

Elevated, combined serum free light chain levels and increased mortality: a 5-year follow-up, UK study

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ABSTRACT

Aims Abnormal serum free light chain (FLC) ratios are diagnostically important in almost all plasma cell disorders. However, absolute increases in polyclonal FLC levels are often discarded as inconsequential. Here we report an association between increased combined polyclonal FLC (cFLC: FLC κ plus FLC λ) concentrations and mortality.

Methods 723 patients sent for 30 routine haematological assessments were enrolled. Patients with a confirmed monoclonal gammopathy were removed. The remaining 527 patients were followed up for up to 4.5 years. Statistical analysis was performed using SPSS (V.19).

Results During follow-up, there were 99 deaths (18.8%). Kaplan-Meier survival analysis revealed 29% of these deaths occurred within the first 100 days (N=29). Multivariate analysis identified only cFLC >65 mg/l, albumin <33 g/l and estimated glomerular filtration rate <30 ml/min/1.73 m² to be independently associated with mortality within 100 days and 4.5 years with, cFLC having the highest HR of 7.1. A simple risk stratification model based only on albumin and cFLC identified 86% mortality within 100 days and 62% over 4.5 years.

Conclusions Elevated cFLC is significantly associated with increased mortality and with albumin can be used to identify patients at risk of mortality at 4.5 years with high-risk patients detected within 100 days.

INTRODUCTION

Monoclonal production of immunoglobulin free light chains (FLC), as indicated by an abnormal κ/λ ratio, have been found to be of diagnostic and prognostic importance in almost all plasma cell disorders.^{1–5} While the relevance of monoclonal FLC production is widely recognised, an increased polyclonal concentration is often considered to be of no clinical significance.

Elevated polyclonal combined serum free light chain (cFLC: FLC κ plus FLC λ) concentrations can result from either increased production, due to infection, inflammation or non B-cell malignancy or alternatively from reduced clearance due to renal, hepatic or reticulo-endothelial dysfunction.^{6,7} It is also likely that significant elevations result from a combination of both increased production and reduced clearance.⁸

Recently, raised polyclonal FLC (normal κ/λ ratio) have been reported in a number of non-haematological malignant, reactive and inflammatory disorders associated with B-lymphocyte activation and proliferation. Patients with chronic

kidney disease (CKD) and diabetes express elevated FLC^{9–10} and FLC correlate with disease activity in various autoimmune disorders including systemic lupus erythematosus¹¹ and rheumatoid arthritis.¹² Elevated FLC have also been shown to be predictive of increased risk in the development of non-Hodgkin's lymphoma in HIV patients¹³ and chronic lymphocytic leukaemia¹⁴ as well as being associated with poorer overall survival in these patients.¹⁵

Here we assessed the utility of cFLC as markers of outcome in a mixed hospital patient population, consisting of in-patient and out-patients, sent for serum protein electrophoresis (SPE) investigation.¹⁶

MATERIALS AND METHODS

The study was approved by the local Research Ethics Committee and the Research and Development Department of Royal Wolverhampton Hospitals, NHS Trust, UK.

Study population

Between 8 November 2005 and 10 January 2006 our laboratory received 723 sera with a request for SPE. Samples from paediatric patients, patients on immunoglobulin replacement, second and subsequent samples from the same patient, were excluded from the analysis. Also excluded were patients with evidence of a monoclonal gammopathy as indicated by an abnormal FLC ratio (<0.26 or >1.65;¹⁷) or by detection of a monoclonal protein by SPE, confirmed by immunofixation electrophoresis (IFE). Therefore, our study comprised 527 selected patients.

Laboratory analyses

Sera were analysed for serum protein abnormalities by SPE (Sebia, UK). Serum IFE (Sebia) was performed on all samples with the presence of an abnormal SPE band or those with a high index of suspicion (unexplained hypogammaglobulinaemia, broad β region or low immunoglobulins supported by clinical observation). As part of an evaluation of FLC analysis in a diagnostic setting, FLC measurements (FreeliteTM, The Binding Site Group Ltd, Birmingham, UK) were made using a Siemens Dade-Behring Prospeg nephelometer, in accordance with the manufacturer's instructions.

