THE DIAGNOSTIC AND PROGNOSTIC UTILITY OF SERUM FREE LIGHT CHAINS IN PATIENTS PRESENTING WITH RENAL IMPAIRMENT IN MULTIPLE MYELOMA

by

PUNIT YADAV

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ABSTRACT

Renal impairment (RI) in multiple myeloma (MM) is a medical emergency and is associated with adverse prognosis. In this thesis, I have focussed on the diagnostic and prognostic utility of serum FLC levels and kidney function in patients with MM including those with biopsy proven myeloma cast nephropathy (MCN) and, to identify factors that were associated with overall survival in patients who recover kidney function from a dialysis-dependent state.

I found a strong relationship between higher serum FLC levels at diagnosis and the severity of RI, with a greater sensitivity and specificity for a FLC level >800 mg/L with severe RI irrespective of the paraprotein type. Renal function at diagnosis was a key determinant of RI post induction (PI). Patients who attained a very good partial response (VGPR) or above were more likely to achieve renal function recovery at PI.

Ninety-eight percent of patients with MCN at diagnosis presented with a serum FLC level >500 mg/L. Serum FLC level at diagnosis was not associated with patient outcomes in MCN. Renal function recovery within 12 months was associated with improved survival in patients with MCN when compared to those who remained dialysis-dependent.

Lastly, I also found better long term overall survival in patients with MCN who remained dialysis-independent, and an early serum FLC reduction as well as duration on dialysis were associated with future renal function.

DEDICATION

To my parents for encouraging and motivating me all my life; and to my wife for her constant support throughout the writing of this thesis.

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ABBREVIATIONS

A	AKI	Acute kidney injury
	AKIN	Acute kidney Injury Network
	ASCT	Autologous stem cell transplantation
B		
C	CKD	Chronic kidney disease
	CRAB	Elevated calcium, renal insufficiency, anaemia, bone lesions
	CrCl	Creatinine clearance
	CKD-EPI	Chronic kidney disease-Epidemiology Collaboration 2009
	CDR	Complementarity-determining domain
	CI	Confidence interval
	CR	Complete response
D	dFLC	Difference between involved and uninvolved FLC level
E	eGFR	Estimated glomerular filtration rate
	ESRD	End stage renal disease
	EULITE	EUropean trial of free LIght chain removal by exTEnded haemodialysis in cast nephropathy
F	FLC	Free light chain
H	HLC	Heavy and light chain
	HCO	High Cut-Off
I	IMWG	International Myeloma Working Group
	Ig	immunoglobulin
	IL	Interleukin
	IQR	Inter-quartile range
K	kDa	Kilo dalton
	κ	Kappa
L	LCO	Light chain only
	λ	Lambda
M	MM	Multiple myeloma
	MCN	Myeloma cast nephropathy
	MDRD	Modification of Diet in Renal Disease

	MRC	Medical Research Council
	MR	Minimal response
	MYRE	Multiple MYeloma and REnal failure due to myeloma cast nephropathy
N	NSAIDS	Non-steroidal anti-inflammatory drugs
O	OS	Overall survival
P	pmp	Per million population
	PR	Partial response
	PD	Progressive disease
	PE	Plasma Exchange
R	RI	Renal impairment
	RRT	Renal replacement therapy
	RIFLE	Risk, Injury, Failure, Loss and End stage renal disease
S	SCT	Stem cell transplant
	SPE	Serum protein electrophoresis
	sIFE	Serum immunofixation electrophoresis
	SD	Stable disease
T	THP	Tamm-Horsfall protein
	TRM	Transplant related mortality
U	UPE	Urinary protein electrophoresis
	uIFE	Urine immunofixation electrophoresis
V	VGPR	Very good partial response
	VEGF	Vascular endothelial growth factor

CHAPTER ONE: RENAL IMPAIRMENT IN MULTIPLE MYELOMA –LITERATURE REVIEW

I have published two papers related to this chapter. Yadav P, Cook M, Cockwell P. Current Trends of Renal Impairment in Multiple Myeloma. Kidney Dis (Basel). 2016 Mar;1(4):241-57. doi: 10.1159/000442511. Epub 2016 Feb 3.

Yadav P, Leung N, Sanders PW, Cockwell P. The use of immunoglobulin light chain assays in the diagnosis of paraprotein-related kidney disease. Kidney Int. 2015 Apr;87(4):692-7. doi: 10.1038/ki.2014.333. Epub 2014 Oct 8.

1.1 Introduction

Multiple myeloma (MM) is a haematological malignancy characterised by a malignant proliferation of plasma cells and production of intact monoclonal immunoglobulin and/or monoclonal immunoglobulin free light chain (FLC). Approximately 95% of patients with intact immunoglobulin MM will also have abnormal serum FLC concentration. Although rare, non-secretory MM characterised by absence of detectable monoclonal protein in serum and urine using immunofixation electrophoresis accounts of 1-5% of all MM cases. The monoclonal FLC is referred to as the pathological or the involved FLC clone (Basnayake et al., 2011). Renal impairment (RI) is common in MM and seen in up to 50% of patients at the time of diagnosis (Knudsen et al., 1994). Severe renal impairment (RI; which in this context is usually acute kidney injury (AKI)) in MM is defined by a creatinine clearance of less than 30 ml/min/1.73m^2 at presentation and is detected in up to 20% of patients (Dimopoulos et al., 2014a), out of which approximately 4% have a requirement for renal replacement therapy (RRT) (Dimopoulos et al., 2014a). Severe AKI in patients with MM can be caused by the

high circulating levels of monoclonal FLC causing the distinct lesion of myeloma cast nephropathy (MCN), which is by far the commonest pattern of renal injury seen in patients in this group who undergo a renal biopsy (Hutchison et al., 2009).

The presence of severe AKI is an important complication of MM and historic data with conventional chemotherapies that were used in the management of MM were associated with adverse early and overall survival (OS) (Haynes et al., 2010). However contemporary anti-myeloma therapy, also referred to as novel therapy, consisting of high dose steroids, immunomodulatory agents and proteasome inhibitors, have led to a significant improvement in OS compared to conventional agents, including patients with RI. Included in these improved outcomes are reports of increased recovery rates of independent renal function in patients with MM and severe AKI requiring dialysis treatment (Dimopoulos et al., 2014a). This is a major focus of the studies reported in this thesis.

1.2 Epidemiology

Multiple myeloma is the 22nd most common cancer worldwide and accounted for 0.9% of all cancer diagnoses and 1.1% of all cancer-related mortality in 2018 (Bray et al., 2018). In the United Kingdom (UK) it is the 19th most common cancer and accounted for 2% of all new cases in 2015, with 5540 patients with a new diagnosis of MM (Cancer Research UK, 2018).

The incidence of MM rises with age; in the UK 45% of all new cases in 2013-2015 were diagnosed in individuals more than 75-years old (Cancer Research UK,

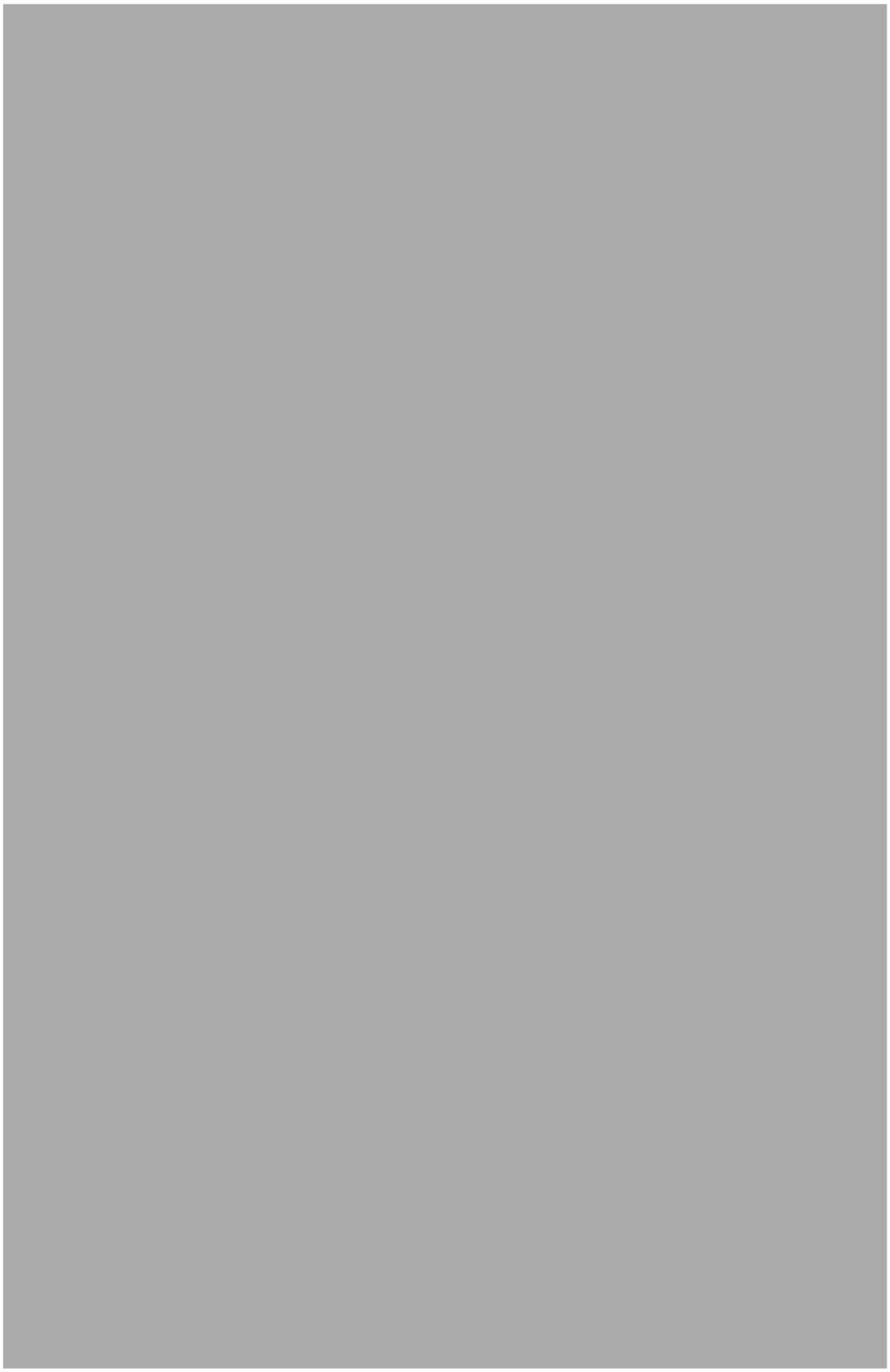
2018). MM is more common in males (58%) than females (42%). The cancer is twice as common in African-Americans than Caucasians, and a similar ethnic pattern is also noted in people of Black ethnicity in the UK. The UK age-standardised mortality rate for MM in 2016 was 51 deaths pmp (Cancer Research UK, 2018).

Between 1971-1973 and 2014-2016, the age-standardised mortality rate for MM increased by 71% for males and 47% for females (Cancer Research UK, 2018). However over the last decade the i.e. between 2004-2006 and 2014-2016 myeloma age-standardised mortality rate has remained stable for both males as well as females combined together. Most of these improvements in outcome have occurred in the last decade; this is likely to reflect better diagnostics, more effective chemotherapy, and perhaps improved coding practices.

1.3 The definition of renal impairment in MM

In 2003 the CRAB criteria (elevated Calcium level, Renal insufficiency, Anaemia and Bone lesions) was introduced to standardise the definition of end-organ damage associated with symptomatic MM. A serum creatinine level above 173 μmol/L (or >2 mg/dL) was the cut-off that was set to define significant RI (International Myeloma Working, 2003). The Greek Myeloma Study Group subsequently utilised this threshold to report an incidence of RI of 21% in a cohort of 756 patients presenting with MM (Eleutherakis-Papaiakovou et al., 2007). However, this threshold does not include the majority of patients if conventional criteria to classify RI are used. The current conventional classification criteria for AKI and for chronic kidney disease are shown in Figure 1.1.

Figure 1.1 Conventional definitions of RI (a) Acute Kidney Injury Network criteria (AKIN) and; (b) Chronic kidney disease (CKD) definition



In addition to the CRAB threshold a number of other definitions for reporting RI in clinical outcome and clinical intervention studies in patients with MM have been used. These are summarised in Table 1.1.

