Early Reduction of Serum-Free Light Chains Associates with Renal Recovery in Myeloma Kidney

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ABSTRACT

Myeloma kidney is the major cause of severe irreversible renal failure in patients with multiple myeloma. This tubulointerstitial injury is a direct consequence of high concentrations of circulating monoclonal free light chains (FLCs) produced by a clonal expansion of plasma cells. Early reduction of serum FLCs associates with renal recovery, but the target threshold of reduction to facilitate renal recovery is unknown. To determine the relationship between the achieved FLC reduction and renal recovery, we identified 39 patients with biopsy-proven myeloma kidney, the majority of whom had severe renal failure at presentation (median estimated GFR 9 ml/min per 1.73 m^2). In a multivariable analysis incorporating demographic, hematologic, and renal variables, only the achieved FLC reduction significantly predicted renal recovery ($P = 0.003$). The relationship between renal recovery and FLC reduction was linear with no absolute threshold for FLC reduction. A 60% reduction in FLCs by day 21 associated with recovery of renal function for 80% of the population. Patient survival strongly associated with renal recovery: the median survival was 42.7 months (range 0 to 80) among those who recovered function compared with 7.8 months (range 0 to 54) among those who did not ($P < 0.02$). Cox-regression analysis demonstrated that the first presentation of myeloma, the kappa isotype of FLC, and renal recovery were independent predictors of survival. In conclusion, recovery of renal function in myeloma kidney depends on early reduction of serum FLCs, and this recovery associates with a significant survival advantage.

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Renal function strongly predicts the survival of patients with multiple myeloma. Bladè and colleagues demonstrated that renal impairment at presentation of multiple myeloma greatly reduced patient survival. However, survival improved if there was an early recovery of renal function.[1] Mild to moderate renal impairment at presentation of multiple myeloma is frequent but the majority of patients will recover renal function when reversible factors are corrected, whereas approximately 8% of all patients with myeloma will develop severe irreversible renal failure, which requires dialysis support.[1–7] Several series have demonstrated that the principal renal pathology in this setting is myeloma kidney (cast nephropathy).[8,9] This tubulointerstitial lesion is a direct consequence of the high concen-

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tration of circulating monoclonal free light chains (FLCs) that are produced by a clonal proliferation of plasma cells.

Recent work has demonstrated that renal recovery in patients with myeloma kidney occurs when an early reduction in serum concentration of monoclonal FLCs is achieved.[10–12] To achieve this early reduction in serum FLCs, production rates must be reduced by effective chemotherapy. In addition, in severe renal failure the prolonged serum half-lives of FLCs may indicate a role for their direct removal from the serum.[13,14] Interest has therefore focused on both the use of novel chemotherapy agents to reduce the production of FLCs and new modalities to directly remove FLCs from the serum.[15–18]

The purpose of the current study was to determine whether there is a target threshold by which serum FLCs should be reduced to facilitate renal recovery in patients with myeloma kidney and to examine the factors that influence patient survival.

RESULTS

Patient Characteristics

Thirty-nine patients with biopsy proven myeloma kidney and serial FLC measurements were identified from the nephrology departments at the University Hospital Birmingham, Birmingham, United Kingdom, and the Mayo Clinic, Rochester, Minnesota. Of these, 23 were male and the median age of the population was 62 years. Patient characteristics from both institutions are provided in Table 1. The majority of the population (79%) had first presentation multiple myeloma. Fifteen percent were known to have a monoclonal gammopathy of undetermined significance (MGUS) before diagnosis. The most common myeloma type was light chain (FLC) only (41%) followed by IgG (36%) and IgA (21%). Forty-nine percent of patients had monoclonal κ FLCs and the median serum concentration of monoclonal FLC at presentation with renal injury was 420 mg/dl (range 103 to 6960). There was no significant difference between the concentration of κ FLCs (308 mg/dl [median]; 103 to 4200 [range]) and λ FLCs (483 mg/dl; 112 to 6960) ($P = 0.56$). Light chain only myeloma was associated with higher concentrations of FLCs (1163 mg/dl; 187 to 6960) than intact Ig myeloma (250 mg/dl; 103 to 4200) ($P < 0.001$).