Total immunoglobulins (IgG, IgA and IgM) were measured by nephelometry (Dade-Behring). Normal range values used for the immunoglobulin concentrations were: IgG 6–16 g/l, IgA 0.8–4.0 g/l and IgM 0.5–2.0 g/l.¹⁸ Serum creatinine was

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Table 1 Patient characteristics

	All patients N=527
Age (years)	59.8 (26.06–87.18)
N	527
Gender (male %)	216 (41.0%)
N	523
Ethnicity (%)	
Caucasian	64.5
Asian	13.7
Afro-Caribbean	4.7
Other	17.1
N	527
Mortality during study period (%)	18.8%
N	99
eGFR (ml/min/1.73 m ²)	78.7 (12.5–139)*
N	494
Bilirubin (μmol/l)	8 (3–48.5)
N	443
ALP (U/l)	82 (46–257.5)
N	480
ALT (U/l)	25 (9.05–175.4)
N	441
Total protein (g/l)	74 (57–87.9)
N	443
Calcium (μmol/l)	2.29 (1.97–2.6)
N	417
Haemoglobin (g/dl)	13.3 (7.95–16.6)
N	509
WCC (×10 ³ /mm ³)	7.2 (3.3–20.88)
N	509
Neutrophils (×10 ³ /mm ³)	4.3 (1.6–14.3)
N	509
FLC κ (mg/l)	18.2 (8.23–102.8)
N	527
FLC λ (mg/l)	20.4 (9–92.04)
N	527
FLC κ/λ ratio	0.9 (0.48–1.7)
N	527
cFLC (mg/l)	39 (18.76–205)
N	527
Serum creatinine (μmol/l)	79 (50–415.7)
N	497
CRP (mg/l)	6 (1–195.65)
N	348
ESR (mm/h)	17 (4–92.45)
N	390
Albumin (g/l)	44 (28.88–51)
N	474
IgG (g/l)	11.8 (5.71–23.9)
N	527
IgA (g/l)	2.57 (0.9–7.77)
N	525
IgM (g/l)	0.94 (0.23–3.06)
N	523
Summated IgG/A/M (g/l)	15.82 (8.78–31.61)
N	522

Continuous variables show median (95%ile range).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; cFLC, combined serum free light chain; CRP, C reactive protein; eGFR, estimated glomerular filtration rate (*3 eGFR values above 120 ml/min/1.73 m²); ESR, erythrocyte sedimentation rate; WCC, white cell count.

determined for the majority of patients (497/527) (Roche; Modular). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation.¹⁹ C reactive protein (CRP) was measured in

348/527 patients (Roche; Modular). Erythrocyte sedimentation rate (ESR) was determined in 390/527 patients (Starstedt; S-Sedivette).

Patient follow-up

In July 2010, 4 years and 6 months after the end of the original study, patient records were reviewed. For all patients, the date of the last follow-up or date of death was recorded and death certificates were obtained.

Clinical outcomes and survival analysis

Kaplan-Meier survival curves were constructed to identify factors influencing mortality over the period of follow-up.

Pearson correlation analysis was performed to determine the degree of correlation between the different biomarkers. Where available, established reference ranges were used, for inclusion of the different biomarkers into a Cox multivariate regression analysis as categorical variables (tables 2 and 3). For eGFR, a cut-off of <30 ml/min/1.73 m² (equivalent to CKD stages 4 and 5;²⁰) was used. There is no published reference range for cFLC and so a cut-off of 50 mg/l was selected, which approximates to the summation of the individual reference ranges for FLCκ and FLCλ (97.5 percentiles¹⁷). Additionally, Receiver-Operator-Characteristic (ROC) analysis was used to select a prognostically optimised cut-off. For age, a cut-off of 75 years was selected to leave 20% of patients in the higher-risk group, comparable to the proportion outside the reference range for the other markers. Cox models were constructed for all deaths and for deaths within the first 100 days. A risk stratification model was constructed, for predicting the likelihood of deaths within 100 days, comprised of the two most significant, independent risk factors.

To simplify the analysis due to the broad range of causes of death observed in this population, the primary causes of death listed on the death certificates were categorised according to the WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).