Table 1.1 Historic definitions and incidence of RI in published studies

Study	Year	Cases	Definition and incidence of RI
Dawson et al (Dawson and Ogston, 1971)	1971	166	Out of 128 patients where blood urea levels were available at diagnosis 57 (44.5%) had serum urea levels >50 mg/dL
Kyle et al (Kyle, 1975)	1975	869	Serum creatinine >1.3 mg/dL in 55% of patients
MacLennan et al (MacLennan et al., 1989)	1989	1205	Serum creatinine >130 µmol/L in 42% of patients that included, 12% with serum creatinine >200 µmol/L, and 10% with serum creatinine >300 µmol/L
Rayner et al (Rayner et al., 1991)	1991	141	Serum creatinine ≥120 µmol/L in 65 (46%) patients, that included 52 (80%) with serum creatinine 120-500 µmol/L and 13 (20%) with >500 µmol/L
Knudsen et al (Knudsen et al., 1994)	1994	1353	Serum creatinine ≥130 µmol/L in 416 (31%) patients, that included 16% with severe RI defined as a serum creatinine >200 µmol/L CrCl was calculated in 1206 patients mild RI was observed in 296 (25%), moderate in 175 (15%) and severe in 115 (9%) patients
Kyle et al (Kyle et al., 2003)	2003	1027	Serum creatinine >1.3 mg/dL in 48% of patients that included 19% with serum creatinine ≥2 mg/dL
Eleutherakis-Papaiakovou et al (Eleutherakis-Papaiakovou et al., 2007)	2007	756	Serum creatinine ≥2 mg/dL in 160 (21%) of the 756 of patients, that included 7% of patients with serum creatinine ≥4 mg/dL, 4% with serum creatinine ≥6 mg/dL, and 1% with serum creatinine ≥8 mg/dL

RI, renal impairment; CrCl, creatinine clearance

The lack of standardisation of reporting of renal function in patients with MM is an important shortfall. Converting serum creatinine into estimated glomerular filtration rate (eGFR) illuminates the potential for inaccuracy. For example, a 65 year-old female with a creatinine level above 87 μmol/L will have RI as defined by an eGFR less than 60 ml/min/1.73 m^2 (stage 3 chronic kidney disease [CKD]); for a male of the same age, the stage 3 CKD threshold is 113 μmol/L. When RI is defined based on the threshold set by the CRAB criteria the same 65 year-old female will have an eGFR less than 27 ml/min/1.73 m^2 that is equivalent to stage 4 CKD; whereas for a male of the same age the eGFR cut-off is less than 37 ml/min/1.73 m^2.

A major additional confounder is that equations that have been developed for renal function estimation in CKD are being used for measurement of renal function in patients with AKI, with the International Myeloma Working Group (IMWG) recommending use of the four-variable Modification of Diet in Renal Disease (MDRD) (Levey et al., 1989) or the CKD-Epidemiology Collaboration 2009 (CKD-EPI 2009) equation (Levey et al., 2009) to define RI in MM (Rajkumar et al., 2014). Furthermore, creatinine-derived equations can also be confounded by other factors relevant to patients with MM (Randers et al., 2000, Jovanovic et al., 2003, Grubb, 2000, Kyhse-Andersen et al., 1994); these include changes in muscles mass, dietary intake, and proximal tubular dysfunction (Shemesh et al., 1985, Rule et al., 2004, Horber et al., 1985). Recent studies have indicated that serum cystatin-C may be superior to creatinine in assessing early RI, including patients with MM (Nuckel et al., 2012, Terpos et al., 2009). An elevated cystatin-C level (>0.95 mg/L)

was reported in 90 (57.3%) of 157 newly diagnosed patients with MM whereas a high creatinine level (>1.4 mg/dL in men and >1.2 mg/dL in women) was detected only in 37 (23.5%) patients, with 97 (61.7%) patients demonstrating a CrCl <80 ml/min/1.73 m^2 (Terpos et al., 2009).

Importantly, the large majority of patients with MM and RI at presentation have AKI and not CKD. There is only one study to date that has utilised accepted AKI criteria to define RI in patients with MM. In the single-centre study by Shi and colleagues (Shi et al., 2014), new onset AKI was reported in 72 (32.5%) of 221 patients with MM who presented to hospital between 1995 and 2000. In another study, Ando and colleagues (Ando et al., 2010) compared the utility of the RIFLE, AKIN and an additional criteria that was introduced by Parikh et al termed as conventional graded criteria (Schrier and Parikh, 2005) to determine RI in haematopoietic stem cell transplant (SCT) recipients for various haematological conditions. In that study only 34 (13.6%) of 249 SCT recipients had MM. They reported minor differences in the number of patients with AKI as classified by AKIN, RIFLE and conventional graded criteria. The IMWG in their most recent guidance for the diagnosis and management of MM related RI also supported the use of RIFLE and AKIN criteria to define RI in myeloma studies (Dimopoulos et al., 2016).

The RIFLE and AKIN classification systems both however have a number of serious limitations:

For the RIFLE classification:

(i) a baseline serum creatinine value is essential to define RI and this is unavailable in many patients at diagnosis.

(ii) the assumption of a normal eGFR in the absence of a baseline serum creatinine level may not be valid, particularly in older patients.

(iii) the use of serum creatinine alone as a measure to define RI (as explored above).

(iv) the lack of routine collection of an hourly urine output measure in patients presenting with RI in clinical practice.

For the AKIN classification:

(i) the definition of AKI is only applicable if the change in serum creatinine occurs within a 48-hour period

(ii) grading patients into stage 3 AKI for those commenced on RRT, irrespective of their serum creatinine values or urine output, is a confounder as there is no clear eGFR defined evidence base for the initiation of RRT.

These shortfalls in classification of AKI are compounded by challenges around criteria for defining a renal response in patients with MM. These specific issues are discussed later.

1.4 The relationship between renal function and survival in MM

An early Medical Research Council (MRC) Myelomatosis trial reported a higher number of deaths (39%) within 100 days of recruitment in patients with a serum

urea ≥15 μmol/L, or creatinine ≥200 μmol/L if the urea was <15 μmol/L at diagnosis. In the same trial patients presenting with RI had an OS of 380 days with 28% surviving at two-years, compared to 52% for the entire study population at the same time point (MacLennan et al., 1989). RI was responsible for 28% of the early deaths in a subsequent analysis that combined data from the MRC IV to MRC VIII trials that excluded a large proportion of patients presenting with severe AKI (Augustson et al., 2005). A total of 3107 patients from the MRC myelomatosis trials between 1980 and 2002 were eligible to participate in this study.

A recent retrospective study from 15 Swedish hospitals reported a significantly inferior OS in patients with RI (eGFR <60 ml/min/1.73 m^2) compared to those who did not have RI. The survival of patients with RI who were treated with bortezomib-based chemotherapy (60 months) was better than those who received conventional agents (27 months) (Uttervall et al., 2014). Mayo Clinic investigators also reported a complete renal response rate in a higher proportion of patients treated with novel agents compared to conventional treatment. Improvement of renal function was associated with better OS, although still inferior to patients with no RI at diagnosis (Gonsalves et al., 2015).

A number of studies have reported on outcomes in patients with MM who required dialysis, a complication sustained by up to 5% of patients at diagnosis (Blade et al., 1998, Torra et al., 1995, Knudsen et al., 2000). The frequency of this complication may be decreasing: in a recent study that reported on 1773 consecutive unselected patients with newly diagnosed MM between 1991-2011, the incidence of patients requiring dialysis was lower (3.5%) for those diagnosed

after 2005 compared to the other three time cohorts; 5.5% for 2000-2004, 6% for 1995-1999, and 5% for 1990-1994 (Dimopoulos et al., 2014a).

Dialysis has a major impact on the prognosis of patients with MM. A median survival of 10.2 months was reported in a single centre study where 82% of patients received dialysis at presentation; only 17% subsequently recovered independent renal function, these patients had a significantly better OS compared to those who remained dialysis dependent (Haynes et al., 2010). These results are comparable to data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), with a median survival of 0.91 years for patients with MM or light chain deposition disease, compared to 4.46 years for those who did not have either of these diagnoses (Tsakiris et al., 2010).

Recent single centre studies are reporting improved renal function recovery rates of around 60% in patients who require dialysis, and an associated improvement in survival (Hutchison et al., 2011b). These findings are now being confirmed in prospective multicentre studies (Bridoux et al., 2017). In chapter 6, I report on long-term survival outcomes in patients who present with severe RI requiring dialysis as a consequence of biopsy confirmed MCN and subsequently recover independent renal function. There is a paucity of data around long term outcomes in this select group of patients and I aimed to identify variables that were associated with patient survival and renal function recovery.

1.5 Pathogenesis of RI in MM

In patients with MM, dehydration, hypercalcaemia and non-steroidal anti-inflammatory drugs (NSAIDs, prescribed for bone pain) may also cause or contribute to AKI. However these patients may have less severe RI at presentation and are more likely to recover kidney function. Whether this recovery is to the previous baseline is not known; there are no studies to date that have assessed this.

The level of the involved immunoglobulin FLC is also associated with RI. However not every patient with an elevated FLC level develops RI; in many of these patients the FLC level is above the threshold level for the development of MCN, highlighting the heterogeneity of immunoglobulin FLC in causing RI.

So although the current 'consensus' around the threshold level for an involved FLC clone causing MCN is 500 mg/L (Hutchison et al., 2011a) many patients with an involved FLC level above this threshold will not have MCN. In some patients MCN will only develop if the patient has co-factors that predispose to the precipitation of the FLC in renal tubules. This has been well characterised in animal models of kidney disease; hypercalcaemia, acidosis, dehydration and use of diuretics all lower the threshold for cast formation (Hoyer and Seiler, 1979, Sanders and Booker, 1992).

Where patients with MM and severe AKI have undergone kidney biopsy, up to 90% of kidney biopsies are reported as showing MCN (Hutchison et al., 2012b); this is the characteristic disease specific renal lesion caused by MM. The typical

histopathologic appearance is of eosinophilic, fractured, proteinaceous distal tubular casts consisting of monoclonal FLC and Tamm-Horsfall protein (THP) along with tubulointerstitial inflammation (Figure 1.2), often accompanied by a proximal tubulopathy injury.

Figure 1.2 Typical appearance of myeloma cast nephropathy on a kidney biopsy



In health, small quantities of polyclonal FLC are reabsorbed by the proximal tubular multi-ligand megalin-cubilin complex receptors (Wochner et al., 1967), and then endocytosed by the clathrin-dependent endosomal/lysosomal pathway and degraded within the lysosomes (Basnayake et al., 2011). However, in MM the excess monoclonal FLC production overwhelms the absorptive capacity of the proximal tubule and the filtered FLC thus enters the distal tubule. Filtered FLC interact with THP (uromodulin), a glycosylated protein that is produced in the medullary thick ascending limb of loop of Henle, resulting in distal tubular cast formation and obstruction. Risk of development of MCN increases with excess

urinary FLC excretion and it is the physcio-chemical property of the monoclonal FLC itself that determines its affinity to bind to THP (Sanders et al., 1990, Sanders and Booker, 1992). A series of animal studies that investigated the interaction between FLC and THP identified a specific binding site on the third complementarity-determining domain (CDR3) in the variable region of the immunoglobulin FLC. It is the difference in the amino acid sequence of the CDR3 domain that is responsible for the diversity in the binding affinity of the involved FLC to the THP (Ying and Sanders, 2001, Huang and Sanders, 1997, Huang and Sanders, 1995, Huang et al., 1993, Sanders and Booker, 1992, Holland et al., 1985) and defines the differential level at which pathological immunoglobulin FLC can cause MCN.

In addition to distal tubular cast formation, endocytosis of the monoclonal FLC by the proximal tubule can provoke intracellular oxidative stress and generation of hydrogen peroxide that leads to activation of the redox pathways. Src dependent activation of nuclear factor κB (Ying et al., 2011) and phosphorylation of mitogen-activated protein kinases especially p38 stimulate apoptosis signal regulating kinase-1 (Ying et al., 2012, Sanders, 2012), leads to induction of pro-inflammatory and profibrotic cytokines such as interleukin (IL)-6, monocyte chemotactic protein-1, IL-8, tumour necrosis factor-alpha and transforming growth factor-beta1, which can cause interstitial fibrosis and phenotypic transformation of the proximal tubular cells to fibroblasts (Sanders, 2012).

Lastly, immunoglobulin FLC are also associated with Fanconi syndrome, characterised clinically by the presence of a type II renal tubular acidosis that

occurs due to a defect in the expression of the proximal tubular apical co-transporters namely sodium glucose co-transporter, sodium phosphate co-transporter, uric acid transporter-1 and a decrease in the Na+/K+ ATPase activity in the basolateral membrane (Messiaen et al., 2000, Nicastri et al., 1998, Sanders et al., 1991, Deret et al., 1999, Yokota et al., 1991). Light chain proximal tubulopathy causing Fanconi syndrome is typically linked with kappa FLC (Vκ1 subfamily) and is characterised by the presence of crystalline inclusions within the proximal tubule. The variable domain of the monoclonal FLC associated with Fanconi syndrome has unique properties which renders the monoclonal FLC resistant to proteolytic degradation and accelerates crystal formation in the endolysosomal compartment of the proximal tubular cells (Bridoux et al., 2005).

Because of the renal toxicity associated with immunoglobulin FLC it is essential that there is a focus on rapid diagnosis and immediate institution of anti-myeloma therapy in patients with MM and RI, to ensure that the risk of irreversible injury is minimised. The most important step towards realising this goal would be to firstly identify patients at risk of developing nephrotoxicity from the underlying pathological clone. There are reports of associations between elevated urinary FLC excretion and RI (Drayson et al., 2006), however, there are no population-based studies that have reported on the association between the level of FLC in serum and the risk of RI in patients with newly diagnosed MM. This is an important clinical shortfall and will be addressed further in chapter 3. In chapter 5, I aim to report levels of FLC in serum that is associated with biopsy confirmed MCN in patients with newly diagnosed MM along with renal and survival outcome in this select group of patient.