The majority of patients had severe renal failure at presentation with a median estimated GFR of 9 ml/min per 1.73 m^2 (range 3 to 34). Twenty-four patients (61.5%) required dialysis support. Patients treated in Birmingham had a higher rate of pre-existing chronic kidney disease (CKD) ($P < 0.01$) and worse renal function at presentation ($P < 0.05$) (Table 1). All patients received a combination treatment of direct removal of FLCs and chemotherapy. In Birmingham, this consisted of extended hemodialysis using a protein permeable dialyser with a thalidomide-based chemotherapy regime for patients with new presentation multiple myeloma or bortezomib for those with relapsing disease.[11] In Rochester, patients received plasma exchange in combination with a chemotherapy regimen consisting of high-dose steroids used alone or together with bortezomib, thalidomide, melphalan, vincristine, doxorubicin, or alemtuzumab.

Table 1. Characteristics of the study participants

Characteristic	Combined ($n = 39$)	Rochester ($n = 20$)	Birmingham ($n = 19$)
Age (years; median[range])	62 (35 to 81)	65 (35 to 81)	61 (38 to 81)
Male (n [%])	23 (59)	9 (45)	14 (73)
Previous CKD (n [%])	6 (15)	0 (0)	6 (31)[b]
Laboratory parameters			
serum creatinine (mg/dl; median[range])	5.7 (2.0 to 18.6)	5.2 (2.0 to 18.6)	6.9 (4.8 to 17.1)[b]
(μmol/L; median[range])	504 (177 to 1644)	455 (177 to 1644)	607 (427 to 1508)[b]
eGFR (ml/min; median[range])	9.0 (3 to 34)	11 (3 to 34)	7 (3 to 13)[a]
New presentation myeloma (n [%])	31 (79)	15 (75)	16 (84)
Previous MGUS (n [%])	6 (15)	5 (25)	1 (5)[a]
Myeloma type (n [%])			
IgG κ	9 (23)	5 (25)	4 (21)
IgG λ	5 (12.8)	1 (5)	4 (21)
IgA κ	3 (7.7)	1 (5)	2 (10.5)
IgA λ	5 (12.8)	3 (15)	2 (10.5)
IgM λ	1 (2.6)	0	1 (5.3)
Free κ	7 (17.7)	3 (15)	4 (21)
Free λ	9 (23.1)	7 (35)	2 (10.5)
FLC type (n [%])			
κ	19 (48.7)	9 (45)	10 (52.6)
λ	20 (51.3)	11 (55)	9 (47.4)
FLC level (mg/dl; median[range])	420 (103 to 6960)	501 (162 to 6960)	253 (103 to 6943)
Dialysis initiated (n [%])	24 (61.5)	5 (25)	19 (100)

[a] $P < 0.05$.
[b] $P < 0.001$.

Table 2. Renal outcomes by institute

	Combined (n = 39)	Rochester (n = 20)	Birmingham (n = 19)
Renal recovery[a] (n [%])	26 (66)	12 (60)	14 (74)
Renal recovery in patients with eGFR of <15 (n [%])	25 of 35 (71)	11 of 16 (68)	14 of 19 (73)
Dialysis independence (n [%])	15 of 24 (62.5)	1 of 5 (20)	14 of 19 (74)[b]
eGFR at 6 months (ml/min; median[range])[c]	36 (12 to 71)	27 (15 to 54)	38 (12 to 71)[b]

[a]Renal recovery was defined as independence of dialysis if previously dialysis-dependent, or for those not dialysis-dependent an increase in eGFR from <15 to >15, or <30 to >30, or <50 to >50.
[b]$P < 0.05$.
[c]eGFR, at 6 months, in patients who had renal recovery.

Serum FLC Reductions and Renal Recovery

Twenty-six of 39 (66%) patients had some degree of renal recovery (Table 2). Thirty-five patients had an estimated GFR of <15 ml/min per 1.73 m^2 at presentation; of these, 25 recovered renal function (71%). Of the 24 patients who required dialysis support, 15 (62.5%) became independent of dialysis. There were no significant differences in the overall renal recovery rate between the institutions nor the renal recovery rate in the patients with estimated GFRs of <15 ml/min per 1.73 m^2. The rate of recovery of independent renal function in those patients who were dialysis-dependent at presentation was higher in the Birmingham population than in the Rochester population ($P < 0.05$).