Mann-Whitney U test, Pearson χ^2 test, Kaplan-Meier curves and Cox regression analysis were performed using SPSS (V.19; Chicago, USA). Correlation analysis was performed using GraphPad Prism (V.5). Analysis using penalised smoothing splines (P-splines) was performed to assess the association of risk of death with cFLC concentration (SAS V.9.1.3; SAS Institute, Cary, USA).

Table 2 Univariate analysis

	All deaths p value	Deaths within 100 days p value
Abnormal IgG	0.323	0.647
Abnormal IgA	0.118	0.251
Abnormal IgM	0.666	0.164
Abnormal IgGAM	0.269	0.181
Albumin <33 g/l	<0.001*	<0.001*
CRP >10 mg/l	0.003*	<0.001*
ESR >12	<0.001*	0.034*
eGFR <30 ml/min/1.73 m ²	<0.001*	<0.001*
Age >75 years	<0.001*	0.03*
Gender (male)	0.495	0.04*
cFLC >65 mg/l	<0.001*	<0.001*

*Factors indicated to be significant (p<0.05) predictors of mortality by univariate analysis.

cFLC, combined serum free light chain; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate.

Table 3 Multivariate analysis: All factors found to be independent predictors using multivariate analysis

	All deaths		Deaths within 100 days	
	p value	HR	p value	HR
eGFR <30 ml/min/1.73 m ²	0.035	2.6	0.024	4.4
Albumin <33 g/l	0.004	3.7	0.002	6.5
cFLC >65 mg/l	0.04	2.3	0.015	7.1
Age >75 years	<0.01	3.8	n/a	n/a

cFLC, combined serum free light chain, eGFR, estimated glomerular filtration rate.

RESULTS

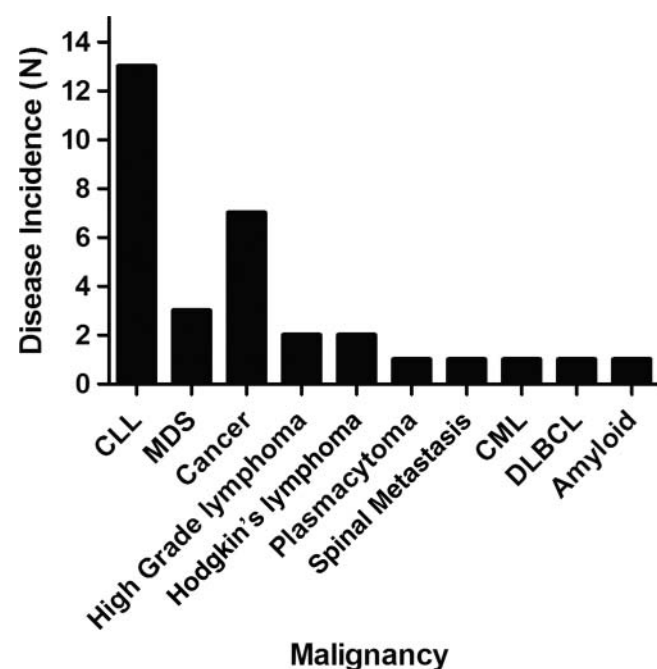
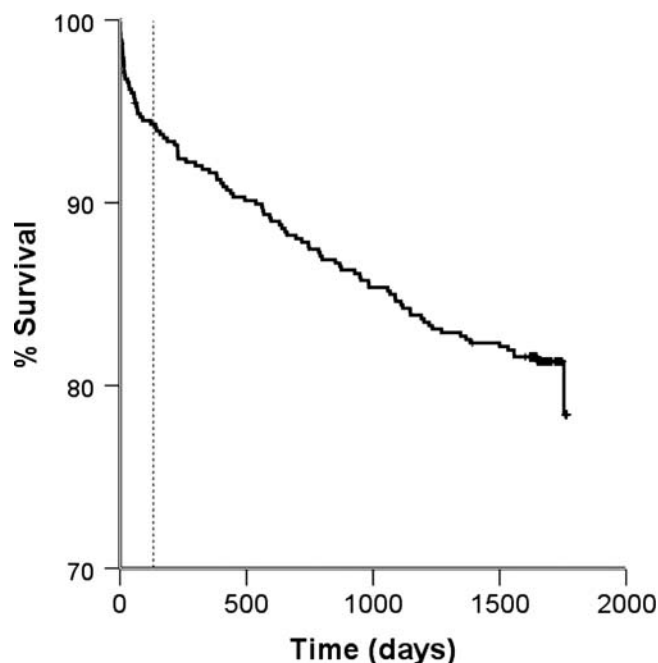
Patient demography

