% CI, 1.52-2.10; $P<.001$), South Asian ethnicity (HR, 0.33; 95% CI, 0.14-0.64; $P=.02$), preexisting cardiovascular disease (HR, 1.59; 95% CI, 1.09-2.31; $P=.02$), and high-sensitivity C-reactive protein (HR, 1.13; 95% CI, 1.00-1.28; $P=.04$). Neither estimated glomerular filtration rate nor albuminuria was an independent risk factor for death.

Conclusion: High cFLC levels independently predict mortality in people with CKD.

■ Mayo Clin Proc. 2014;89(5):615-622

Chronic kidney disease (CKD) affects more than 10% of the adult population,[1,2] and a high proportion of total health care budgets is used in managing patients with CKD.[3,4] The mortality associated with CKD is high and is related to both baseline kidney function and the rate of progression of CKD.[5,6] The major cause of increased mortality is cardiovascular disease (CVD), although there is also increased mortality from cancer and infections.[7,8]

To better target management in CKD, enhanced risk stratification is required.[1] At present, risk assessment is based on the measurements of kidney function (estimated glomerular filtration rate [eGFR]) and kidney injury (proteinuria). However, as chronic inflammation is an important component of risk in CKD,[9] the serum levels of molecules that are affected by both kidney function and immune/inflammatory status may represent better tools for risk assessment than do current routine tests.

Immunoglobulin light chains are a component of the intact immunoglobulin molecule produced by plasma cells and other cells of the B-cell lineage. Free light chains (FLCs) are produced in excess during immunoglobulin synthesis and are cleared from the serum by the kidneys; therefore, a decrease in the GFR is associated with an increase in serum FLC levels. An assessment of the ratio of the 2 isotypes of FLC—κFLC and λFLC—is widely used in the diagnosis and management of plasma cell disorders to identify and quantify monoclonal FLC.[10,11] However, the measurement of serum polyclonal FLC may also identify global immune activation. Recent studies have found an association between increased levels of polyclonal FLC and outcomes in the general population and in people with autoimmune disease, cancer, and kidney disease.[12-18]

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Therefore, the objective of this study was to evaluate the hypothesis that serum levels of polyclonal FLC are predictive of mortality in people with CKD. To address this, we performed a large cohort study of people with CKD (non–renal replacement therapy) incorporating other bioclinical variables of known importance for outcomes.

PATIENTS AND METHODS

The study was approved by the Solihull and South Birmingham Research Ethics committees (reference number 05/Q2702/50) and the R&D department of University Hospitals Birmingham NHS Foundation Trust. All patients gave informed written consent to participate in the study.

Study Population

From January 2, 2006, through July 31, 2007, we recruited a cohort (n=916) of patients under follow-up in adult kidney disease clinics at University Hospitals Birmingham. Patients were approached on the basis of the following selection criteria: they fulfilled the K/DOQI criteria for CKD,[19] and they were not receiving renal replacement therapy (through dialysis or a functioning kidney transplant). All patients who fulfilled these criteria and who had an appointment in a clinic attended by the enrolling investigator (C.A.H.) were provided with written information about the study and then approached and asked to provide informed consent for the study. Once the patients were enrolled in the study, the following baseline parameters were collected: age, sex, ethnicity, CVD comorbidity (ischemic heart disease, cardiac failure, cerebrovascular disease, and peripheral vascular disease), diabetes mellitus, blood pressure (BP), medications, urinary albumin/creatinine ratio (ACR), and serum laboratory variables (albumin, phosphate, calcium, creatinine, cystatin C, high-sensitivity C-reactive protein (hsCRP), estimated glomerular filtration rate (eGFR) by the abbreviated modification of diet in renal disease equation (MDRD), and serum FLC. Sixty-eight patients (7.4%) were excluded from the analysis because they had a monoclonal gammopathy of undetermined significance (MGUS) at the time of recruitment. A diagnosis of MGUS is independently associated with an increased mortality[20,21] and abnormalities in FLC independent of kidney function.[22] Therefore, 848 patients (92.6%) were included in this analysis.