Logistic regression analysis was undertaken to determine which variables were associated with renal recovery. There was a significant association with the percentage reduction in FLC concentrations achieved, from starting levels, at days 12 and 21 with renal recovery (Figure 1, Table 3). This was the case whether the variable was examined on a continuous or a categorical scale (Table 4). At day 12, each increment of 10% FLC reduction was associated with a 60% increase in the likelihood of renal recovery. The odds of recovery for patients with a reduction >50% were more than sevenfold that for patients with a reduction <50%. Similar results were observed with FLC reduction at day 21 (an additional 10% FLC reduction was associated with a 60% increased likelihood of renal recovery and the odds of recovery were 13 times higher with a reduction of >50%). Figure 2 shows the fitted regression line that plots the probability of renal recovery against the percentage reduction in serum FLC concentration [(A) day 12; (B) day 21]. No other variables were significantly associated with renal recovery, although review of the renal histology revealed other variables which may be important. The presence of significant fibrosis on the kidney biopsy was associated with a nonsignificant re-

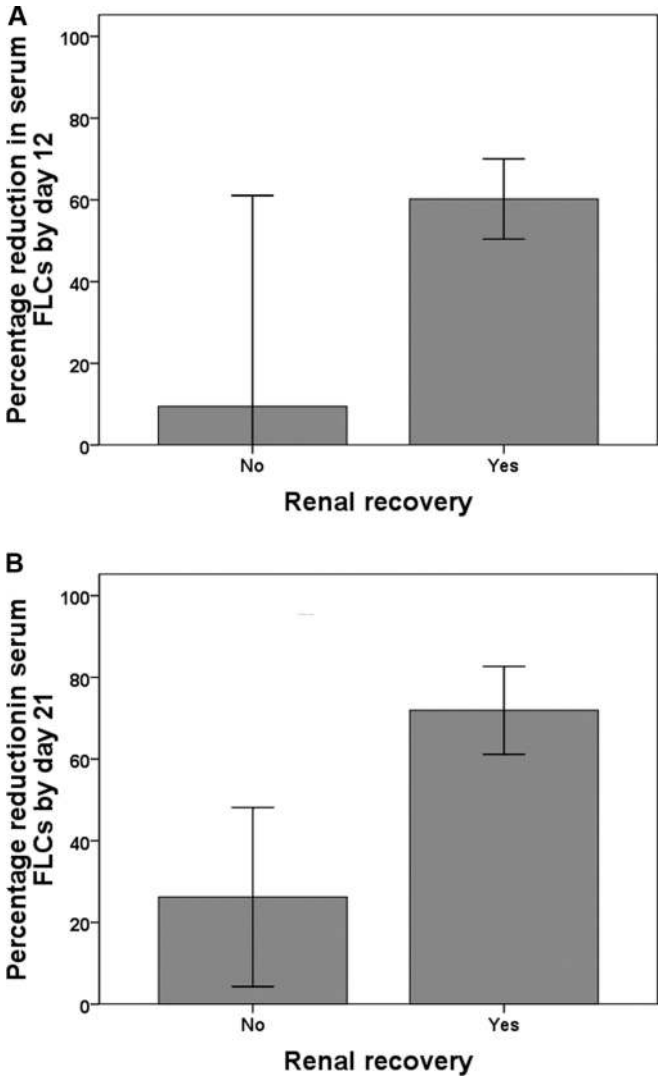

Figure 1. Renal recovery associates with an early reduction in serum FLC concentrations. By day 12 (A) and by day 21 (B).

Table 3. FLC reductions and renal recovery

Time point	FLC reduction	Renal recovery[a] (n [%])[b]
Day 12	No reduction	0 of 3
	<25%	3 of 5 (60)
	25 to 49%	4 of 5 (80)
	50 to 74%	9 of 12 (75)
	>75%	8 of 8 (100)
Day 21	No reduction	0 of 3
	<25%	2 of 5 (40)
	25 to 49%	1 of 1
	50 to 74%	6 of 9 (66)
	>75%	13 of 14 (93)

[a]Renal recovery was defined as independence of dialysis if previously dialysis-dependent, or for those not dialysis-dependent an increase in eGFR from <15 to >15, or (15 to 30) to >30, or (30 to 50) to >50.
[b]At both time points the rate of renal recovery increased significantly with increasing FLC percentage reductions ($P < 0.05$).