Median age of the patients was 60 years (range 26–87), male/female ratio (216:307; table 1). Of the total population, 122 were hospitalised, 367 were outpatient referrals and 38 were primary care patients. The known malignancies recorded in this population included patients with chronic lymphocytic leukaemia (CLL), cancers and lymphomas (figure 1). Eleven of 32 patients with known malignancies including CLL, cancer and myelodysplastic syndrome died. Patients with impaired kidney function (N=128, eGFR <60 ml/min/1.73 m², equivalent to CKD stage 3 and above) had higher concentrations of cFLC versus CKD stages 1 and 2 patients (median 64.6 mg/l vs 35.5 mg/l, $p<0.001$).

Early death and risk factor analysis

Over the 4.5 years of follow-up, there were 99 deaths (=18.8% mortality). A Kaplan-Meier curve revealed that almost a third of the deaths (29%) occurred within the first 100 days (figure 2). For this reason, subsequent analyses were performed separately for early deaths (<100 days) and all deaths (throughout follow-up).

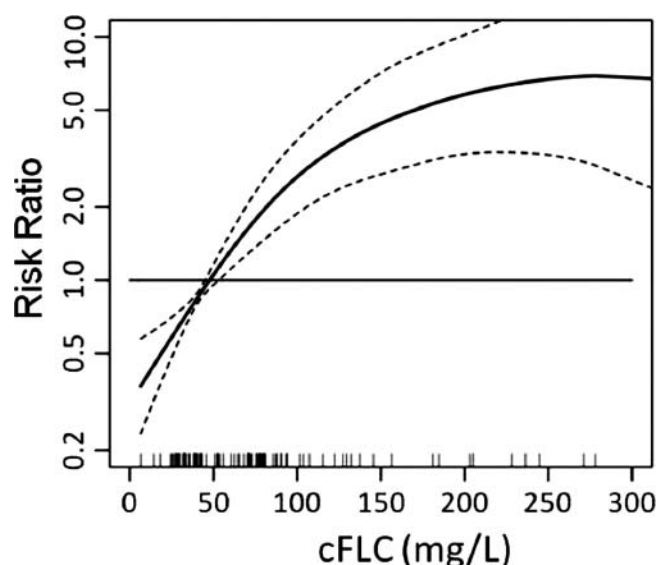
In this study, cFLC were evaluated as a potential new 'mortality predictor' biomarker, in addition to established risk factors including, ESR, CRP, albumin, eGFR and age.

**Figure 1** Figure detailing the malignancies recorded for the study population.**Figure 2** Kaplan-Meier survival curve for all patients over the full period of follow-up. The large number of deaths within the first 100 days is apparent. The vertical line indicates the 100 day time point.

Early risk factors: univariate analysis

Univariate analysis identified albumin <33 g/l, CRP >10 mg/l, ESR >12 mm/h, eGFR <30 ml/min/1.73 m², age >75 years, elevated cFLC and gender (male) as being significant ($p<0.05$) predictors of mortality within 100 days (table 2).

The relative risk of death increased proportionally with increasing cFLC concentrations (figure 3); patients with a lower cFLC concentration (<50 mg/l) had a reduced risk of death compared to patients with a higher concentration (>50 mg/l). ROC analysis indicated 65 mg/l as the optimum cut-off for identifying patients with a greater risk of death.

**Figure 3** Figure illustrating how the risk of death (within the full period of follow-up) varied with combined serum free light chain concentration (solid line). The broken lines represent the 95% CIs.