1.6 Recovery of renal function and clinical outcomes

In an early study that included 94 patients with RI defined as a creatinine level ≥177 μmol/L, renal function recovery, as defined by a sustained decrease in the serum creatinine level to <133 μmol/L, occurred in 26% of patients. Renal recovery was associated with an improved survival. A creatinine level <354 μmol/L, calcium level ≥2.88 mmol/L and a lower urinary FLC excretion (<1 g/day) were independently associated with renal function recovery (Blade et al., 1998).

Since the widespread adoption of dexamethasone as a key component in chemotherapy regimens in patients with MM and RI, better rates of renal function recovery are being reported. A single centre series that consisted of 41 patients with newly diagnosed MM reported that 73% of patients who received high-dose dexamethasone, either with or without a novel agent, had a serum creatinine less than 1.5 mg/dL (<133 μmol/L) at a median of 1.9 months. The introduction of novel agents has further improved the potential for renal function recovery. Reversibility of RI was seen in 80% at a median of 0.8 months in patients who were treated with dexamethasone and a novel agent (Kastritis et al., 2007).

The relationship between disease specific responses as measured by serum FLC levels and renal function recovery is of great interest. A study from two specialist centres reported a cohort of patients presenting with a median eGFR of 9 ml/min/1.73 m^2 with 62% of patients requiring dialysis. A 60% reduction in serum FLC at day 21 was associated with increased likelihood of renal function

recovery; 71% of patients either became independent of dialysis or had an improvement in renal function from presentation. The median survival in patients who recovered independent renal function was 42.7 months compared to 7.8 months in patients who did not recover renal function (Hutchison et al., 2011b).

The current consensus definition for a renal response in patients presenting with less severe RI was introduced by Ludwig and colleagues (Dimopoulos et al., 2010c). These criteria are based on changes in eGFR calculated by the four-variable MDRD equation. A complete renal response (CRrenal) is defined as a sustained (at least two-month) improvement in baseline eGFR from <50 ml/min/1.73 m^2 to ≥60 ml/min/1.73 m^2; partial renal response (PRrenal), a sustained improvement in baseline GFR from <15 ml/min/1.73 m^2 to 30-59 ml/min/1.73 m^2; minor renal response (MRrenal), a sustained improvement in baseline GFR from <15 ml/min/1.73 m^2 to 15-29 ml/min/1.73 m^2 or from 15-29 ml/min/1.73 m^2 to 30-59 ml/min/1.73 m^2.

The renal response criteria were validated in a study that assessed the efficacy of a bortezomib-based chemotherapy regimen in 46 consecutive patients with MM and RI. A renal response was reported in 59%, with 30% achieving a CRrenal and with a higher probability of response amongst those with light chain only MM. When cystatin-C was used to measure renal function, patients with levels of >2 mg/L or a cystatin-C calculated eGFR <30 ml/min/1.73 m^2 had a lower probability of achieving a CRrenal response (Dimopoulos et al., 2009b).

Another single centre study reported on 96 previously untreated MM patients, who were divided into three-groups based on their chemotherapy regimen. Thirty-seven patients were treated with conventional agents, 47 received a thalidomide- or lenalidomide-based regimen, and 17 received a bortezomib-based regimen. A sustained renal response was recorded in 94% of patients treated with a bortezomib-based regimen, 79% in those treated with thalidomide- or lenalidomide-based regimen, and 59% amongst patients treated with conventional chemotherapy (Roussou et al., 2010). Several other studies have reported on the efficacy of novel agents when used as first-line chemotherapy for the management of patients with MM and RI (Hutchison et al., 2009, Hutchison et al., 2012b, Ludwig et al., 2010, Cockwell and Hutchison, 2010). The clinical benefits of renal function recovery, especially in patients who present with severe RI requiring dialysis treatment, are now well established. However, there are no data that have explored the relationship between renal function at diagnosis and haematological disease response post-treatment in patients with newly diagnosed MM. Amongst those presenting with RI, it is not known to what extent patients recover renal function and if achieving a favourable haematological disease response has an effect on renal function; this area is studied in chapter 4.

1.7 Investigative strategy for screening of a monoclonal gammopathy

1.7.1 Screening for intact monoclonal gammopathy

1.7.1.1 Serum protein electrophoresis

The most commonly used screening test for an intact immunoglobulin paraprotein is serum protein electrophoresis (SPE), which through identification of a myeloma protein spike (Figure 1.3), can detect a monoclonal immunoglobulin

FLC at a concentration above 500 mg/L (Bradwell et al., 2001). SPE is however unhelpful in patients with non-secretory MM and with light chain MM.

Figure 1.3 SPE pattern demonstrating a myeloma protein spike



1.7.1.2 Serum immunofixation electrophoresis

Serum immunofixation electrophoresis (sIFE) is more sensitive than SPE. It can detect monoclonal paraprotein at serum concentrations above 150 mg/L and also provides isotype characterisation of a monoclonal gammopathy (Figure 1.4) (Bradwell et al., 2001). However, IFE is labour-intensive and does not quantify the monoclonal immunoglobulin and is therefore impractical for measurement of a disease response. sIFE is therefore generally used if there is an abnormality on SPE or if there is a high clinical suspicion of a monoclonal gammopathy. sIFE is particularly useful in identifying and monitoring a pathological clone when there is more than one clone present.

Figure 1.4 sIFE strip demonstrating an immunoglobulin G lambda paraprotein



1.7.2 Screening for light chain only monoclonal gammopathy

Although SPE and sIFE can detect a FLC clone at levels above 500 mg/L and 150 mg/L respectively, the sensitivities of these tests are inadequate as a clinically relevant monoclonal FLC may be present in the serum at levels below these thresholds. Specific tests are therefore required for detection of an FLC clone. These tests can be carried out on urine as well as on serum.

1.7.2.1 Urine assays

Due to the insensitivity of SPE and IFE, urinary testing for FLC (Bence Jones proteinuria) has been the long-term standard of care for the screening and monitoring of an involved FLC clone. FLC are physiologically concentrated in urine, which can then be further (mechanically) concentrated before analysis. Urinary protein electrophoresis (UPE) and urine immunofixation electrophoresis

(uIFE) are both used and can be sufficiently sensitive to identify an abnormal FLC clone in the urine down to a concentration of 10 mg/L.

However there are shortfalls in the use of a urine assay in clinical practice, in particular the frequent failure to provide an appropriate 24-hour urine collection or a paired serum sample to accompany a urine collection (Holding et al., 2011). Other important variables include the degree of urine concentration, the IFE method used and the affinity of the polyclonal antibodies utilised in the IFE assay (Marshall and Williams, 1999). Furthermore, urine FLC concentrations may not necessarily correlate with serum concentrations and are therefore not directly related to tumour size and FLC production (Graziani et al., 2003).

1.7.2.2 Serum FLC assays

The first marketed assay used for quantifying serum FLC was a nephelometric assay (Freelite®) that works on the principle of measurement of the density of the scatter of particles or proteins suspended in a sample by directing light at an angle (Ritchie, 1967). The serum FLC assay utilises rabbit anti-human polyclonal antibodies that are targeted against epitopes which are hidden when the light chain is bound to the intact immunoglobulin molecule and exposed when the light chain is present in a free form. Of the assays that are available to measure serum FLC level the large majority of studies have been carried out using the Freelite® assay.

The assay measures the concentration of both the light chain isotypes (i.e. kappa and lambda), with results provided for both isotypes and for the ratio of the isotypes. The normal reference range for both the FLC isotypes and the ratio of free kappa-to-lambda FLC by Freelite® is illustrated in Table 1.2. When interpreting the test both the ratio and the level of each FLC isotype should be considered. The FLC assay is highly sensitive and can detect both isotypes to levels that are below the normal physiological range.

Table 1.2 Normal serum FLC range and ratio by Freelite assay

	Normal reference range
Kappa FLC	3.30 19.40
Lambda FLC	5.71 26.30
Kappa-Lambda FLC ratio	0.26 1.65

Each cell of B-cell lineage produces one isotype of immunoglobulin light chain. An excess production of the involved light chain isotype occurs with clonal proliferation, which in turn leads to abnormality of the FLC ratio. An elevated serum FLC ratio (i.e. more than 1.65) indicates the presence of a kappa FLC clone whilst a low ratio (i.e. less than 0.26) a lambda FLC clone. In MM, it is not uncommon for the level of excess monoclonal FLC to be several thousand-fold above the upper limit of normal; however, in some cases of monoclonal gammopathy the light chain clone can be very subtle and within the normal range of the serum FLC ratio or within the measurement uncertainty of the assay.

Elevation in levels of both the FLC isotypes (a polyclonal rise) can also occur in conditions that are associated with immune activation (Festa et al., 2000, Streja et al., 2003), or in the presence of RI as the main route of clearance of FLC is via the kidneys (Hutchison et al., 2008a). However, in those settings the ratio of both the FLC isotypes in the serum is maintained within a normal range. In the absence of a clonal proliferation, the ratio of kappa to lambda FLC production is preserved at a constant rate of 2:1 (Hutchison et al., 2008a).

The nephelometric assay has thus enhanced the diagnostic accuracy and sensitivity of monoclonal gammopathy assessment and has contributed to:

(i) introduction of stringent complete response as a new criterion of MM response

(ii) improved risk stratification in monoclonal gammopathy

(iii) the identification and characterisation of light chain only monoclonal gammopathy of undetermined significance

(iv) diagnosis and monitoring of light chain only myeloma and oligosecretory myeloma

(v) diagnosis and monitoring of light chain escape (phenomenon in which FLC increase is not associated with a concomitant rise in the original intact monoclonal paraprotein)

(iv) defining response criteria in other paraproteinemias such as immunoglobulin light chain (AL) amyloidosis.

1.7.2.2.1 FLC assay variability with Freelite®

The serum FLC assay has some limitations that should be considered when interpreting the test result.

(i) An optimal FLC antibody specificity requires an antiserum to have an equal affinity to both polyclonal and monoclonal FLC; however polymerized FLC can yield oligomeric complexes that can cause overestimation of FLC concentration by the assay due to multi-reactivity of these polymers (Abraham et al., 2002, Drayson et al., 2001).

(ii) The light chain assay results by Freelite® are within 20% of the specified concentration in matched quality control specimens. With repeated measurements there can be higher intra-assay variation for the individual isotypes and this fluctuation will amplify variability in the calculated kappa-to-lambda ratio, such that doubling or halving of the ratio can occur in the absence of a change in the status of the disease (Tate et al., 2009). This means that a ratio around the limits of the normal reference range may be misclassified as either normal or abnormal.

(iii) FLC concentration has a wide dynamic range i.e. between 1 mg/L and 100,000 mg/L. An excess of FLC in the serum can sometimes prevent formation of precipitating immune complexes, which can lead to underestimation of FLC concentrations resulting in a false-negative result, this phenomenon is termed antigen excess (Bosmann et al., 2010, Daval et al., 2007, Murata et al., 2010). Hence it is extremely important to interpret serum FLC test results in light

of other laboratory data and the clinical picture; all contentious test results should be retested at higher dilution to eliminate the risk of antigen excess.

1.7.2.2.2 Role of the 'renal reference range' in the serum FLC assay

Katzmann and colleagues (Katzmann et al., 2002) utilized the serum FLC assay (Freelite®) to produce a normal serum ratio and range for both the FLC isotypes. The recommended FLC ratio of 0.58 with a range of 0.26-1.65 was based on a 100% confidence interval (CI) in healthy individuals without monoclonal gammopathy. The authors noted an increase in serum FLC levels with age with a higher median kappa-to-lambda FLC ratio of 0.70 in normal elderly people compared to 0.49 in younger people (Katzmann et al., 2002). However, they reported that this age-related increase in FLC levels and ratio in elderly people was due to a decline in renal function.

Increase in FLC in patients with RI starts early and can be identified at an eGFR consistent with stage 2 CKD (Hutchison et al., 2008a). A larger study more accurately characterised the impact of RI on serum FLC level and kappa-to-lambda FLC ratio. This study analysed a cohort of patients with stages of CKD up to and including people with end stage renal disease (ESRD) (Hutchison et al., 2008a). The median serum FLC ratio for the cohort was 1.12 (range, 0.37-3.10), with more precise levels and ratios defined by stage of CKD. As with the study by Katzmann and colleagues (Katzmann et al., 2002), a 100% CI was utilised for all the patients

included in the dataset, following the exclusion of any patient with a monoclonal gammopathy.

The increase in serum FLC ratio in people with RI reflects the differential clearance of FLC isotypes. Kappa FLC is a monomeric molecule (molecular weight 22.5 kDa) and is cleared in 2-4 hours at 40% of the glomerular filtration rate; lambda FLC is typically a dimeric molecule (molecular weight 45 kDa) and is cleared in 3-6 hours at 20% of the glomerular filtration rate. The alternative route of removal of FLC is through pinocytosis by the reticulo-endothelial system; this slow route of clearance removes both FLC isotypes at the same rate. Therefore as the renal function declines, there is both an increase in the serum levels of both isotypes and the median serum ratio increases.