Table 4. Univariate analysis of factors influencing renal recovery

Variable	Category	Renal Recovery (*n* [%])	Odds Ratio (95% CI)
FLC reduction			
day 12[d]			1.61 (1.09–2.38)[a]
day 12 (categorical)	<50%	7 (54%)	1
	≥50%	18 (90%)	7.71 (1.25 to 47.8)[a]
day 21[d]			1.66 (1.19 to 2.32)[b]
day 21 (categorical)	<50%	3 (33%)	1
	≥50%	20 (87%)	13.3 (2.11 to 84.1)[b]
Age[d]			0.76 (0.37 to 1.57)
Gender	Women	9 (56%)	1
	Men	18 (78%)	2.80 (0.69 to 11.3)
eGFR[c]			0.68 (0.37 to 1.23)
eGFR (categorical)	<15	25 (74%)	1
	≥15	2 (40%)	0.24 (0.03 to 1.68)
Previous CKD	No	22 (67%)	1
	Yes	5 (83%)	2.50 (0.26, 24.1)
New Myeloma	No	4 (57%)	1
	Yes	23 (72%)	1.92 (0.36 to 10.3)
Myeloma type	Intact	15 (65%)	1
	Free	12 (75%)	1.60 (0.39 to 6.62)
FLC type	κ	14 (74%)	1
	λ	13 (65%)	0.66 (0.17 to 2.62)
FLC concentration[e]			1.07 (0.55 to 2.08)
Biopsy result	MK	25 (74%)	1
	MK + LCDD	2 (40%)	0.24 (0.03, 1.67)
Fibrosis	No	25 (76%)	1
	Yes	2 (33%)	0.16 (0.02, 1.04)

MK, myeloma kidney; LCDD, light chain deposition disease.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]Five-unit increase in explanatory variable.
[d]Ten-unit increase in explanatory variable.
[e]Variable analyzed on the log scale.

duction in the rate of renal recovery (Table 4). Additionally, patients who had both light chain deposition disease (LCDD) and myeloma kidney present on renal biopsy had a nonsignificantly reduced chance of renal recovery (2 of 5; Table 4). Potentially these histologic changes are clinically relevant and this finding should be further examined in a larger population.

The degree of very early FLC reduction (day 12) both preceded renal recovery and subsequently predicted the duration of dialysis dependence. In the dialysis-dependent patients there was a median reduction in serum FLC levels of 62% (range 0 to 95%) by day 12 and the median time to independence of dialysis was 27 days (7 to 170). A reduction in serum FLC levels of >75% was associated with a median time to independence of dialysis of 13 days (range 7 to 29); in comparison, a 50 to 74% reduction this time increased to 26 days (14–50) and was 34 days (18 to 150) for patients with a 25 to 49% reduction in serum FLC levels.

After univariate analyses, the following variables were included in a multivariate analysis: FLC reduction at days 12 and 21, gender, biopsy results, and fibrosis. Analysis of FLC reductions as both categorical and continuous variables demonstrated that only FLC reduction at day 21 had independent significance.

Long-Term Clinical Outcomes and Survival

The median estimated GFRs of patients who recovered renal function continued to improve during the follow-up time at 1, 3, and 6 months: 21 ml/min per 1.73 m^2 (range 10 to 48), 33 (13 to 76), and 36 (12 to 71) Kruskal-Wallis $P < 0.01$, respectively.

The median survival of the population was 21.5 months (range 0 to 80). Cox regression analysis was undertaken to determine the variables that were associated with patient survival (Table 5). Univariate analysis indicated that patients with new presentation of myeloma, κ FLCs, and renal recovery had a better survival compared with patients with relapsing disease, λ FLCs, and no renal recovery, respectively (Figure 3, A through D). The risk of death was 3 times lower for patients with a new myeloma compared with those with relapsing disease. Patients with λ FLCs had a significantly higher likelihood of death (2.4 times) and a decreased survival, compared with patients with a κ FLC. The risk of death was nearly 3 times lower in those that recovered renal function compared with those who did not. The median survival of patients who recovered renal function was 42.7 months (range 0 to 80) compared with 7.8 months (0 to 54) in those who did not ($P < 0.02$).