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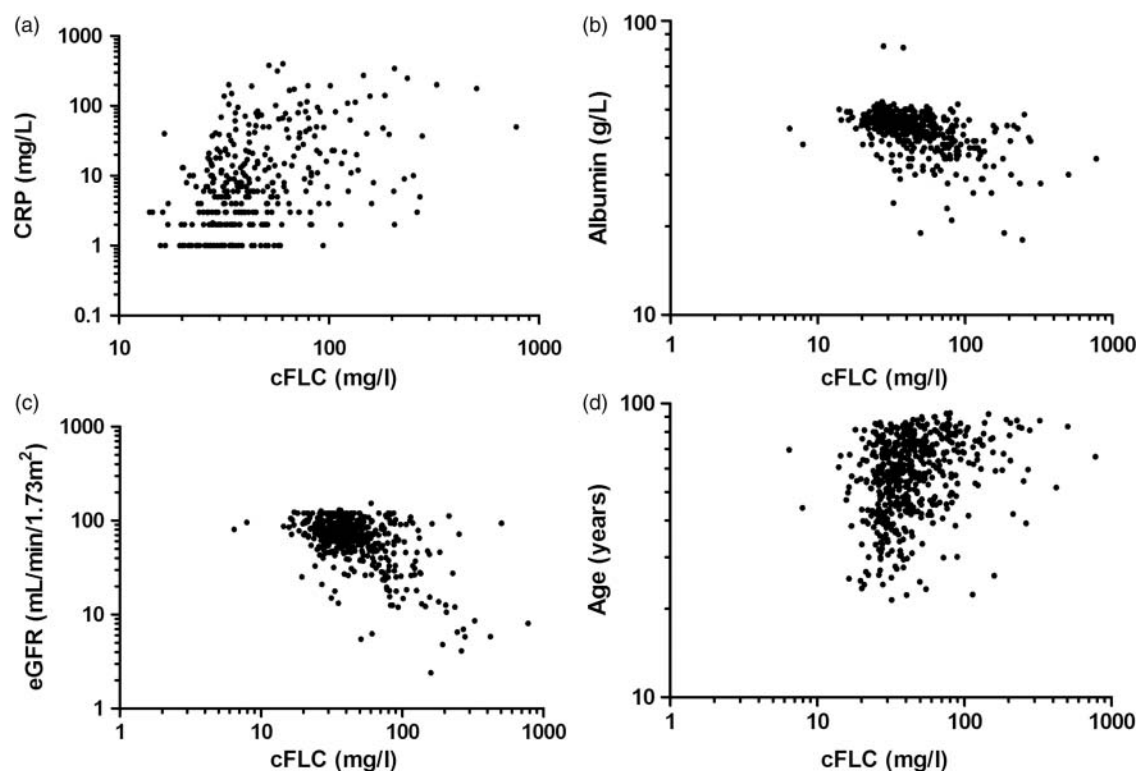


Figure 4 Correlation analysis between combined serum free light chain and (A) C reactive protein $r=0.44$, $p<0.001$, (B) albumin $r=-0.48$, $p<0.001$, (C) estimated glomerular filtration rate $r=-0.38$, $p<0.001$ and (D) age $r=0.32$, $p<0.001$.

Early risk factors: multivariate analysis

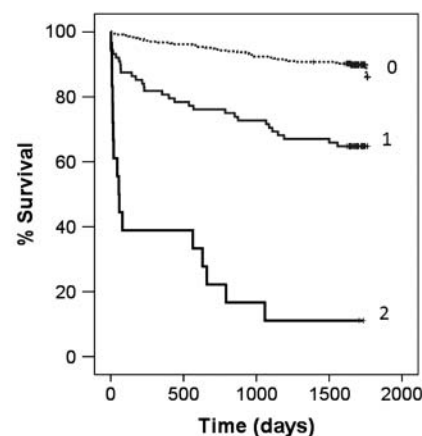
Using multivariate analysis, only cFLC >65 mg/l, albumin concentrations <33 g/l and eGFR <30 ml/min/1.73 m² were independently associated with mortality within 100 days (table 3). cFLC was shown to correlate moderately with these factors, with the strongest correlation observed between cFLC and albumin ($r=-0.48$, $p<0.001$; figure 4).

cFLC risk stratification model

A simple risk stratification model was constructed combining albumin <33 g/l and/or cFLC >65 mg/l as risk factors. This separated patients with 0 (Hazard Ratio (HR)=1), 1 (HR=4.2; CI 2.6 to 6.7, $p<0.001$) or 2 (HR=24; CI 13.2 to 43.8, $p<0.001$) risk factors, (termed as the Combylite Risk Score; figure 5). Of the patients who died within 100 days, 86% had either one or both risk factors. For deaths throughout the period of follow-up, 56% of the patients had either one or two risk factors. For the same risk factors analysed independently, the proportion of associated deaths within 100 days and throughout follow-up were 50% and 24% for albumin <33 g/l and 73% and 50% for cFLC >65 mg/l.