Laboratory Analysis

Creatinine, albumin, calcium, and phosphate were measured using a Roche Modular Analyser (Roche Diagnostics); the normal ranges were as follows: 50 to 125 μmol/L, 35 to 50 g/L, 2.25 to 2.75 mmol/L, and 0.8 to 1.4 mmol/L, respectively. Urine albumin and creatinine were measured by using automated immunoturbidimetry with antibody against human albumin and a compensated version of the Jaffe reaction (Roche Diagnostics). A normal ACR was defined as less than 2.5 mg/mmol for men and less than 3.5 mg/mmol for women. The results reported for ACR, systolic BP, and diastolic BP are the median of 3 clinic appointments: the recruitment clinic, the clinic before recruitment, and the clinic after recruitment.

To diagnose a MGUS, sera were tested by serum protein electrophoresis (Sebia Hydragel Protein kit on the Hydrasys system, Sebia) and serum FLC immunoassays (Freelite on the Dade-Behring BN II Analyser, The Binding Site Group Ltd). If either test gave abnormal results, serum immunofixation electrophoresis was used (Sebia Hydragel Immunofixation PE kit on the Hydrasys system). The presence of a monoclonal protein indicative of a MGUS was defined by an intact immunoglobulin band using immunofixation electrophoresis or an abnormal serum FLC ratio with a corresponding elevation in the concentration of involved FLC isotype (FLC-MGUS). The reference range for the serum FLC ratio in renal disease is 0.37 to 3.1.[23,24] Polyclonal FLC concentrations were determined by combining serum κFLC and λFLC concentrations (combined FLC [cFLC]); the reference range was 9.3 to 43.3 mg/L.[17]

Statistical Analyses

Excluding patients who died, the cohort was prospectively followed up for a median of 68 months (interquartile range [IQR], 52-93 months). The cause of death was that recorded on the death certificate held by the General Register Office. The causes of death were categorized as CVD, infection, cancer, renal failure, or other.

The Kaplan-Meier method was used to analyze quintiles of cFLC levels. Cox proportional hazards regression analysis was used to

Mayo Clin Proc. ■ May 2014;89(5):615-622 ■ http://dx.doi.org/10.1016/j.mayocp.2014.01.028
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examine factors associated with survival times. Those alive at the end of the study period were censored according to their follow-up time. In addition, logistic regression was used to examine factors associated with 1-year survival.

Univariate analyses were performed to the end of the study period and for 1-year survival in relation to the variables collected at baseline. These comprised age, sex, ethnicity, CVD comorbidity (ischemic heart disease, cardiac failure, cerebrovascular disease, and peripheral vascular disease), BP, and the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and serum laboratory variables (albumin, phosphate, calcium, creatinine, cystatin C, hsCRP, eGFR, and serum FLC). Continuous variables with a highly skewed distribution were log transformed before analysis. Indicator variables were used to fit categorical predictor variables.

Those variables with $P<0.2$ in a univariate analysis were included in a multivariate analysis. For overall survival, this analysis comprised all independent variables. For CVD, the variable any CVD (not individual diseases) was included to represent one or more CVD comorbidities. For survival at 1 year, ethnicity, diastolic BP, and ACR had a $P\geq.2$ and were not included in the multivariate analysis. Before the multivariate analysis, the colinearity between the variables was determined; variance inflation factors with a value above 10 were considered as evidence of colinearity. The variables serum creatinine and the abbreviated modification of diet in renal disease estimated glomerular filtration rate (MDRD eGFR) were colinear, and eGFR was included in the multivariate analysis. κFLC, λFLC, and cFLC were also colinear; cFLC was included in the multivariate analysis. A backward selection procedure was used to retain variables that were statistically significant by using a significance level of .05.

Continuous variables were compared between groups using the analysis of variance and the Kruskal-Wallis test, as appropriate. Analyses using receiver operating characteristic curves examined the utility of routine laboratory tests for kidney function and serum cFLC for the prediction of death at 1 year. The area-under-the-curve (AUC) values for each variable with the corresponding CI were calculated.

In addition, analyses examined factors associated with individual causes of death. Cox proportional hazards regression models were again used for the analysis. Patients who did not die were censored at the time of last follow-up, whereas those who died of a different cause were censored at the time of death.

Analysis was performed using SPSS (version 21, IBM Corporation) and Stata Statistical Software (version 12.1, Stata Corporation).