There was no significant association between percentage reduction in serum FLC concentration (at either day 12 or day 21) and survival. No other factors were found to have a significant association with patient survival (Table 5). A multivariate analysis was subsequently undertaken (including myeloma presentation, FLC type, renal recovery, and age). Results indicated that new presentation of myeloma disease, FLC type, and renal recovery were all independently associated with survival (Table 6). The influence of each variable was similar to those observed in the univariate analyses. Again, the risk of death was reduced with new presentation of myeloma, κ FLCs, and renal recovery.

DISCUSSION

The management of patients with multiple myeloma and renal failure is rapidly changing. Recent advances in diagnostic tests, chemotherapy agents, and dialysis techniques are providing clinicians with new approaches for the management of this complex group of patients. There are currently no clear treat-

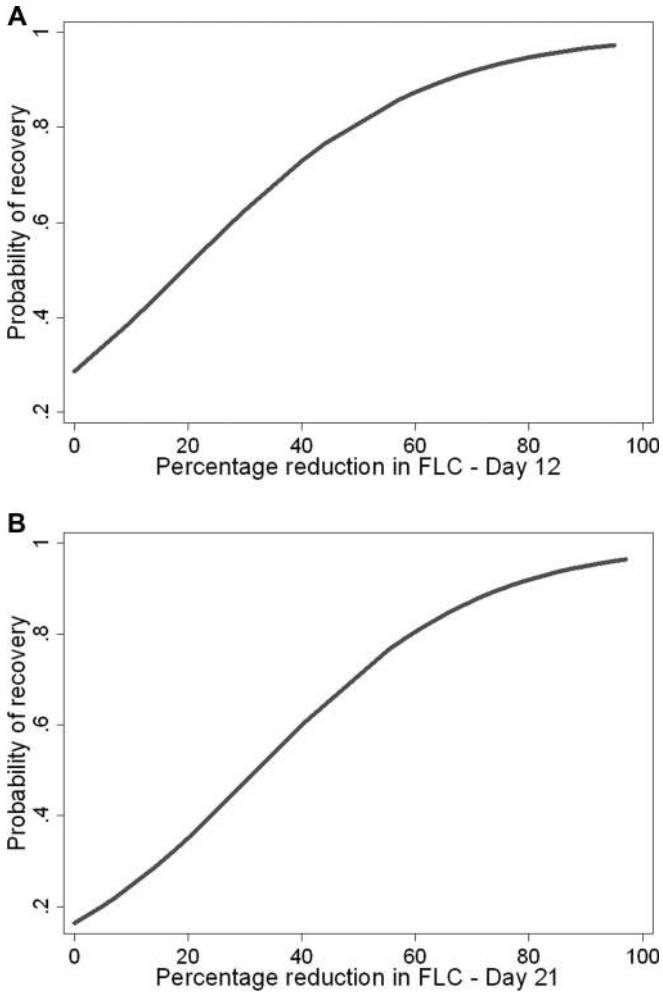

Figure 2. The relationship of reduction in serum FLCs and renal recovery is linear in patients with myeloma kidney. To enable a renal recovery rate of 80%, a 60% reduction in FLC levels by day 21 is required. Probability plot of renal recovery in relation to serum FLC reductions at days 12 (A) and 21 (B).

ment targets or guidelines for the management of patients with myeloma kidney. The primary purpose of this study was to determine whether there is a target threshold by which serum FLCs must be reduced to facilitate renal recovery. The results indicate that the relationship between reduction in serum FLC concentrations and renal recovery is linear and as such there is no absolute threshold by which FLCs must be reduced. Multivariate analysis demonstrated that FLC reduction at day 21 was the most significant predictor of renal recovery. To enable 80% of the population to recover renal function, a reduction of 60% in serum FLCs was required by day 21.