Late risk factors

For all deaths within the period of follow-up, univariate analysis identified the same risk factors as for death within 100 days, with the exception of male gender (table 2). The independent risk factors identified by multivariate analysis were eGFR, albumin, cFLC and age (table 3). Apart from age, which was not identified as an independent risk factor for death within 100 days, the variables had lower HRs and significance levels than for the prediction of early deaths.



Score	Risk factors	n	Hazard ratio (HR)	p value
0	Albumin >33 g/L and cFLC <65 mg/L	368	1	n/a
1	Albumin <33 g/L or cFLC >65 mg/L	88	4.2	<0.001
2	Albumin <33 g/L and cFLC >65 mg/L	18	24	<0.001

Figure 5 A simple risk stratification model (Combylite-Risk Score) using low albumin (<33 g/l) and high combined serum free light chain concentrations (>65 mg/l) as risk factors. Probability of survival throughout the period of follow-up is compared for patients with 0 (dotted line), 1 (grey line) or 2 (black line) risk factors.

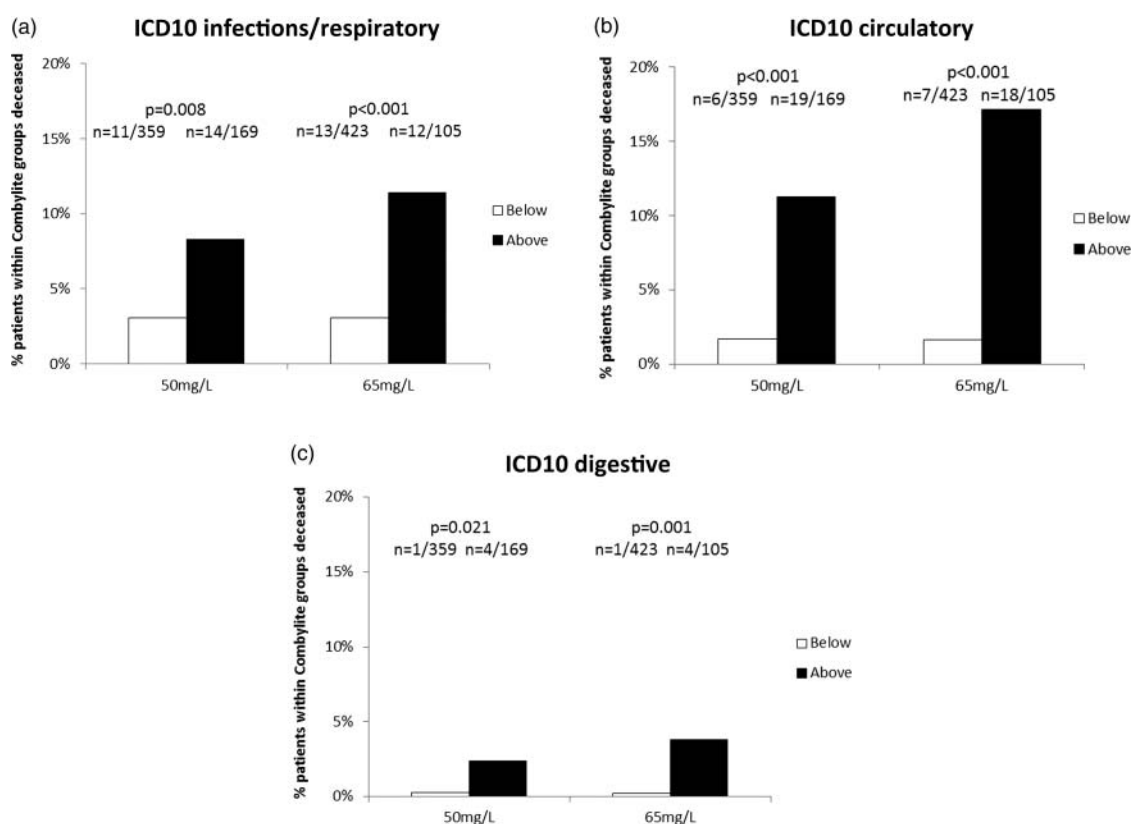


Figure 6 Histograms illustrating the greater proportion of deaths recorded among patients with higher combined serum free light chain concentrations (>50 or >65 mg/l). This reached significance for the ICD10 death certificate classifications of infections/respiratory, circulatory and digestive.

Causes of death

The most frequent classifications for the primary cause of death were 'circulatory', 'respiratory', with 'neoplasm' and 'digestive' being the next common. For circulatory, respiratory and digestive deaths, the incidence (%) was significantly higher in patients with cFLC >65 mg/l (figure 6). The same predominant causes of death were seen for those who died in <100 or >100 days (data not presented).

Circulatory deaths comprised mostly strokes and heart attack/failure while infections/respiratory deaths were predominantly attributed to pneumonia. Digestive deaths included multiple organ failure, gastrointestinal haemorrhage and several forms of liver disease. Deaths due to neoplasms were not significantly associated with high cFLC.