The extended or 'renal reference range' of 0.37-3.10 was associated with an improvement in the specificity of the serum FLC assay for the diagnosis of monoclonal gammopathy in a single centre study that consisted of 142 patients including patients who were receiving dialysis treatment for end-stage renal failure (Hutchison et al., 2008b). In this study all 41 patients with a clinical diagnosis of MM had an abnormal serum FLC ratio, by both the normal reference range and the 'renal reference range'. However with the normal reference range seven additional patients with no clinical diagnosis of MM had an abnormal FLC ratio (false positive), whereas only one patient had an abnormal FLC ratio when the 'renal reference range' was utilised. There are several other single centre (albeit smaller) studies that have supported the use of 'renal reference range' for

screening on monoclonal gammopathy in patients with RI (Diamantidis et al., 2009, Abadie et al., 2009, Park et al., 2012).

1.7.3 New generation FLC and intact immunoglobulin assays

In addition to Freelite®, there are three other assays that have now been developed for the identification of a monoclonal FLC protein:

(a) N-latex FLC assay (Siemens assay)

This is an immuno-nephelometric assay that, in contradistinction to the Freelite® assay, utilises monoclonal antibodies directed against FLC isotypes (te Velthuis et al., 2011). Studies comparing the N-Latex assay to the Freelite® assay have demonstrated a good concordance rate (Kim et al., 2014, Hoedemakers et al., 2012); however one should be aware that either assay could misclassify some patients (Hutchison et al., 2012a). Recent reports on patients with AL amyloidosis showed the two assays had similar diagnostic sensitivity but did not correlate sufficiently to be interchangeable for haematological response criteria (Mollee et al., 2013). This study showed that in combination with serum and urine immunofixation, both FLC assays had a diagnostic sensitivity of 98%.

(b) Luminex® assay (Seralite®)

This utilises four bead immobilised mouse anti-human monoclonal antibodies in a multi-plex Luminex® immunoassay. The initial

results from this assay are encouraging and it has been shown to demonstrate excellent sensitivity, sustained assay linearity and minimal cross-reactivity to bound light chain. Each of the monoclonal antibodies exhibited good quantitative concordance with Freelite® assay. The assay was also able to correctly identify all monoclonal FLC for both the isotypes from a total of 13,090 urine samples that were detected by IFE (Campbell et al., 2013).

(c) Heavy and light chain isotype assay (Hevylite®)

The heavy and light chain (HLC) isotype assay is also a nephelometric assay that targets the junctional epitopes between the bound HLC constant regions. It quantifies each of the intact immunoglobulins i.e. IgG kappa, IgG lambda, IgA kappa, IgA lambda, IgM kappa and IgM lambda, which in turn allows measurement of the ratios of the HLC pair and thereby provides information on clonality, on the same lines as would serum FLC assay (Bradwell et al., 2009). The Hevylite® assay is used particularly when the recognition and quantification of a small amount of paraprotein from the beta-globulin and gamma-globulin fraction on SPE is difficult (Wolff et al., 2013). It is also helpful when the SPE migration pattern is diffuse such that conventional electrophoretic markers are not useful for the diagnosis and monitoring of monoclonal disease (Bradwell et al., 2013, Ludwig et al., 2013, Boyle et al., 2014).

The most pragmatic approach for measuring the light chain level involves using either a serum or a urine test for diagnostic purposes, however; if the test is negative and the diagnosis of a monoclonal gammopathy is suspected then the test should be repeated and the alternative test should also be used. This approach recognises that a false negative test by either serum or urine is possible, in patients with a low-level light chain clone. The IMWG also recommended that SPE, sIFE, and serum FLC assay is a sufficient screening panel for monoclonal gammopathy except for AL amyloidosis, where it recommended that screening should also include uIFE (Dispenzieri et al., 2009).

1.8 Management of MM in patients with RI

1.8.1 Supportive management of MM

Acute kidney injury in MM is a medical emergency. Optimal management comprises early institution of anti-myeloma therapy along with good supportive care. Accurate assessment of fluid balance is essential; if volume depleted, treatment with intravenous fluids should be commenced immediately. Intravenous hydration along with alkalinisation of urine has shown to increase the solubility of the involved FLC clone and prevent the formation of intratubular casts (Holland et al., 1985, MacLennan et al., 1989).

Non-steroidal anti-inflammatory drugs, aminoglycosides, contrast agents, angiotensin-converting enzyme inhibitor, angiotensin-II receptor blocker, and loop diuretics should be stopped. Further prescriptions of these agents should be

avoided, as they are associated with an increased risk of development of MCN. Hypercalcemia is very common and bisphosphonates can be used for the treatment of elevated calcium levels (Bataille, 1996, Berenson et al., 1997, Morgan et al., 2010).

1.8.2 Treatment of Myeloma

Historically, treatment options for MM with RI were limited, and drug combinations with cytotoxic agents such as melphalan and cyclophosphamide in patients with RI were associated with significant toxicities. Patients presenting with severe AKI were usually excluded from clinical trials of therapy, the evidence for this group of patients is therefore derived from post-hoc subgroup analysis or from trials performed in patients with relapsed MM. Management of patients with MM has however evolved considerably over the last two decades and novel agents are now the backbone of contemporary anti-myeloma therapy (Table 1.3).

Table 1.3 Published studies of novel agent based regimen in MM patients with RI

Study	Year	Patient number	Requiring dialysis	Disease status	Chemotherapy	Myeloma response	Renal response
Bortezomib-based studies							
Jagannath et al (Jagannath et al., 2005)	2005	52 (CrCl ≤50 ml/min/1.73 m^2 with 10 patients with CrCl ≤30 ml/min/1.73 m^2)	0	relapsed or refractory	V or VD	Overall response (CR+PR+MR) was seen in 25%	Not reported
Malani et al (Malani et al., 2006)	2006	4 (Creatinine >3 mg/dL)	0	de novo and relapsed or refractory	V or VD	Near CR 3 PR 1	Improvement in renal function in all patients with three patients demonstrating creatinine <2 mg/dL
Channan-Khan et al (Chanan-Khan et al., 2007)	2007	24	23	relapsed or refractory	V VD VTD VAT	Overall response (≥PR) seen in 75% with 30% achieving a	4 (16%) patients became dialysis independent.

						CR or near CR	
Ludwig et al (Ludwig et al., 2007)	2007	8 (CrCl <20 ml/min/1.73 m^2)	5	de novo and relapsed or refractory	V VD VAD	CR or near CR -3 VGPR-1 PR-1	5 (62.5%) achieved reversal of renal impairment (Creatinine ≤2 mg/dL 2 Creatinine <3 mg/dL 3)
Blade et al (Blade et al., 2008)	2008	193 (CrCl <60 ml/min/1.73 m^2)	0	relapsed or refractory	PLD+V vs V	≥PR-49% in PLD+V group; ≥PR-42% in V group	Improvement in renal function in both treatment groups, with slightly better response in those on PLD+V.
San-Miguel et al (San-Miguel et al., 2008)	2008	62 (CrCl ≤50 ml/min/1.73 m^2; that included 45 [14%] with CrCl 30-50 ml/min/1.73 m^2 and 17 [5%] with CrCl <30	0	relapsed or refractory	V	Overall response (≥PR) seen in 23 (40%) patients	Not reported

		ml/min/1.73 m^2)					
San-Miguel et al (San Miguel et al., 2008)	2008	185 (CrCl <60 ml/min/1.73 m^2)	0	de novo	VMP	CR 28%	Not reported
Roussou et al (Roussou et al., 2008)	2008	20 (CrCl ≥2 mg/dL)	5	de novo and relapsed or refractory	VD VTD VAD VMTD	Overall response was seen in 65% CR 1 PR 11 MR 1	Reversal of RI (Creatinine <1.5 mg/dL) was seen in 8 [40%] patients. One of the 5 patients became dialysis independent.
Dimopoulos et al (Dimopoulos et al., 2009a)	2009	111 (eGFR ≤50 ml/min/1.73 m^2; that included 92 patients with eGFR 31-50 ml/min/1.73 m^2 and 19 with eGFR ≤30	0	de novo	VMP	Overall response seen in 68% that included 31% achieving a CR	Renal function reversal (eGFR >60 ml/min/1.73 m^2) seen in 49 [44%] patients that included 42 patients with eGFR 30-50 ml/min/1.73 m^2 and 7 with eGFR ≤30

		ml/min/1.73 m^2)					ml/min/1.73 m^2 at presentation.
Dimopoulos et al (Dimopoulos et al., 2009b)	2009	46 (eGFR <50 ml/min/1.73 m^2)	9	de novo and relapsed or refractory	VD VTD VAD VMTD	≥PR 29 (63%)	Overall renal response seen in 27 (59%) patients that included CRrenal 14 (30%) PRrenal 5 (11%) MRrenal 8 (17%) Two (22.2%) of the 9 patients became dialysis independent.
Li et al (Li et al., 2009)	2009	18 (Creatinine ≥2 mg/dL)	5	de novo	VD-T	Overall response rate was seen in 83.3% (CR 6 near CR 3 VGPR 3 PR 3)	Overall renal response defined as 50% reduction in serum creatinine level was seen in 7 (38.9%) patients.

							One of the 5 patients became dialysis independent.
Qayum et al (Qayum et al., 2010)	2010	6 (CrCl <30 ml/min/1.73 m^2 in all patients)	3 required one or two sessions of dialysis prior to bortezomib treatment	de novo and relapsed or refractory	V VD	CR 2 PR 3	Renal function improved in all patients with three patients achieving CrCl ≥60 ml/min/1.73 m^2.
Morabito et al (Morabito et al., 2010)	2010	117 (eGFR <80 ml/min/1.73 m^2 that included 12 [10.3%] with eGFR 51-80 ml/min/1.73 m^2, 23 [19.7%] with eGFR 30-50 ml/min/1.73 m^2 and 82	14	de novo and relapsed or refractory	VD V combined with other agents	Overall response seen in 83 (73%) patients; which included CR 23 (19%) near CR 8 (8%) VGPR 19 (17%) PR 33 (29%)	Reversal of RI (normalisation of eGFR) was seen in 41% eGFR 51-80 ml/min/1.73 m^2 67% 30-50 ml/min/1.73 m^2 78% and <30 ml/min/1.73 m^2 27% Three (21.4%) of the 14 patients

		[70.1%] with eGFR <30 ml/min/1.73 m^2					became dialysis independent.
Roussou et al (Roussou et al., 2010)	2010	17 (CrCl <50 ml/min/1.73 m^2)	All together 9 patients from the three treatment arms were on dialysis	de novo	VD	≥PR 82%	≥PRrenal 82% Two out of the 9 patients recovered renal function both of who were on bortezomib.
Ludwig et al (Ludwig et al., 2010)	2010	68 (CrCl <50 ml/min/1.73 m^2)	9	de novo and relapsed or refractory	VAD	Overall response was seen 72% (CR or near CR 38%, VGPR 15%, PR 13%, MR 6%)	Overall renal response was seen in 62% (CRrenal 31%, PRrenal 7%, MRrenal 24%) Three (33.3%) of the 9 patients became dialysis independent.
Morabito et al (Morabito et al., 2011)	2011	149 (eGFR ≤50 ml/min/1.73 m^2; VMPT-	0	de novo	VMPT-VT vs VMP	Overall response rate was 93.7% in	Reversal of RI (eGFR >60 ml/min/1.73 m^2) was seen in

		VT 70 patients and VMP 79 patients)				VMPT-VT arm and 77.9% in VMP arm	25.4% of patients in VMPT-VT arm and 40.3% in VMP arm. Time to renal function reversal was not significantly different between the two arms.
Costa et al (Costa et al., 2012)	2012	14 (CrCl <50 ml/min/1.73 m^2)	0	de novo	VCD	≥PR 14 (100%) that included CR in 57.1%	Overall renal response seen in 10 (71.4%) patients CRrenal 5 PRrenal 4 MRrenal 1
Dimopoulos et al (Dimopoulos et al., 2013b)	2013	43 (eGFR ≤60 ml/min/1.73 m^2)	6	de novo	VD VTD VCD	≥PR 81%	≥PRrenal 33 (77%) that included 29 patients with CRrenal. Three (50%) of the 6 patients became dialysis independent.