The quantitative measurement of monoclonal FLC in the serum, by nephelometric immunoassays,[19] sensitively allows identification of nephrotoxic monoclonal proteins in patients with acute kidney injury (AKI).[20] Use of these assays as a screening tool has overcome logistic delays and analytic inaccuracies associated with other laboratory methods used for the identification of monoclonal FLCs (serum and urine protein

Table 5. Cox regression analysis of variables influencing survival

Variable	Category	Hazard Ratio (95% CI)
FLC reduction		
day 12[c]		0.96 (0.79 to 1.16)
day 12 (categorical)	<50%	1
	≥50%	0.76 (0.30 to 1.90)
day 21[c]		0.94 (0.82 to 1.09)
day 21 (categorical)	<50%	1
	≥50%	0.68 (0.26 to 1.78)
Age[c]		1.30 (0.88 to 1.92)
Gender	Women	1
	Men	1.17 (0.53 to 2.62)
eGFR[b]		1.00 (0.69 to 1.45)
eGFR (categorical)	<15	1
	≥15	1.00 (0.32 to 3.14)
Previous CKD	No	1
	Yes	1.08 (0.37 to 3.21)
New myeloma	No	1
	Yes	0.33 (0.13 to 0.86)[a]
Myeloma type	Intact	1
	Free	0.66 (0.29 to 1.48)
FLC type	κ	1
	λ	2.38 (1.02 to 5.59)[a]
FLC concentration[d]		1.41 (0.92 to 2.16)
Renal recovery	Yes	0.36 (0.16 to 0.82)[a]

[a] $P < 0.05$.
[b] Five-unit increase in explanatory variable.
[c] Ten-unit increase in explanatory variable.
[d] Variable analyzed on the log scale.

electrophoresis and immunofixation). In an assessment of 1877 patients with plasma cell dyscrasias, Katzmann *et al.* identified that analysis of serum protein electrophoresis (SPE) and serum FLCs alone identified all patients with multiple myeloma and macroglobulinemia, 99.5% of patients with smouldering multiple myeloma, 96.5% of patients with amyloid light chains (AL-amyloid), and 78% of patients with LCDD.[21] Separately, other groups have also reported that, for the identification of AL-amyloid, assessment of the urine provides an additional diagnostic advantage.[22] International guidelines now recommend that screening of serum alone (with SPE and FLCs) is a viable alternative to urinary assessment.[23,24] Particularly in the context of AKI resulting from myeloma kidney where there is the need for a rapid diagnosis to enable early initiation of disease-specific treatment, these assays would appear to have a role. However, when patients are evaluated for potential LCDD or AL-amyloid, the limitations of these assessments need to be recognized.

In addition to these diagnostic advantages, the FLC immunoassays offer the ability to monitor disease response.[24] This has particular relevance in patients with myeloma kidney where an early reduction in serum FLC concentrations is associated with renal recovery. The reduction of FLC production rates by effective chemotherapy is essential. Novel chemotherapy agents, such as bortezomib, offer a potential advantage for patients with myeloma kidney because they have an earlier and