DISCUSSION

Here we have demonstrated that, in a hospital referral population, elevated cFLC concentrations were associated with increased risk of mortality. This extends the preliminary reports of cFLC prognosis in general populations.^{21 22} Furthermore, this prognostic value was independent of other previously defined biomarkers notably, decreased albumin,²³ elevated ESR,²⁴ reduced eGFR²⁵ and elevated CRP.²⁶

Patients from a diverse background were included in this study, including patients from primary care, out-patients and hospitalised groups which may be perceived as a weakness of the study. However, the purpose of selecting such a cohort was to avoid selection bias and as a pilot study indicator for a larger prospective study. In this population, there was an increased frequency of death within the first 100 days and cFLC had the largest HR

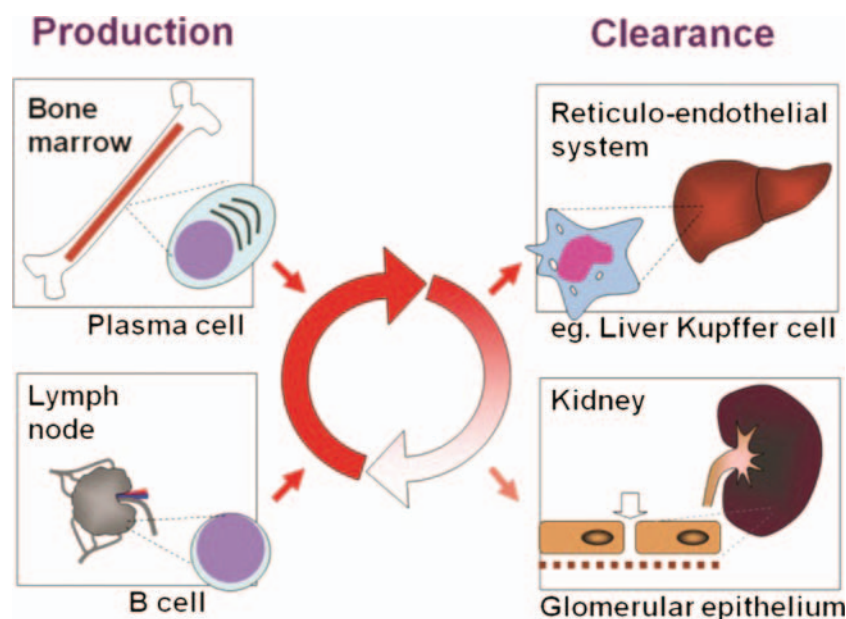
associated with outcome within this period (HR=7.1), with 73% of deceased patients having a cFLC >65 mg/l. Cardiovascular disease (CVD) accounted for a large proportion of these deaths (12/29, 41%) but CRP was not an independent risk factor for mortality. A simple, 3-tiered, risk-stratification model incorporating reduced serum albumin and/or elevated cFLC identified 86% of all-cause mortality within 100 days, suggesting this could constitute a sensitive and very effective method of identifying patients with high risk of early death who might benefit from prompt and more detailed further investigation. While this risk stratification has been demonstrated with a patient population who all had SPE requests, a more appropriate application might be with patients referred to a medical assessment unit. A prospective evaluation in this setting, to evaluate the Combylite-Risk Score, alongside currently used physiological assessments,²⁷ is being planned.