RESULTS

Demographic characteristics, laboratory data, and renal diagnoses are given in Table 1. The cohort was predominately white (79% of stated; 656), with a mean age of 60 years; 54% (455) were men. Twenty-one percent of the patients had diabetes as a comorbidity. The patients were distributed according to the CKD stage: stage 1, 2% (17); stage 2, 17% (142); stage 3a, 19% (158); stage 3b, 27% (229); stage 4, 25% (212); stage 5, 8% (70) and not stated 2% (20). The median duration of follow-up for the whole cohort (including deaths) was 63 months (IQR range, 0-93 months),

TABLE 1. Population Demographic and Baseline Characteristics of 848 Patients With CKD[a,b]

Age (y)	60±17
Sex: male	54
Ethnicity	
White	79
South Asian	11
African Caribbean	7
Other	3
ACR (mg/mmol)	10 (2-59)
Albumin (g/L)	43±4.42
Calcium (mmol/L)	2.29±0.15
Phosphate (mmol/L)	1.30±0.28
Creatinine (μmol/L)	153 (112-222)
eGFR (mL/min per 1.73 m^2)	45±27.63
κFLC (mg/L)	27 (16-47)
λFLC (mg/L)	28 (18-44)
cFLC (mg/L)	56 (35-91)
Renal disease	
Glomerulonephritis	39
Pyelonephritis/renal tract calculi	7
Interstitial nephritis	3
Hereditary nephropathies	8
Hypertensive/renovascular	23
Diabetic nephropathy	8
Other	14

[a]ACR = albumin creatinine ratio; cFLC = combined free light chain; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; κFLC = kappa free light chain; λFLC = lambda free light chain.
[b]Values are presented as mean ± SD, No. (percentage), or median (interquartile range).

TABLE 2. Cox Regression Analysis of Variables Associated With All-Cause Mortality: Univariate Analysis[a,b]

Variable	Hazard ratio (95% CI)	*P* value
Age (y)[c]	2.20 (1.90-2.53)	<.001
Sex		
Male	1.76 (1.28-2.43)	.001
Female	1	
Ethnicity		
White	1	.05
South Asian	0.42 (0.22-0.83)	
African Caribbean	0.72 (0.37-1.41)	
Other	0.55 (0.17-1.71)	
CKD stage		
1-2	1	<.001
3a	1.00 (0.38-2.70)	
3b	4.53 (2.14-9.56)	
4	7.37 (3.55-15.30)	
5	9.97 (4.55-21.80)	
ACE inhibitors		
No	1	.05
Yes	0.73 (0.53-1.00)	
IHD		
No	1	<.001
Yes	2.60 (1.81-3.74)	
MI/angioplasty		
No	1	.01
Yes	1.94 (1.17-3.20)	
PVD		
No	1	<.001
Yes	3.08 (1.95-4.88)	
CVA		
No	1	<.001
Yes	2.90 (1.73-4.86)	
Cardiovascular disease (any)		
No	1	<.001
Yes	3.54 (2.58-4.85)	
Diabetes		
No	1	<.001
Yes	1.98 (1.43-2.73)	
Systolic BP (mm Hg)[c]	1.15 (1.07-1.23)	<.001
Diastolic BP (mm Hg)[c]	0.79 (0.68-0.92)	.002
ACR (mg/mmol)[d]	1.12 (1.03-1.22)	.01
Albumin (g/L)[e]	0.85 (0.74-0.97)	.02
Calcium (mmol/L)	0.21 (0.09-0.51)	.001
Phosphate (mmol/L)	3.72 (2.24-6.19)	<.001
Creatinine (μmol/L)[d]	3.58 (2.72-4.72)	<.001
MDRD eGFR (mL/min per 1.73 m^2)	0.64 (0.58-0.71)	<.001
hsCRP (mg/L)[d]	1.44 (1.27-1.62)	<.001
Cystatin C (mg/L)	1.69 (1.53-1.87)	<.001
cFLC (mg/L)[d]	3.21 (2.56-4.02)	<.001
κFLC (mg/L)[d]	3.06 (2.40-3.80)	<.001
λFLC (mg/L)[d]	3.00 (2.40-3.76)	<.001
Renal disease		
Glomerulonephritis	1	<.001
Pyelonephritis/renal tract calculi	1.81 (0.85-3.81)	
Interstitial nephritis	2.55 (0.99-6.60)	
Hereditary nephropathies	1.23 (0.54-2.82)	
Hypertensive/ renovascular	4.29 (2.76-6.66)	
Diabetic nephropathy	4.35 (2.48-7.63)	
Other	3.47 (2.11-5.72)	