Yang et al (Yang et al., 2013)	2013	30 (Creatinine ≥2 mg/dL)	12	de novo	VTD	Overall response was 80%. CR 6 (20%) VGPR 8 (26.7%) PR 10 (33.3%)	10 (33.3%) achieved reversal of renal function. Eight (66.6%) of the 12 patients became dialysis independent.
Dimopoulos et al (Dimopoulos et al., 2013a)	2013	58 (eGFR <50 ml/min/1.73 m^2)	0	relapsed or refractory	VD VCD VDR	Among those achieving a renal response ≥PR seen in 14 (58.3%) patients	Overall renal response seen in 24 patients (43.6%). CRrenal 54.1% MRrenal 45.8%
Scheid et al (Scheid et al., 2014)	2014	81 (Creatinine ≥2 mg/dL that included 45 patients VADa)	0	de novo	VADa-T VAD-V	Overall response rate in VADa-T arm was 36% (≥VGPR in 9%) and in the VAD-V arm was 75% (≥VGPR in 33%)	Overall renal response in VADa-T arm was 63% and in the VAD-V arm was 81%.
Breitkreutz	2014	13	13	de novo	VAD	Overall response rate prior to	After induction with VAD 38.5% became dialysis

et al (Breitkreutz et al., 2014)						ASCT was 83.3% which improved to 100% post-ASCT	independent with a further 15.4% recovering renal function post-ASCT.
Girnius et al (Girnius et al., 2015)	2015	27 (eGFR <60 ml/min/1.73 m^2)	0	de novo	VD	Not reported separately for patients with RI	52% had an improvement in eGFR of >20%.
Pragnya et al (Pragnya et al., 2015)	2015	27 (eGFR <60 ml/min/1.73 m^2)	8 patients with eGFR <15 ml/min/1.73 m^2 or on dialysis)	de novo	VD (some patients also received Thalidomide or Lenalidomide)	Not reported separately for patients with RI	CRrenal 70.3%, PRrenal 14.8%, MRrenal 11.1% and no renal response 3.7%.
Soleymanian et al (Soleymanian et al., 2016)	2016	57 (median serum creatinine 3.5 mg/dL (1.4 14.5)	28 (49.1%)	de novo	Bortezomib based regimen 16% TD 84%	NA	NA
Tessenow et al (Tessenow et al., 2017)	2017	18	6	de novo	BPV	Not given separately for patients with RI	12 (66.6%) of the 18 patients with at least moderate RI improved renal function; 3 (50%) of the 6

							patients became dialysis independent.
Thalidomide-based studies							
Fakhouri et al (Fakhouri et al., 2004)	2004	7 (CrCl <50 ml/min/1.73 m^2)	1	relapsed or refractory	TD or T alone	CR 3 PR 1 MR 3	Out of the 5 patients with Cr Cl <30 ml/min/1.73 m^2, 2 patients progressed to RRT; remaining 3 patients maintained CrCl <30
Tosi et al (Tosi et al., 2004)	2004	20 (serum creatinine >130 µmol/L and CrCl <60 ml/min/1.73 m^2)	3	relapsed or refractory	TD or T alone	≥PR 9 (45%)	12 (80%) of 15 patients achieved renal function recovery i.e. serum creatinine <130µmol/L
Tosi et al (Tosi et al., 2010)	2010	31 (CrCl <50 ml/min/1.73 m^2)	7	de novo	TD	≥PR 23 (74%) [included 3 (10%) patients with	17 patients (55%) achieved CrCl >50 ml/min/1.73 m^2

						CR, and 5 (16%) with VGPR]	2 (28.5%) out of the 7 patients became dialysis independent.
Lenalidomide-based studies							
Niesvizky et al (Niesvizky et al., 2007)	2007	14 (CrCl <40 ml/min/1.73 m^2)	0	de novo	RD	Not reported	3 (21.4%) out of the 14 patients improved renal function with CrCl >40 ml/min/1.73 m^2.
Dimopoulos et al (Dimopoulos et al., 2010b)	2010	12 (CrCl <50 ml/min/1.73 m^2; includes 4 patients with CrCl <30 ml/min/1.73 m^2)	1	relapsed or refractory	RD	58% of patients with RI at presentation achieved ≥PR	5 (42%) of 12 patients demonstrated improvement in renal function (3 CRrenal; 2 MRrenal)
Dimopoulos et al (Dimopoulos et al., 2010a)	2010	98 (CrCl <60 ml/min/1.73 m^2; includes 16 patients with CrCl	0	relapsed or refractory	RD	Overall response seen in 54 (55%) patients	Amongst those with CrCl <60 ml/min/1.73 m^2 renal function improvement was

		<30 ml/min/1.73 m^2)				(CR 14; VGPR 14; PR 26)	demonstrated in 72%.
de la Rubia et al (de la Rubia et al., 2010)	2010	15	15 (2 patients were on RRT prior to myeloma diagnosis)	relapsed or refractory	RD	Overall response seen in 9 (60%) patients (CR 4; VGPR 1; PR 4)	1 patient became dialysis independent.
Klein et al (Klein et al., 2011)	2011	33 (moderate to severe RI defined as CrCl <50 ml/min/1.73 m^2)	5	relapsed or refractory	RD	Overall response seen in 16 (48.5%) patients (CR 1; VGPR 3; PR 12)	28.6% demonstrated improvement in renal function.
Oehrlein et al (Oehrlein et al., 2012)	2012	26 (CrCl <60 ml/min/1.73 m^2; included 11.5% with CrCl <30 ml/min/1.73 m^2)	3	relapsed or refractory	RD	Overall response seen in 21 (84%) patients (CR 1; PR 20)	Overall renal response seen in 11 (42.3%) patients. All the 3 patients achieved dialysis independence (CRrenal 6;

							PRrenal 1; MRrenal 4)
Hou et al (Hou et al., 2013)	2013	62 (CrCl <60 ml/min/1.73 m^2 which included 12 (6.4%) with CrCl <30 ml/min/1.73 m^2)	0	relapsed or refractory	RD	Overall response seen in 89 (47.6%) patients (CR 7; VGPR 23; PR 59)	Not reported
Tosi et al (Tosi et al., 2013)	2013	20 (CrCl <50 ml/min/1.73 m^2; 11 (55%) patients with CrCl <30 ml/min/1.73 m^2)	4	relapsed or refractory	RD	CR 1 VGPR 1 PR 6	CRrenal 4 PRrenal 3 MRrenal 1 1 patient achieved dialysis independence.
Dimopoulos et al (Dimopoulos et al., 2013b)	2013	28 (eGFR ≤60 ml/min/1.73 m^2)	0	de novo	RD or MPR	Overall response seen in 82%	Major renal response (≥PRrenal) seen in 12 patients that included 10 patients with CRrenal.

Ludwig et al (Ludwig et al., 2015)	2015	35 (eGFR <50 ml/min/1.73 m^2)	15	de novo and relapses or refractory	RD	Overall response seen in 24 (68.6%) of 35 patients (CR 7 VGPR 3 PR 14)	Renal response seen in 16 (45.7%) patients CRrenal 5 PRrenal 4 MRrenal 7 5 (38.4%) patients achieved dialysis independence.
Yamasaki et al (Yamasaki et al., 2015)	2015	15 patients (median eGFR 38.5 ml/min/1.73 m^2 pre-lenalidomide treatment)	0	relapsed or refractory	RD	≥PR 15 (2 patients achieved CR)	Post-treatment median eGFR 49.7 ml/min/1.73 m^2.
Joao et al (Joao et al., 2016)	2016	23 (CrCl <30 ml/min)	13 (56%)	relapsed or refractory	RD	≥PR 56%	9 patients had renal improvement, none of the 13 patients became dialysis independent

V-bortezomib; VD-bortezomib and dexamethasone; VTD-bortezomib, thalidomide and dexamethasone; VAT-bortezomib, adriamycin and thalidomide; PLD+V-pegylated liposomal doxorubicin and bortezomib; VMP-bortezomib, melphalan and prednisolone; VAD-bortezomib, adriamycin and dexamethasone; VMTD-bortezomib, melphalan, thalidomide and dexamethasone; VMPT-VT-bortezomib, melphalan, prednisolone, thalidomide followed by bortezomib and thalidomide maintenance; VCD-bortezomib, cyclophosphamide and dexamethasone; VDR- bortezomib, dexamethasone and lenalidomide; VADa-vincristine, adriamycin and dexamethasone; T-thalidomide; TD-thalidomide and dexamethasone; RD-lenalidomide and dexamethasone; MPR-melphalan, lenalidomide and prednisolone; BPV-bendamustine, prednisolone and bortezomib.

1.8.2.1 Dexamethasone

Glucocorticoids exert a cytotoxic effect on myeloma cells by inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and IL-6 (Auphan et al., 1995, Ray et al., 1990, Herrmann et al., 1991). Dexamethasone is a potent steroid that has been used both alone and in combination with other agents. In a study that included 112 newly diagnosed MM patients; a 75% reduction in serum M-protein was reported in 43% of patients treated with intermittent courses of dexamethasone. The response rate to dexamethasone used as a single agent was approximately 15% less than that of a vincristine-doxorubicin-dexamethasone (VAD) combination in a previous study, which implied that the majority of the anti-myeloma response by VAD regimen was due to dexamethasone alone (Alexanian et al., 1992).

In another study high-dose dexamethasone with a novel agent was associated with a shorter length of time to renal response compared to high-dose dexamethasone in combination with conventional agents (Kastritis et al., 2007). A similar finding was reported in a further study where treatment with high-dose dexamethasone (≥160 mg/month) when used in combination with thalidomide based, bortezomib based or lenalidomide based regimens (Dimopoulos et al., 2013b).

1.8.2.2 Proteasome inhibitors

1.8.2.2.1 Bortezomib

Bortezomib is a first-in-class selective and reversible 26S proteasome inhibitor with proven efficacy in newly diagnosed MM and in relapsed or refractory MM. It targets the ubiquitin-proteasome pathway that promotes the proliferation and survival of all cells, in particular cancer cells (Adams, 2004). It decreases myeloma cell binding to bone marrow stromal cells and blocks NF-κB mediated synthesis of IL-6 by stromal cells (Hideshima et al., 2001). It has anti-angiogenic properties and inhibits vascular endothelial growth factor (VEGF) and IL-6 secretion by the endothelial cells (Roccaro et al., 2006). Among other effects, bortezomib can modulate intracellular signalling mechanisms and gene expression to protect the renal proximal tubular cell from the anti-apoptotic effects of NF-κB (Sarkozi et al., 2008). It is metabolised primarily in the liver via cytochrome P450 enzymes and no dose alteration is necessary in patients with RI. The commonest side effects are peripheral neuropathy and haematological toxicity; electrolyte abnormality, mood disturbances, hypotension and gastrointestinal disturbances can also occur.

A subgroup analysis of the Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisolone (VISTA) trial reported no difference in CR rate (28%), time to progression and the OS in the 185 patients with CrCl <60 ml/min/1.73 m^2 compared to the remaining 159 patients who had no RI from the bortezomib arm (San Miguel et al., 2008).

A recent phase-II study that evaluated the efficacy and tolerability of an alternate dosing regimen for bortezomib in newly diagnosed patients with MM ineligible for stem cell transplantation reported an improvement in renal function in 52% of patients with an eGFR <60 ml/min/1.73 m^2 at diagnosis. The weekly bortezomib regimen was well tolerated by the elderly and frail cohort of patients with the majority of the adverse events reported to be of grade 1/2 severity; only one patient in this study developed a grade 3/4 peripheral neuropathy from bortezomib therapy (Girnius et al., 2015).

In another study subcutaneous bortezomib was an effective alternative in relapsed MM compared to intravenous therapy in a multicentre phase-III trial that showed comparable efficacy in the overall response rate, time to progression, and one-year OS in the two treatment groups. RI defined as CrCl ≤60 ml/min/1.73 m^2 at presentation was present in 41% who received subcutaneous and 32% who received intravenous bortezomib. Patients on subcutaneous bortezomib had less grade 3 or worse adverse events than those on intravenous treatment (57% vs 70% respectively) (Moreau et al., 2011b).

A retrospective pooled analysis of the Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT) and the Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST) investigated the response rate and safety of bortezomib in recurrent and/or refractory MM in patients with severe RI as defined by a CrCl of 10-30 ml/min/1.73 m^2. Ten patients were reported, of whom six also received dexamethasone. Overall response was noted in three patients (30%); two patients

achieving partial response (PR) and one patient achieving a minimal response (MR). This was one of the earliest studies to report on the clinical benefit of bortezomib in this high-risk group of patients (Jagannath et al., 2005).

A subgroup analysis of the Assessment of Proteasome Inhibition for Extending Remissions (APEX) study also studied bortezomib in relapsed MM. Patients treated with bortezomib had a superior disease response (≥PR 38% vs 18% in CrCl >50 ml/min/1.73 m^2 group; 40% vs 16% in ≤50 ml/min/1.73 m^2 group) and longer time to progression (6.2 months vs 3.5 months in CrCl >50 ml/min/1.73 m^2 group; 4.9 months vs 2.8 months CrCl ≤50 ml/min/1.73 m^2 group) compared to treatment with high-dose dexamethasone. Adverse event rates were comparable for each group for bortezomib; however, higher adverse events and drug discontinuation was seen in the dexamethasone arm (San-Miguel et al., 2008). A number of other studies (Malani et al., 2006, Chanan-Khan et al., 2007, Ludwig et al., 2007, Blade et al., 2008, San-Miguel et al., 2008, Roussou et al., 2008, Dimopoulos et al., 2009a, Dimopoulos et al., 2009b, Li et al., 2009, Qayum et al., 2010, Morabito et al., 2010, Roussou et al., 2010, Ludwig et al., 2010, Morabito et al., 2011, Costa et al., 2012, Dimopoulos et al., 2013a, Yang et al., 2013, Dimopoulos et al., 2013b, Scheid et al., 2014, Breitkreutz et al., 2014) have reported on bortezomib in patients with RI, these are summarised in Table 1.3.