The prognostic value of cFLC diminished during the course of follow-up (from HR=7.1, p=0.015 at 100 days to HR=2.3, p=0.04 after 4.5 years) and indeed predicting overall outcome over such a long period of time may not suggest many practical applications. However, in 25% of these patients, death was attributed to CVD-related causes. It could, therefore, be argued that it would be appropriate to evaluate cFLC as a cardiovascular risk factor alongside other established evaluations such as blood pressure and lipoprotein concentrations.

We surmise that it is the combination of pathological influences on FLC production and/or the different routes of FLC clearance that result in the association of raised cFLC with increased all-cause mortality rates. A simplified mechanistic model for elevated serum FLC is shown in figure 7. While this

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Figure 7 Schematic illustration of the principal processes controlling the concentration of combined serum free light chain (cFLC) in the blood: production by plasma cells and earlier B-cells and clearance via the kidney and the reticulo-endothelial system. Pathologies which influence one or more of these processes could result in a change in the cFLC concentration. This figure is only reproduced in colour in the online version.



may partially describe the factors which may influence FLC concentrations it does not reflect the complexity of the system and further studies are required (figure 7). It has already been noted that increased polyclonal FLC production is associated with disease activity/outcomes in autoimmune diseases, infections, ageing and CKD; although it is noteworthy that in these data cFLC is independent of both age and renal function.^{9 11 28 29} Increased polyclonal production, suggesting general B-cell stimulation, is also associated with some haematological malignancies and has been reported to be prognostic for Hodgkin's disease,³⁰ non-Hodgkin's lymphoma^{13 31} and chronic lymphocytic leukaemia.^{15 32 33}

However, the most common cause for increased polyclonal FLC is probably reduced clearance due to renal impairment⁹ and CKD is well known to be associated with increased morbidity and mortality, particularly from CVD.²⁵ FLC are also cleared via pinocytosis by cells of the reticulo-endothelial system. The liver is a major site for this removal and it is possible that reduced clearance via this route contributes to the increased FLC concentrations seen in some liver disease patients.³⁴ While renal clearance of FLC is the dominant mechanism in healthy subjects, a reduction in reticulo-endothelial clearance is likely to have a significant influence on cFLC concentrations if there is already a reduction in eGFR.

Monoclonal FLC measurements are associated with adverse outcome in the majority of monoclonal gammopathies studied. Polyclonal FLC levels have been associated with adverse outcome in other haematological malignancies and as markers of malignant transformation. Our study highlights a potential utility for these enigmatic molecules in all-cause mortality, both in early detection of adverse outcome (<100 days) and over a 4.5-year follow-up.

What the paper adds

- This publication describes a novel method of detecting high-risk patients in a referral and hospitalised population using markers of inflammation and adaptive immunity (including combined serum free light chains).

Take-home messages

- Polyclonal combined free light chain (cFLC) concentrations can be influenced by renal dysfunction, inflammation and infection.
- cFLC levels identify patients at high risk of adverse outcomes in a referral and hospitalised population.
- cFLC are independent markers of inflammation including C-reactive protein.
- Accurate markers are required to identify patients with multiple disease outcomes.

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Contributors Conceptualised the work and wrote the paper: SB, SA, SHarding. Collected and verified the data: TL, JP, AM, JT, AJ, SH. Analysed data: TL, JP, AM, JT, AJ, SH, LKA.

Competing interest LKA is an employee of The Binding Site Group Ltd and SHarding is R&D Director of The Binding Site Group Ltd.

Ethics approval The local Research Ethics Committee and the Research Development Department of Royal Wolverhampton Hospitals, NHS Trust, UK.

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