[a]ACE = angiotensin-converting enzyme; ACR = albumin creatinine ratio; BP = blood pressure; cFLC = combined free light chain; CKD = chronic kidney disease; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C reactive protein; IHD = ischemic heart disease; κFLC = kappa free light chain; λFLC = lambda free light chain; MDRD = modification of diet in renal disease; MI = myocardial infarction; PVD = peripheral vascular disease.
[b]ACR, systolic BP, and diastolic BP values presented are the median of 3 clinic appointments.
[c]Analyzed in 10-unit increases.
[d]Analyzed on a log scale.
[e]Analyzed in 5-unit increases.

whereas the median duration for the patients who did not die was 68 months (IQR range, 52-93 months). In total, there were 50,675 patient-months available for analysis. At the end of follow-up, 20% (167) of the patients had died.

Serum FLC Levels and Survival

The median serum polyclonal FLC levels were as follows: κFLC, 27 mg/L (IQR, 16-47 mg/L); λFLC, 28 mg/L (IQR, 18-44 mg/L); cFLC, 56 mg/L (IQR, 35-91 mg/L) (Table 1). The cFLC levels were inversely related to eGFRs (Kruskal-Wallis test, $P<.001$). Univariate Cox regression analysis indicated that a number of demographic, clinical, and laboratory variables were associated with survival (Table 2). Higher levels of serum FLC, both as single isotypes and as cFLC, were associated with reduced survival; a 1-unit increase in cFLC (on the log scale) was associated with a 3-fold increased risk of death (hazard ratio [HR], 3.21; 95% CI, 2.56-4.02). This finding was true for both κFLC (HR, 3.06; 95% CI, 2.40-3.80) and λFLC (HR, 3.00; 95% CI, 2.40-3.76) isotypes (Table 2). A Kaplan-Meier survival plot for the cohort by quintiles of cFLC levels is shown in the Figure.

Mayo Clin Proc. ■ May 2014;89(5):615-622 ■ http://dx.doi.org/10.1016/j.mayocp.2014.01.028
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Because there was marked colinearity between the level of the 2 FLC isotypes and cFLC level, only cFLC was included in the multivariate analysis. Similarly, creatinine was excluded from the multivariate analysis and eGFR retained. Multivariate analysis indicated that cFLC, age, ethnicity, cardiovascular comorbidity, and hsCRP were all independently associated with mortality (Table 3). Of these variables, cFLC had the highest HR for death (HR, 2.71; 95% CI, 1.98-3.70). All other variables, including eGFR and ACR, were not independent significant predictors of mortality.

Importantly, cFLC remained significantly associated when deaths within the first year of follow-up were analyzed (odds ratio [OR], 3.70 for a 1-unit increase on the log scale; 95% CI, 2.14-6.41; $P<.001$). The multivariate analysis of significant variables found age (OR, 1.75 for a 10-year increase; 95% CI, 1.19-2.56; $P=.005$), CVD (OR, 3.14; 95% CI, 1.34-7.37; $P=.008$), cFLC (OR, 2.20; 95% CI, 1.03-4.75; $P=.04$), and hsCRP (OR, 1.50; 95% CI, 1.10-2.02; $P=.009$) to be independently predictive of mortality within 1 year. Furthermore, the AUC statistic was greater for the prediction of survival when using this combination of variables (AUC statistic, 0.86) compared with any of the classically measured renal markers (Table 4).