1.8.2.2.2 Carfilzomib

Carfilzomib is a new generation proteasome inhibitor approved in the United States for patients with relapsed and/or refractory MM. The PX-171-005 study evaluated the safety and efficacy of carfilzomib in 50 patients with relapsed and/or refractory MM and included 18 (36%) patients with CrCl <50 ml/min/1.73 m^2 and an additional 8 (16%) patients on dialysis. There was no impact of RI on clearance of carfilzomib. A PR or greater response occurred in 23.5% with a CrCl <50 ml/min/1.73 m^2 and 37.5% of those on dialysis, one of who became dialysis independent (Badros et al., 2013). An analysis of four separate phase-II studies that totalled 526 patients, including 23.8% with a CrCl <50 ml/min/1.73 m^2, demonstrated no worsening in renal function in 86.8% following treatment with carfilzomib; 13.2% had at least one episode of RI and with grade 3/4 adverse events as a consequence occurred in 7.2% (Siegel et al., 2013).

1.8.2.3 Immunomodulatory (IMiD) therapy

1.8.2.3.1 Thalidomide

Thalidomide was the first immunomodulatory agent to show promise in the treatment of MM. The drug has anti-angiogenic, anti-inflammatory and anti-immunomodulatory properties (Singhal et al., 1999). Specific effects include blockade or down-regulation of TNF-α, cyclooxygenase (COX)-2, and myeloma cell targeted stromal derived factor-1α and its receptor CXCR-4 (Fujita et al., 2001, Oliveira et al., 2009). Thalidomide undergoes biotransformation by non-enzymatic hydrolysis in the liver to form multiple metabolites with <1% excretion of these metabolites in the urine (Chen et al., 1989, Lepper et al., 2006).

Thalidomide has limited haematological toxicity, and can therefore be used both as a single agent and in combination with other chemotherapeutic agents (Lokhorst et al., 2010, Lokhorst et al., 2008, Rajkumar et al., 2008, Rajkumar et al., 2006, Morgan et al., 2012a). The pharmacokinetics in patients receiving dialysis has not been extensively studied and there are reports of hyperkalaemia in patients with RI (Singhal et al., 1999, Harris et al., 2003). The most common side effects are peripheral neuropathy that is usually encountered after a prolonged exposure (Palumbo et al., 2008), and thromboembolic events. The risk of thrombo-embolism increases when used in combination with other agents, especially high-dose dexamethasone (Bennett et al., 2006). Despite over 15 years of clinical use, there is a disappointingly low quantity of useful data on thalidomide in RI.

The efficacy of thalidomide-dexamethasone prior to autologous stem cell transplantation (ASCT) in previously untreated patients presenting with a CrCl of <50 ml/min/1.73 m^2 was reported by Tosi and colleagues. They noted a ≥PR in 74% of patients that included 26% with a very good partial response (VGPR). An improvement in renal function post-induction occurred in 82% of patients with a ≥PR, compared to 37% of those who did not achieve a PR (Tosi et al., 2010).

In a study of 20 consecutive advanced, refractory or relapsed patients with MM and RI (including 3 patient requiring dialysis), treated with thalidomide alone or in combination with dexamethasone, a PR was noted in nine patients and a MR in six additional patients. Renal function recovery occurred in 12 of 15 patients who responded to treatment, thalidomide alone was associated with a maximal disease response at a median of six weeks, and thalidomide plus dexamethasone at a

median of four weeks. The toxicity of thalidomide as monotherapy or in combination with dexamethasone was similar to that observed in patients with MM and normal renal function (Tosi et al., 2004). .

1.8.2.3.2 Lenalidomide

Lenalidomide is a second generation immunomodulatory agent which has direct tumoricidal activity in MM (Verhelle et al., 2007, Davies et al., 2001, Gandhi et al., 2010, Tai et al., 2005). The kidney is the primary route of elimination, with 84% of the drug secreted in the urine in patients with normal renal function. Therefore clearance of lenalidomide decreases with a progressive decline in renal function; from 69% in patients with a CrCl 50-80 ml/min/1.73 m^2, to 38% in patients with CrCl 30-49 ml/min/1.73 m^2, and 43% in patients with CrCl <30 ml/min/1.73 m^2. In moderate to severe RI or ESRD, the area under the concentration-time curve increases by approximately 185% to 420% and the median half-life increases by 6-12 hours; furthermore a single session of four-hour haemodialysis only removes 31% of the administered dose (Chen et al., 2007). As a result, dose recommendations in patients with MM and RI are in place (Dimopoulos et al., 2011). Lenalidomide therapy is associated with an increased risk of thromboembolic events (Tosi et al., 2004) and neutropenia and thrombocytopenia are also important side effects (Reece et al., 2012).

Lenalidomide and dexamethasone was assessed in patients with RI in the MM-009 and MM-010 multicentre, phase-III clinical trial. 71%, 24% and 5% had a CrCl of ≥60 ml/min/1.73 m^2, 30-59 ml/min/1.73 m^2, and <30 ml/min/1.73 m^2

respectively. There was no significant difference in the overall response, time to progression, and progression free survival between groups. However patients with a CrCl <30 ml/min/1.73 m^2 had a shorter survival (18.4 months) than those with a CrCl 30-59 ml/min/1.73 m^2 (29.0 months) or CrCl ≥60 ml/min/1.73 m^2 (38.9 months). A renal response occurred in 72%. Thrombocytopenia and discontinuation of lenalidomide (mainly due to cytopenia) was more common in those with severe RI (Dimopoulos et al., 2010a).

Rubia and colleagues reported the use of lenalidomide and dexamethasone in 15 refractory and/relapsed MM patients on dialysis. Thirteen patients received lenalidomide three-times a week after dialysis treatment at a dose of 15 mg/day and two patients received lenalidomide at a dose of 5mg/day and 5 mg on alternate days respectively. 29% achieved a CR, 7% a VGPR and 29% a PR. One patient who achieved a PR attained independence from dialysis. Haematological toxicity was common; 53% of patients required a reduction in the dose of lenalidomide due to the development of cytopenia. This study showed that with careful monitoring and with appropriate dose adjustments lenalidomide could be used for relapsing or refractory MM in patients requiring dialysis (de la Rubia et al., 2010). Overall the results of studies to date indicate that lenalidomide therapy is an important treatment option in the management of MM in patients with RI (Tosi et al., 2013, Oehrlein et al., 2012, Klein et al., 2011, Dimopoulos et al., 2014b, Ludwig et al., 2015).

1.8.2.3.3 Pomalidomide

Pomalidomide is another new generation immunomodulatory agent used in combination with dexamethasone for the management of relapsed and/or refractory MM. The superiority of pomalidomide with low-dose dexamethasone compared to pomalidomide alone or high-dose dexamethasone alone was reported in a phase-II (Richardson et al., 2014) and a phase-III (San Miguel et al., 2013) study respectively; however, individuals with moderate to severe RI at presentation were excluded from both the studies. It is metabolised extensively via multiple pathways with <5% of the administered pomalidomide dose excreted unchanged in the urine. Studies to assess the efficacy and safety of pomalidomide in patients with severe RI are currently underway (Dimopoulos et al., 2015).

1.8.3 Autologous Stem cell transplantation (ASCT)

High-dose chemotherapy followed by ASCT is an established treatment option for MM. Renal impairment had no impact on stem cell collection and post-transplant engraftment in small single centre studies (Tricot et al., 1996, Ballester et al., 1997), with some centres reporting cases of recovery from requiring dialysis(Ballester et al., 1997, Tauro et al., 2002).

High-dose melphalan (200 mg/m2) is associated with excessive toxicity; when the dose of melphalan was reduced to 140 mg/m2 in a study where 21 of the 81 patients had advanced RI (creatinine >177 μmol/L with 47% on dialysis), transplant related mortality (TRM) was observed in 6% and 13% of patients after single and tandem ASCT respectively. Dialysis dependence and melphalan dose

did not affect event free survival or OS (Badros et al., 2001). In a subsequent study in dialysis patients a further reduction in melphalan dose (100 mg/m2) produced a similar toxicity profile, TRM, disease response, and OS compared to patients with no RI (Raab et al., 2006).

Published data around the disease and renal response in patients with advanced RI is variable. In a single centre study of 59 patients requiring dialysis, ASCT was associated with independence of dialysis in 13 of 54 who survived more than 30 days. A shorter duration of dialysis (≤6 months), achievement of a CR or near CR, and CrCl ≥10 ml/min/1.73 m^2, were all associated with recovery of independent kidney function (Lee et al., 2004).

More recently, Mayo clinic investigators reported long term outcomes following ASCT in 30 patients with advanced RI (creatinine >3 mg/dL); 15 patients were receiving dialysis, and only one recovered renal function. The non-dialysis patients had a modest improvement in eGFR from 15 ml/min/1.73 m^2 to 19 ml/min/1.73 m^2. CR was noted in 14 patients. Although patients who achieved a CR had a better median eGFR than those who did not, the authors found no association between haematological response and baseline eGFR with renal outcome (Glavey et al., 2013).

Current guidelines support the idea that ASCT is an attractive treatment option in the management of MM; however careful patient selection is required, especially in patients with advanced RI (Bird et al., 2011).

1.8.4 Role of extra-corporeal removal of FLC

1.8.4.1 Therapeutic plasma exchange (PE)

The largest randomised control trial in patients with MM and severe AKI recruited between 1998-2003 failed to show a benefit of PE on patient and renal outcomes; the limitations of this study included the lack of a renal biopsy confirming a diagnosis of MCN and the absence of serum or urinary light chain measurement (Clark et al., 2005).

Subsequently, Leung and colleagues (Leung et al., 2008) investigated the efficacy of PE in 40 patients with MM and severe RI that included nine (22.5%) patients on dialysis. A renal response was noted in 18 (45%) patients, which included 14 patients with MCN who had sFLC levels measured before and after treatment with PE. Of these 14 patients, an sFLC reduction of ≥50% was reported in 64.3%, seven of these patients had a significant renal response. Two (22%) patients subsequently became dialysis independent. The authors concluded that PE for extra-corporeal FLC removal only had a role in biopsy confirmed MCN and in patients who demonstrated a ≥50% reduction in sFLC levels from baseline (Leung et al., 2008).

However; PE as an isolated treatment does not provide clinical benefit and the improvements in clinical outcome associated with a ≥50% reduction in FLC in this study most likely reflects a chemo-sensitive FLC clone. As FLC have a molecular weight of 25-50 kilodalton (kD) and are distributed in both the intra- and extravascular compartments, a single session of PE removes <10% of extracellular

FLC. The current consensus is that FLC removal by PE is unlikely to contribute to improving patient outcome (Cserti et al., 2007, Winearls, 1995) and the present focus is on high cut-off haemodialysis, which has greater efficacy for FLC removal than PE.

1.8.4.2 High Cut-Off (HCO) haemodialysis

Hutchison and colleagues (Hutchison et al., 2007) performed a series of in vitro and in vivo studies to assess the efficacy of several protein-leaking haemodialysers and developed a theoretical model and clinical strategy for extra-corporeal FLC removal in patients with MM presenting with severe RI. From the dialysers tested, the Gambro™ HCO 1100 with a molecular weight cut-off in vivo of around 65 kD was found to be highly efficient for FLC removal. The model found that extended (8-12 hours) daily dialysis would accelerate reduction in sFLC levels provided that the involved FLC was chemo-responsive (Hutchison et al., 2007).

A pilot study reported outcomes in 19 patients with MM who received dialysis for severe AKI, using the HCO 1100 membrane. Thirteen patients who had uninterrupted courses of chemotherapy and extended dialysis demonstrated a sustained FLC reduction, reflecting single session reductions of 69% in kappa FLC and 71% in lambda FLC levels. Twelve (86%) of the 14 patients who became dialysis independent also had an early and sustained reduction in sFLC levels; median time from presentation to dialysis independence was 24 days. Median survival in patients who had uninterrupted chemotherapy was significantly better

compared to those who has treatment suspended due to potential complications (Hutchison et al., 2009).

A further report from a multicentre study assessed the relationship between FLC level and renal function in dialysis dependent patients treated with HCO haemodialysis and chemotherapy. The majority of patients in this study received a novel chemotherapeutic agent. A ≥50% reduction in sFLC level was seen in 68% of patients by day 12 and in 83% of patients by day 21. The majority of patients who demonstrated early reduction in sFLC level also became dialysis independent. Patients who did not achieve independence from dialysis were more likely to have sustained a delay in initiating HCO haemodialysis treatment. In a multivariable model, the factors that were associated with independence from dialysis were FLC reduction at day 12 and day 21 and time to initiating HCO haemodialysis (Hutchison et al., 2012b).