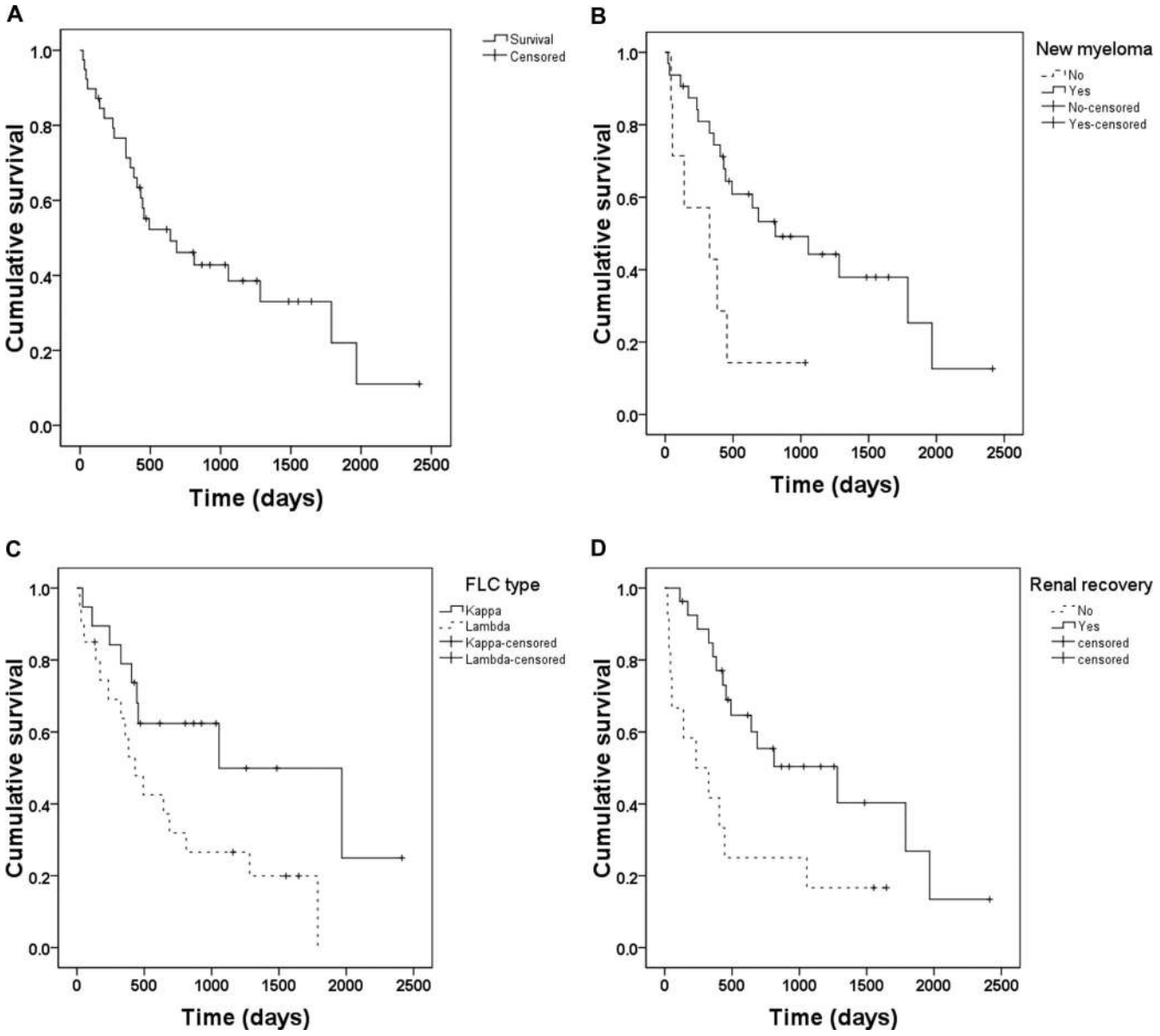

Figure 3. The survival of patients with cast nephropathy (A) is significantly influenced by presentation of myeloma (B, $P = 0.018$), FLC type (C, $P = 0.039$), and renal recovery (D, $P = 0.011$).

greater rate of myeloma response.[25] Uncontrolled pilot studies have suggested that the use of bortezomib in patients with renal impairment complicating multiple myeloma may be associated with improved clinical outcomes.[7,26,27]

Table 6. Multivariate analysis of survival in patients with cast nephropathy

Variable	Category	Hazard Ratio (95% CI)	*P*
New myeloma	No	1	
	Yes	0.26 (0.09 to 0.72)	0.01
FLC	κ	1	
	λ	2.29 (0.96 to 5.46)	0.06
Kidney recovery	No	1	
	Yes	0.34 (0.14 to 0.81)	0.02

The clearance of FLCs from the serum is closely linked to renal function.[13] In severe renal failure, the serum half-life of FLCs is significantly prolonged. For this reason, to enable an early reduction in serum FLC concentrations, the direct removal of FLCs from the serum may offer an additional benefit to effective chemotherapy.[14] There are two alternative approaches for the direct removal of FLCs from the serum, plasma exchange and high cut-off hemodialysis. Plasma exchange effectively removes FLCs from the serum but its capacity to reduce total body FLCs is limited by the short duration of treatment and its failure to provide time for intercompartmental redistribution of FLCs. In comparison, high cut-off hemodialysis may be used safely for extended treatment periods and provides a greater capacity for reducing total body FLCs. De-

spite three randomized controlled trials (RCTs) the role of plasma exchange in renal failure secondary to multiple myeloma remains in debate.[28–30] The major reason for this debate relates to inadequacies in the design of these studies. Unfortunately, with the recent closure of a fourth RCT of plasma exchange because of inadequate accrual, it is unlikely that there will be additional evidence in the future. The first RCT to evaluate the role of high cut-off hemodialysis in myeloma kidney is currently recruiting in the United Kingdom and Germany.[31]