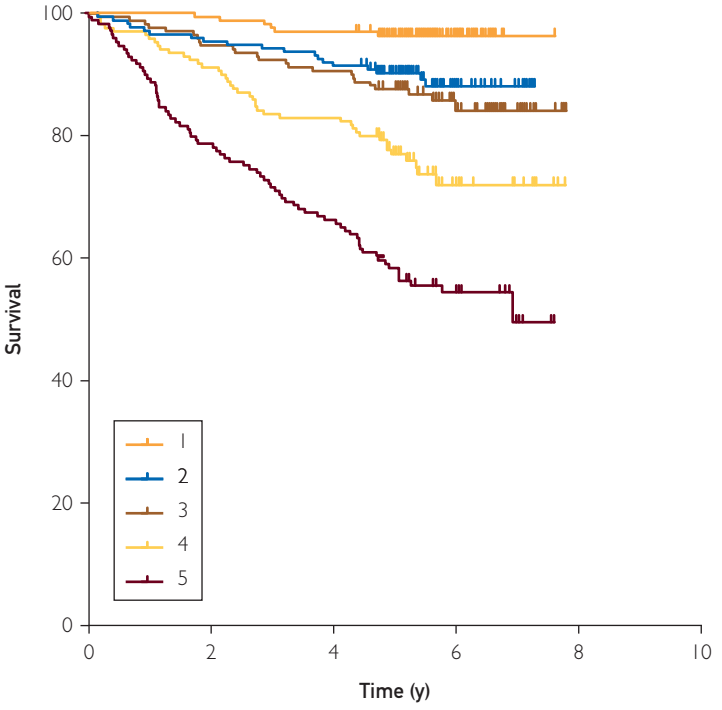

FIGURE. Survival by quintiles of combined FLC levels. Higher combined FLC levels were associated with a significantly reduced survival ($P<.001$).

Causes of Death

The causes of death were identified in 164 of 167 patients who died. The major causes of death (where reported) were CVD (39%), infections (27%), cancers (18%), and renal failure (11%). Eight percent of the patients died of other causes. The proportion of individuals who died progressively increased with higher FLC quintiles (3.7%, 10.9%, 14.1%, 24.1%, and 43.8%); however, the distribution of causes of death was not significantly different between the FLC quintiles: CVD (50.0%, 21.1%, 33.3%, 41.5%, and 43.2%), infection (16.7%, 31.6%, 33.3%, 31.7%, and 23.0%), and cancer (16.7%, 36.8%, 16.7%, 4.9%, and 20.3%) (χ^2 test, $P=.245$). Univariate Cox regression analysis found a significant association between cFLC and each cause of death (CVD HR, 3.65; infection HR, 3.00; renal HR, 3.91; cancer HR, 2.53, all $P<.001$ for a 1-unit increase on the log scale). Multivariate analysis found that cFLC independently predicted deaths from CVD (HR, 2.97; $P<.001$), cancer (HR, 2.06; $P=.02$), and infection (HR, 1.84; $P=.03$); in addition, age was an independent risk factor for death from all 4 causes (CVD HR, 1.68, $P<.001$; infection HR, 2.11, $P<.001$; renal HR, 2.85, $P<.001$; cancer HR, 1.76, $P=.001$ for a 10-year increase on the log scale); history of CVD was associated with cardiovascular mortality (HR, 2.08; $P=.005$); hsCRP (HR, 1.32; $P=.02$) and male sex (HR, 2.70; $P=.02$) were independently associated with deaths from infection; cystatin C (HR 1.70; $P=.04$) and systolic BP (HR 1.30; $P=.02$) were predictive of renal mortality.

DISCUSSION

The objective of this study was to determine whether serum levels of polyclonal immunoglobulin cFLC can stratify people with CKD for the risk of mortality. In this cohort of 848 individuals with CKD, cFLC predicted mortality independently of all other factors studied, including kidney function and hsCRP.

Increasing serum levels of both κFLC and λFLC and the summation of the 2 isotypes (cFLC) predicted increased mortality. As anticipated, the colinearity between these 3 variables

TABLE 3. Cox Regression Analysis of Variables Associated With All-Cause Mortality: Multivariate Analysis[a]

Variable	Hazard ratio (95% CI)	*P* value
Age (y)[b]	1.79 (1.52-2.10)	<.001
Ethnicity		
White	1	
South Asian	0.33 (0.14-0.64)	
African Caribbean	0.72 (0.32-1.67)	.02
Other	0.73 (0.24-2.42)	
Cardiovascular disease (any)		
No	1	
Yes	1.59 (1.09-2.31)	.02
cFLC (mg/L)[c]	2.71 (1.98-3.70)	<.001
hsCRP (mg/L)[c]	1.13 (1.00-1.28)	.04

[a]cFLC = combined free light chain; hsCRP = high-sensitivity C reactive protein.
[b]Analyzed in 10-unit increases.
[c]Analyzed on a log scale.

was high; therefore, in the multivariate analysis, only cFLC was evaluated.