There are several other small studies which have highlighted the benefit of HCO haemodialysis in renal function recovery in patients with MM and severe RI (Table 1.4) (Zannetti et al., 2015a, Borrego-Hinojosa et al., 2013, Khalafallah et al., 2013, Sinisalo et al., 2012, Martin-Reyes et al., 2012, Heyne et al., 2012). However, supplementation of HCO haemodialysis to current standard of care failed to reach its primary end-point and show any significant difference in dialysis independence rate at three months in the prospective MM and renal failure due to MCN (MYRE) randomised controlled trial (Bridoux et al., 2017). Dialysis independence rate was nevertheless significant both at six- and twelve-months in patients recruited in the HCO haemodialysis group compared to those receiving

conventional haemodialysis using a high-flux dialyser. Preliminary results from the EUropean trial of free LIght chain removal by exTEnded haemodialysis in cast nephropathy (EuLITE) study also indicates that there is no additional benefit of HCO haemodialysis in achieving renal function recovery in patients who were treated with bortezomib containing chemotherapy regimens (Hutchison C. A., 2016). There were however some key differences between the two trials: overall the dose of prescribed HCO haemodialysis was higher in the EuLITE trial compared to the MYRE study i.e. 6-hour haemodialysis on day 0 followed by 8-hour of subsequent dialysis sessions in comparison to 5-hour haemodialysis respectively. Patients recruited in the EuLITE trial received HCO haemodialysis for up to three months, whilst those in the MYRE study remained on HCO haemodialysis only up until the completion of their third cycle of chemotherapy. Another fundamental difference between the two trials was the choice of chemotherapy regimen. Patients in the EuLITE trail received a combination of bortezomib, doxorubicin, and dexamethasone whereas patients in the MYRE study only received bortezomib and dexamethasone at recruitment with reinforcement by cyclophosphamide after three months if clinically indicated.

Table 1.4 Published studies of use of HCO haemodialysis in MM patients with severe RI

Study	Year published	Number of patients on RRT	Disease status	Renal biopsy findings	Chemotherapy	Myeloma response	Renal response
Hutchison et al (Hutchison et al., 2007)	2007	5	de novo	MCN	Dexamethasone based regimen	Not available	3 (60%) out of 5 patients achieved dialysis independence
Hutchison et al (Hutchison et al., 2009)	2009	19	16 patients de novo 3 patients relapsed	MCN	Cyclophosphamide 7, Thalidomide 14, Vincristine + doxorubicin 1, Dexamethasone 1	Not available; however sustained FLC reduction noted in 13 patients (68.4%)	14 (73.6%) patients achieved dialysis independence.
Peters et al (Peters et al., 2011)	2011	5	all de novo	MCN	BD	Not reported (however a mean FLC reduction of 90±6% seen after the third	3 (60%) out of the 5 patients on HCO dialysis became dialysis independent.

						session of HCO dialysis; with a FLC reduction of 61±20% per session over 2 weeks)	
Sinisalo et al (Sinisalo et al., 2012)	2012	7	all de novo	available in 6 patients (85.7%); all demonstrating MCN	BD 3 BD + MP 1 BD + VAD 1 RVD 1 VTD 1	Not available	6 (85.7%) patients achieved dialysis independence
Hutchison et al (Hutchison et al., 2012b)	2012	67	50 patients de novo 17 patients relapsed	available in 38 (56.7%) patients with 86.7% demonstrating MCN	Novel agent used in 56 patients	42 patients (61%) had a reduction in FLC levels. Amongst these 83% had a ≥50% decline in FLC levels	42 (63%) patients achieved dialysis independent
Heyne	2012	19	10 patients de novo	available in 6	Novel agent used in 14 patients	≥PR 6 (42.8%)	14 (73.7%) patients

et al (Heyne et al., 2012)			9 patients relapse or refractory	(31.5%) patients; all demonstrating MCN			achieved dialysis independence.
Khalahfallah et al (Khalafallah et al., 2013)	2013	4	3 patients de novo 1 patient relapsed	Unknown if renal biopsy performed	VAD 2 BD 1 TD 1 (switched to RD)	≥VGPR 3 (75%) patients	3 (75%) patients achieved dialysis independence.
Tan et al (Tan et al., 2014)	2014	6	all de novo	MCN	VCD 3 CTD 1 CD 2	≥PR 4 (66.6%)	3 (50%) patients achieved dialysis independence.
Zanetti et al (Zannetti et al., 2015a)	2015	21	all de novo	15 (71.4%) patients demonstrating MCN	VTD 13 (ASCT eligible) VMP 8 (ASCT ineligible)	sCR 4 (19%) VGPR 10 (48%) PR 3 (14%) SD 3 (14%) PD 1 (5%)	16 (76%) achieved dialysis independence MRrenal 5 (24%) Prrenal 4 (19%) Crrenal 3 (14%)

Bridoux et al	2017	94	de novo	MCN	VD		

RRT = Renal replacement therapy; PRrenal = partial renal response; MRrenal = minor renal response; VD = bortezomib and dexamethasone; MP = melphalan and prednisolone; VADa = vincristine, adriamycin and dexamethasone; RVD = lenalidomide, bortezomib and dexamethasone; VTD = bortezomib, thalidomide and dexamethasone; VAD = bortezomib, adriamycin and dexamethasone; TD = thalidomide and dexamethasone; RD = lenalidomide and dexamethasone; CD = cyclophosphamide and dexamethasone; VCD = bortezomib, cyclophosphamide and dexamethasone; CTD = cyclophosphamide, thalidomide and dexamethasone; VMP = bortezomib, melphalan and prednisolone; sCR = stringent complete response.

1.8.5 Future Directions

The outcomes in patients with MM and RI are improving, and newer classes of agents including antibodies (e.g. anti-SLAMF7 elotuzumab, anti-CD38 daratumumab) and histone deacetylase inhibitors (e.g. panobinostat and vorinostat) have shown great promise in phase II/III studies, and it would be reasonable to expect the improved myeloma response rates that are being sustained with these agents to lead to better renal outcomes for patients with MM who have RI. There are important research questions that can stratify the management of patients with MM and RI in the next decade, some of these questions provide the basis of this thesis. These include: better defining the relationship between FLC level and renal function at diagnosis; describing the relationship between FLC response and renal function in patients who do not require dialysis at presentation, and understanding the impact of mild-to-moderate RI on long-term patient outcome. Finally, patients with severe RI are usually excluded from major intervention trials; future studies need to address this to improve the evidence base of novel and next-generation therapies.

CHAPTER TWO: AIMS AND OBJECTIVES

2.1 Background

Renal impairment (RI) at presentation in patients with MM is associated with worse prognosis than in patients who do not have RI at presentation. Outcomes are however improving, especially over the last decade with the availability of potent anti-myeloma therapies. Studies that have published on outcome data in patients with MM and RI have reported a better prognosis for patients who start treatment promptly and in those who demonstrate an early reduction in serum FLC level following start of chemotherapy. Early survival is significantly better in patients who achieve renal function recovery, and achieving this is now an important treatment goal in patients with MM presenting with severe AKI at diagnosis.

Hence early identification and correction of factors that are associated with RI in patients with MM is essential. Studies have shown that an elevated FLC level is associated with RI, however; the threshold of FLC level in serum beyond which the risk of RI increases is yet unknown. In addition it is uncertain what the long-term outcomes are of patients who require dialysis for AKI and MM and who then recover kidney function.

2.2 Overall aim of the research

The principle aim of the research is to study the relationship between serum FLC levels and kidney function in patients with MM and to identify factors that are associated with OS in individuals who recover kidney function from a dialysis-dependent state. This

would enable clinicians to identify patients with MM who are at a greater risk from RI at presentation and to determine factors that are associated with RI post-treatment.

2.3 Specific objectives

1. To evaluate the relationship between serum FLC level and kidney function at diagnosis and to determine the level of FLC in serum that increases the risk of RI in a population-based study.

   Study design: An observational study of patients with newly diagnosed MM who were recruited in a multicentre, randomised, open-label, phase-III, factorial design trial conducted in the United Kingdom.

2. To investigate the relationship between haematological responses based on serum FLC response criteria and renal response post-treatment by eGFR category in newly diagnosed patients with MM.

   Study design: An observational study of patients with newly diagnosed MM who were recruited in a multicentre, randomised, open-label, phase-III, factorial design trial conducted in the United Kingdom.

3. To describe range of serum FLC level at diagnosis in patients with MM and biopsy confirmed MCN.

   Study design: An observational study that included patients with newly diagnosed MM and biopsy confirmed MCN in a multi-centre setting.

4. To report contemporary long-term outcomes in patients who recover independent renal function from a dialysis-dependent state, as a consequence of MCN.

Study design: A single centre observational study from a specialist centre in Birmingham, UK.

CHAPTER THREE: ASSOCIATION BETWEEN RENAL FUNCTION AND SERUM FLC LEVEL AT PRESENTATION USING THE MYELOMA IX TRIAL DATA

I have published a paper related to this chapter. Yadav P, Cockwell P, Cook M, Pinney J, Giles J, Aung YS, Cairns D, Owen RG, Davies FE, Jackson GH, Child JA, Morgan GJ, Drayson MT. Serum free light chain levels and renal function at diagnosis in patients with multiple myeloma. BMC Nephrol. 2018 Jul 13;19(1):178. doi: 10.1186/s12882-018-0962-x.

3.1 Introduction

Renal impairment (RI), as defined by an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2, is present in up to 50% of patients when first diagnosed with multiple myeloma (MM) and is associated with worse survival (Knudsen et al., 2000, Dimopoulos et al., 2008). Renal impairment in MM can be multi-factorial; with a median age of 70 years for patients presenting with a new diagnosis of MM, some RI will be attributable to longstanding unrelated co-morbidities that include hypertension and diabetes mellitus and will be largely irreversible (Kleber et al., 2011, Song et al., 2016). Renal impairment in MM can also be associated with concurrent infection, dehydration, hypercalcaemia and use of non-steroidal anti-inflammatory drugs; these factors are potentially reversible with supportive care. Finally, MM can cause RI through nephrotoxicity of the secreted immunoglobulin free light chain (FLC), which can be potentially reversed by the rapid lowering of the involved FLC with effective anti-myeloma therapy (Stringer et al., 2012, Hutchison et al., 2012b, Hutchison et al., 2011b).

Up to one in five patients with MM have severe RI at diagnosis (eGFR <30 ml/min/1.73m^2), this incidence is ten-fold the prevalence of severe RI in an age- and

gender-matched population from which MM arises (Jain et al., 2014, Zoccali et al., 2010). Approximately 4% of patients can have RI of sufficient severity to require dialysis treatment (Dimopoulos et al., 2014a). Patients with MM and severe RI have a risk of death that is at least twice compared to patients with MM and normal renal function (Torra et al., 1995).

Renal biopsy series from patients with MM have been restricted to individuals with severe RI, often requiring dialysis, and up to 90% of patients in these series have myeloma cast nephropathy (MCN) (Hutchison et al., 2012b). MCN occurs because in some patients the FLC secreted by the neoplastic plasma cells is both at a high level and is nephrotoxic. Renal biopsies are rarely carried out in patients who do not have severe RI and hence it is not known what proportion of mild to moderate impaired renal function at diagnosis is attributable to nephrotoxicity of the secreted FLC, or to other myeloma related causes of renal damage or to longstanding RI due to unrelated comorbidities. Defining the levels of FLC in serum in relation to the level of renal function is important, as it will provide a mechanistic basis for the development of RI and may direct future changes in treatment based on FLC levels and renal function at presentation.

In this study we assessed the relationship between serum FLC levels and renal function across all stages of RI except for patients receiving or likely to require dialysis and analysed for a threshold level in serum above which there is a higher likelihood of FLC induced nephrotoxicity in patients with MM. We utilised the Medical Research Council (MRC) Myeloma IX trial dataset and included patient demographic and disease parameters, with a focus on paraprotein types and serum FLC levels at diagnosis, and renal function as measured by estimated glomerular filtration rate (eGFR).

3.2 Aims

The aims of this study that provides the basis for this chapter were:

1. To evaluate the relationship between renal function (eGFR) and serum FLC level at presentation in newly diagnosed patients with MM.
2. To identify the association between patient demographics and renal function (eGFR) at presentation in newly diagnosed patients with MM.
3. To investigate the role of disease (myeloma) parameters in causing RI in newly diagnosed patients with MM.
4. To determine level of serum free light chain level at presentation that is associated with RI.

3.3 Methods

3.3.1 Study design

An observational study of patients that were recruited to participate in a multicentre, randomised, open-label, phase III and factorial design trial (Myeloma IX trial) conducted in the UK by the Medical Research Council (MRC) (International Standard Randomised Controlled Trial Number 68454111). A brief description of the Myeloma IX trial is described below.

3.3.1.1 Myeloma IX trial protocol

Patients were allocated to an intensive or non-intensive treatment arm based on their performance status, clinician discretion and patient choice. In essence, younger and fitter

patients were allotted to intensive treatment arm where they received high-dose/intensive chemotherapy followed by autologous stem cell transplant (ASCT); and older or less fit patients were assigned to the non-intensive treatment arm.

In the intensive treatment arm of Myeloma IX trial, patients were randomised to receive either CVAD (oral cyclophosphamide, continuous infusion of vincristine along with doxorubicin and oral dexamethasone) or CTD (oral cyclophosphamide, thalidomide and dexamethasone) chemotherapy. Following 4-6 cycles with either of the induction agents, all patients recruited in the intensive treatment arm received high-dose melphalan and ASCT (Morgan et al., 2012a).