On the basis of a review of the available studies and our experience, we continue to recommend direct removal of FLCs from the serum as an option for patients with biopsy-proven myeloma kidney. Recent work from Fish *et al.* demonstrated the relative safety of kidney biopsies in patients with multiple myeloma.[32] Therefore, before invasive treatment is started, clarification of the nature of the patient's renal injury would be reasonable, particularly given the potential importance of histologic findings to predict outcome. Any direct removal of FLC treatment should be accompanied by aggressive treatment of the patient's myeloma, with a regimen including novel chemotherapy agents such as bortezomib or thalidomide with dexamethasone. The results of our study show that the survival of patients with myeloma kidney is closely linked to renal recovery. Targeting treatment to reverse renal failure in myeloma kidney by the early reduction of serum FLCs is critical.

In conclusion, the relationship between reduction in serum FLC concentrations and renal recovery from myeloma kidney is linear. To enable 80% of the population to recover renal function, a FLC reduction of 60% by day 21 is required. Future studies are needed to determine the role of novel chemotherapy agents and direct removal of FLCs from the serum by high cut-off hemodialysis.

CONCISE METHODS

The study was approved by the Solihull and South Birmingham Research Ethics Committee, and the Research and Development Department at the University Hospital Birmingham in Birmingham, United Kingdom; and the Institutional Review Board at the Mayo Foundation in Rochester, Minnesota.

Patients and Laboratory Assessment

Thirty-nine patients with biopsy-proven myeloma kidney (cast nephropathy) and serial FLC measurements were identified from the departments of nephrology at the University Hospital Birmingham and the Mayo Clinic, Rochester. Clinical outcomes were obtained on all patients from prospectively collected data. Serum FLCs were measured by nephelometry using the immunoassays Freelite (The Binding Site, Birmingham, United Kingdom) on a BN II analyzer (Dade Behring, Deerfield, Illinois).

Clinical Outcomes and Statistical Analysis

The first aim of the analysis was to examine factors associated with kidney recovery; this outcome was measured as a binary measure (yes or no). Renal recovery was defined as independence of dialysis if previously dialysis-dependent, or for those not dialysis-dependent an increase in eGFR from <15 to >15, or <30 to >30, or <50 to >50 ml/min per 1.73 m^2. Analysis was performed using logistic regression. Univariate and subsequently multivariate analysis of variables affecting recovery was performed. A backward selection procedure was used to retain only those variables that were statistically significant. Because of the relatively small sample size, only variables showing some effect upon recovery from the univariant analyses ($P < 0.2$) were considered for the multivariate analyses. For continuous variables the odds ratios represent the odds of recovery for a one-unit increase in the variable (unless otherwise stated). For the categorical explanatory variables the odds ratios are given as the odds of recovery for each category relative to that of a baseline category. In each case a 95% confidence interval is given, together with a P value indicating the significance of the result.

Percentage reduction in serum FLCs, at both days 12 and 21, were considered as both continuous variables and secondly as categorical variables (reduction $<$ or $>50\%$). The distribution of the serum FLC values, at presentation, was highly skewed. Therefore, to enable a better fit, the data were log-transformed before analysis. Significant fibrosis on a renal biopsy was defined as $>25\%$ interstitial fibrosis.

Factors associated with patient survival were subsequently examined. Analysis was performed using Cox regression. Again, the influence of each variable was examined individually, and then in a multivariate analysis.

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DISCLOSURES

C.H. has received speaker's fees from The Binding Site (Birmingham, United Kingdom), the makers of the assays used to measure FLCs in this study. A.B. is a director and shareholder at The Binding Site.

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