To date, this is the largest study on associations between polyclonal FLC and clinical outcomes in patients with CKD. In a recent study on associations between monoclonal and polyclonal FLC in patients with CKD, we found an overall association between λFLC and survival in a multivariable analysis of a range of clinical variables, including markers of cardiac injury (N-terminal prohormone of brain natriuretic peptide and troponin). The cohort was smaller, had advanced CKD (median eGFR, 21.9 mL/min per 1.73 m^2), and had high comorbidity as compared with those measured in the present study.[16]

TABLE 4. AUC Analysis of Variables Associated With Renal Function or Significant by Multivariate Analysis and Survival at 1 y[a]

Variable	AUC (95% CI)
MDRD eGFR	0.67 (0.60-0.75)
ACR	0.54 (0.45-0.63)
Cystatin C	0.74 (0.67-0.82)
cFLC	0.74 (0.67-0.82)
Multivariate regression model[b]	0.86 (0.79-0.93)

[a]AUC = area under the curve; ACR = albumin creatinine ratio; cFLC = combined free light chain; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease.
[b]Multivariate regression model consisting of age, cardiovascular disease, FLC, and hsCRP.

In the general population, there are 2 large cohorts with data available on the association between polyclonal FLC and outcomes. First, Dispenzieri et al[17] analyzed outcomes in approximately 16,000 people included in the Olmsted county cohort and found, by using multivariable analysis, an independent mortality risk associated with high polyclonal cFLC levels. Second, the German Heinz Nixdorf Recall health-screening study found an independent association between polyclonal FLC and survival in 4350 people.[25] In addition, a recent study has used data from patients who have undergone routine hematological assessments for a monoclonal gammopathy; in patients with a monoclonal gammopathy excluded, elevated cFLC levels were independently associated with increased mortality.[12]

Serum levels of cFLC are representative of 2 factors: (1) their production rates and (2) their serum half-lives. The basic immunoglobulin molecule consists of 2 heavy chains and 2 light chains that are linked by disulfide bonds. The production of FLC is related to an excess production of light chains over heavy chains, such that excess FLCs are released into the circulation in health at an estimated rate of 500 mg/d. Although any cell derived from the B-cell lineage can produce FLC, most of the FLCs will be released from mature plasma cells. The production rate of FLC therefore represents the activity of the adaptive immune system.

The second effect on the serum levels of FLC is serum half-life, which is predominantly affected by kidney function.[23] Both isotypes of FLC are molecules that are cleared by glomerular filtration, and so as kidney function levels (GFR) decrease, serum FLC levels increase. There was a close association between the absolute serum FLC levels and kidney function, and so cFLC levels increased with the decreasing levels of kidney function. Serum cFLC levels were predictive of overall survival in both univariate and multivariate analyses. A further evaluation of the cause of death established that cFLC levels were independently associated with deaths from CVD and infection. Moreover, the risk associated with cFLC was independent of eGFR and ACR.

The association described herein between serum levels of cFLC and mortality identifies FLC as a biomarker of potential clinical utility.

Mayo Clin Proc. ■ May 2014;89(5):615-622 ■ http://dx.doi.org/10.1016/j.mayocp.2014.01.028
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However, FLC could also be mechanistically involved in the poor outcomes of this population, although the data for this are currently sparse. Although the pathways by which monoclonal FLC cause direct tissue injury in diseases such as multiple myeloma and amyloid light chain amyloidosis are well described,[26,27] there is less evidence to date for polyclonal FLC, with studies limited to in vitro experiments establishing a role of polyclonal FLC in the inhibition of leukocyte phagocytosis and in chronic inflammation.[28]

CONCLUSION

This study reports a potential role of polyclonal cFLC to act as a biomarker by which patients with CKD can be risk stratified for mortality. The principal limitation of the study is the cross-sectional design and short follow-up. Further studies are required to identify how the association between serum FLC levels and mortality can be used to improve outcomes for people with CKD and the mechanistic basis for this association.

Abbreviations and Acronyms: **ACR** = albumin creatinine ratio; **AUC** = area under the curve; **BP** = blood pressure; **cFLC** = combined free light chain; **CKD** = chronic kidney disease; **CVD** = cardiovascular disease; **eGFR** = estimated glomerular filtration rate; **FLC** = free light chain; **hsCRP** = high-sensitivity C-reactive protein; **HR** = hazard ratio; **IQR** = interquartile range; **κFLC** = kappa free light chain; **λFLC** = lambda free light chain; **MGUS** = monoclonal gammopathy of undetermined significance

Grant Support: Research and travel funding were provided by the Binding Site Group Ltd. Research funding for Drs Jesky and Stringer was provided by the JABBS Foundation.

Potential Competing Interests: Dr Burmeister is an employee of the Binding Site Group Ltd. Dr Harding is the director of R&D at the Binding Site Group Ltd.

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