In the non-intensive treatment arm, patients were randomised to receive either oral MP (melphalan and prednisolone) or attenuated oral CTD (cyclophosphamide, thalidomide and dexamethasone) chemotherapy. Treatment for patients in the non-intensive arm was carried out until they achieved a best haematological response (minimum of six cycles or a maximum of nine cycles if tolerated) (Morgan et al., 2011).

For each treatment pathways patients were further randomised to receive one of the two bisphosphonates i.e. oral clodronic acid or intravenous zolindronic acid, along with the induction chemotherapy which was continued thereafter every four weekly (Morgan et al., 2010). Patients were finally randomised to receive either thalidomide maintenance or no thalidomide maintenance, which along with bisphosphonates was administered until disease progression (Morgan et al., 2012b). A multicentre research ethics committee and local ethics committees had approved the Myeloma IX trial protocol and all patients gave a written informed consent in accordance to the Declaration of Helsinki.

3.3.1.2 Inclusion and exclusion criteria for Myeloma IX trial

In brief, all patients aged 18 years or older with symptomatic new presentation MM were eligible to participate in the Myeloma IX trial. Exclusion criteria included pregnancy, asymptomatic MM, solitary bone plasmacytoma or extramedullary plasmacytoma, previous or concurrent active malignancies, and presence of severe AKI unresponsive to up to 72-hours of rehydration, characterised by creatinine more than 500 μmol/L or urine output less than 400 mL/day or requirement for dialysis (Morgan et al., 2011, Morgan et al., 2012a).

3.3.1.3 Myeloma IX trial outcomes

The primary end points of the Myeloma IX trial were progression free survival, overall haematological disease response and OS. Blood and urine samples were sent to the Clinical Immunology Service, University of Birmingham, Birmingham, UK for central laboratory analysis. Haematological disease response was evaluated using the modified European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry criteria at the end of induction chemotherapy and 100 days after ASCT (Morgan et al., 2012b, Morgan et al., 2012a, Morgan et al., 2011, Morgan et al., 2010).

3.3.2 Patients

All newly diagnosed patients with MM recruited in the intensive and non-intensive treatment arms of the Myeloma IX trial, who had blood samples sent for central laboratory analysis at entry to the trial were eligible to participate in this study. Ethical approval for secondary analyses of data from the Myeloma IX trial was already available hence no further approval was sought for this study.

3.3.3 Data collection

Following data that were recorded at the time of recruitment for the Myeloma IX trial were included in this study:

(a) Age

(b) Gender

(c) Serum creatinine

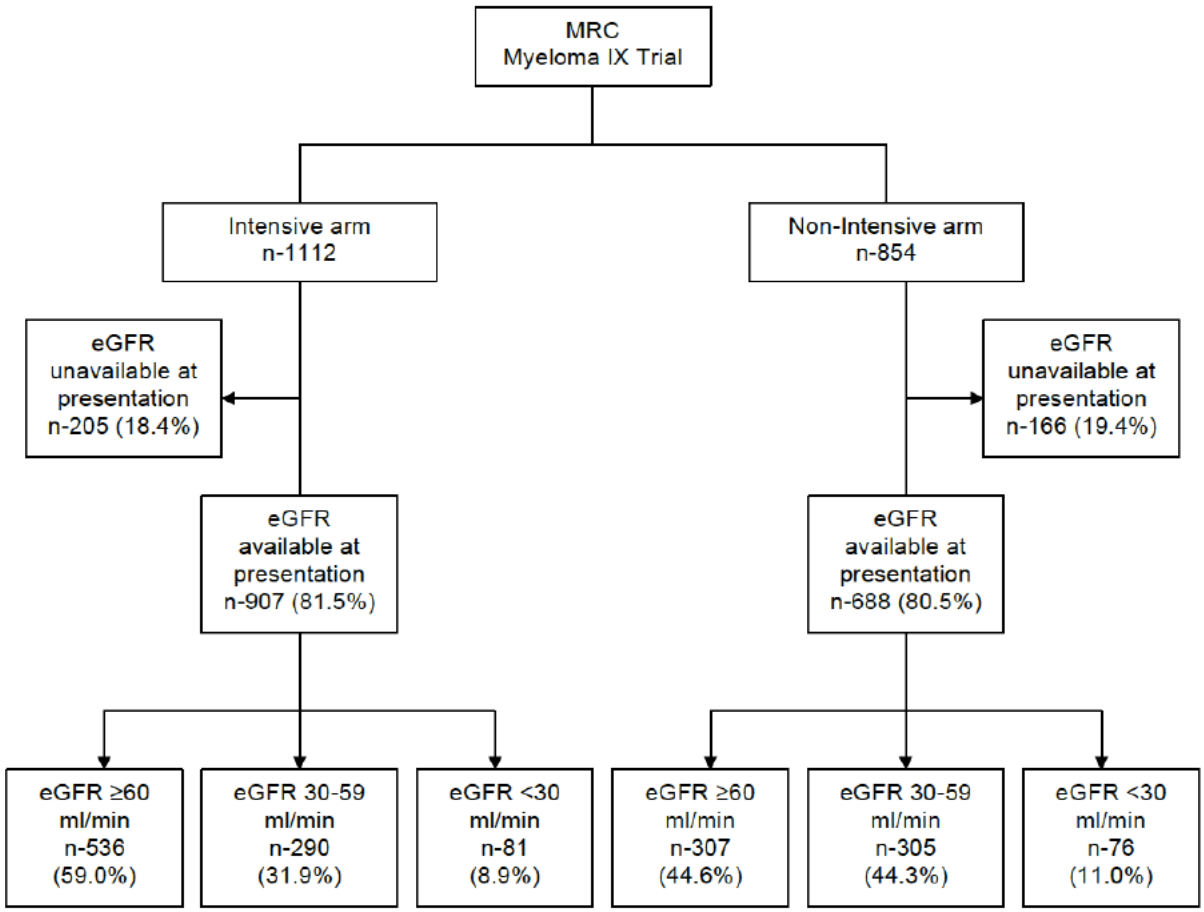
(d) Paraprotein and FLC type

(e) Serum FLC level (Freelite® assays from The Binding Site Ltd., Birmingham, UK)

Myeloma-protein level and urine FLC level were also recorded for patients in Myeloma IX trial, however; as our aim was to study the relationship between serum FLC level at presentation and kidney function, these parameters were excluded from analysis in this study.

eGFR at presentation was calculated using the Modification of Diet in Renal Disease (MDRD) formula i.e. eGFR (ml/min/1.73 m^2) = 186 x (Serum creatinine / 88.4)-1.154 x (Age)-0.203 x (0.742 if female gender) x (1.210 if black ethnicity). Thereafter, patients were divided into three categories depending on their eGFR at presentation. These categories were based on those used in clinical practice for the classification of chronic kidney disease (CKD): no RI (eGFR ≥60 ml/min/1.73 m^2), mild to moderate RI (eGFR 30 59 ml/min/1.73 m^2) and severe RI (eGFR <30 ml/min/1.73 m^2). eGFR distribution for patients recruited from both the treatment arms including those that were excluded from analysis due to non-availability of renal function result at presentation are shown in Figure 3.1.

Figure 3.1 CONSORT diagram showing patient distribution by renal function



3.3.4 Statistical analysis

Statistical analysis was performed using SPSS® for Windows, version 21.0 (SPSS Inc, Chicago, IL) and Graph Pad Prism 5.0 (GraphPad Software Inc, San Diego, CA). Categorical variables were summarised as frequencies and percentages. Comparisons for categorical variables among different groups were made with the chi-square test and Fisher's exact test where appropriate. Continuous variables were expressed as mean and standard deviation (SD) if the data were normally distributed or median with interquartile range (IQR) for non-normally distributed data. Kruskal-Wallis test was used to compare

differences in age, involved kappa FLC level, involved lambda FLC level, involved FLC level as per paraprotein type and eGFR at diagnosis by eGFR categories. Mann-Whitney U test was used to compare the differences in eGFR by gender and treatment arms at diagnosis based on eGFR categories. Differences in the involved serum FLC level at diagnosis for the two FLC isotypes by eGFR categories was also compared by the Mann-Whitney U test. Association between serum FLC level categories and eGFR categories was assessed by the chi-square test. The association between FLC level in serum and severe RI was evaluated by the receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) of sensitivity was plotted against 1-specificity and was reported with a 95% confidence interval (CI). ROC curve analysis was used to determine the optimal cut-off point that maximized the threshold value with the highest specificity and sensitivity for severe RI. Spearman's correlation coefficient (rs) was calculated to evaluate the relationship between age and log10 transformed FLC and eGFR. A multivariable linear regression analysis was performed with factors that were independently associated with eGFR at diagnosis.

3.4 Results

3.4.1 Patient demographics and renal function

1966 patients with newly diagnosed symptomatic MM were recruited in the Myeloma IX trial; 1112 (56.6%) were assigned to the intensive arm and 854 (43.4%) to the non-intensive arm of the trial (Figure 3.1). Renal function from samples sent for central laboratory analyses at diagnosis were available in 1595 patients who are the focus of attention of this study. Out of these 1595 patients, 907 patients were from the intensive arm and 688 patients from the non-intensive arm. The remaining 371 patients had no

samples sent for central laboratory analysis at diagnosis and were excluded from analysis in this study.

Table 3.1 Patient demographics at diagnosis

Variables	**All patients (n-1595)**	**Patients with eGFR ≥60 ml/min (n-843)**	**Patients with eGFR 30 - 59 ml/min (n-595)**	**Patients with eGFR <30 ml/min (n-157)**	***P* value**
Median eGFR at diagnosis (ml/min/1.73 m^2) (IQR)	61 (45 79)	78 (68 92)	48 (40 54)	21 (16 25)	<0.0001
Treatment arm					
Intensive (%)	907 (56.9)	536 (63.6)	290 (48.7)	81 (51.6)	<0.0001
Non-intensive (%)	688 (43.1)	307 (38.4)	305 (51.3)	76 (48.4)	
Median age - years (IQR)	66 (58 73)	64 (57 70)	67 (60 75)	67 (60 73)	<0.0001
Gender					
Male	959 (60.1)	531 (62.9)	342 (57.4)	86 (54.7)	0.049
Female	631 (39.5)	311 (36.9)	250 (42.0)	70 (44.6)	
Unknown	5 (0.3)	1 (0.1)	3 (0.5)	1 (0.6)	
Myeloma Type					
IgG (%)	977 (61.2)	534 (63.3)	371 (62.3)	72 (45.8)	<0.0001
IgA (%)	347 (21.7)	194 (23.0)	130 (21.8)	23 (14.6)	
IgM (%)	9 (0.5)	8 (0.9)	-	1 (0.6)	
IgD (%)	30 (1.9)	13 (1.5)	12 (2.0)	5 (3.2)	
LCO (%)	215 (13.5)	83 (9.8)	76 (12.8)	56 (35.7)	

Non-secretory MM (%)	17 (1.1)	11 (1.3)	6 (1.0)	-	
FLC type					
Kappa (%)	1029 (65.2)	568 (68.3)	373 (63.3)	88 (56.1)	0.006
Lambda (%)	549 (34.8)	264 (31.7)	216 (36.7)	69 (43.9)	
Involved FLC level (mg/L)					
Median Kappa FLC (IQR)	391.20 (79.51 1106.00)	224.10 (36.96 632.20)	474.60 (115.20 1427.00)	2217.00 (668.30 5424.00)	<0.0001
Median Lambda FLC (IQR)	503.00 (90.65 1848.00)	266.90 (57.11 942.10)	722.50 (151.40 2022.00)	3071.00 (1181.00 9079.00)	

Table 3.1 shows the baseline patient characteristics. The median age was 66 years (IQR 58 73) and 959 (60.1%) were of male gender. By renal function group, 843 (52.8%) had an eGFR ≥60 ml/min/1.73 m^2 (no RI); 595 (37.3%) an eGFR 30 59 ml/min/1.73 m^2 (mild to moderate RI); and 157 (9.8%) an eGFR <30 ml/min/1.73 m^2 (severe RI). There was a significant association between age at diagnosis and the severity of RI (*P* <0.0001); patients with RI were older compared to patients with no RI. There was no difference in median eGFR by gender in patients presenting with mild to moderate (*P* = 0.494) or severe RI (*P* = 0.745), however males had a higher eGFR compared to females in the no RI group (males 80 ml/min/1.73 m^2 [IQR 69 93] vs females 75 ml/min/1.73 m^2 [IQR 66 91]) (*P* = 0.006).

Overall a higher number of patients were recruited in the intensive arm compared to the non-intensive treatment arm, this was more evident in patients presenting with no RI at diagnosis compared to those who presented with mild to moderate RI or severe RI (*P* <0.0001). Patients entering the intensive arm with no RI had a greater eGFR at diagnosis compared to those recruited in the non-intensive arm with no RI (intensive arm median eGFR 79 ml/min/1.73 m^2, IQR [69 94] vs non-intensive arm median eGFR 75 ml/min/1.73 m^2, IQR [66 89]) (*P* = 0.0006); no such difference in eGFR at diagnosis was noted in patients presenting with mild to moderate RI (*P* = 0.865) or severe RI (*P* = 0.094).

3.4.2 Paraprotein and FLC isotype distribution and eGFR

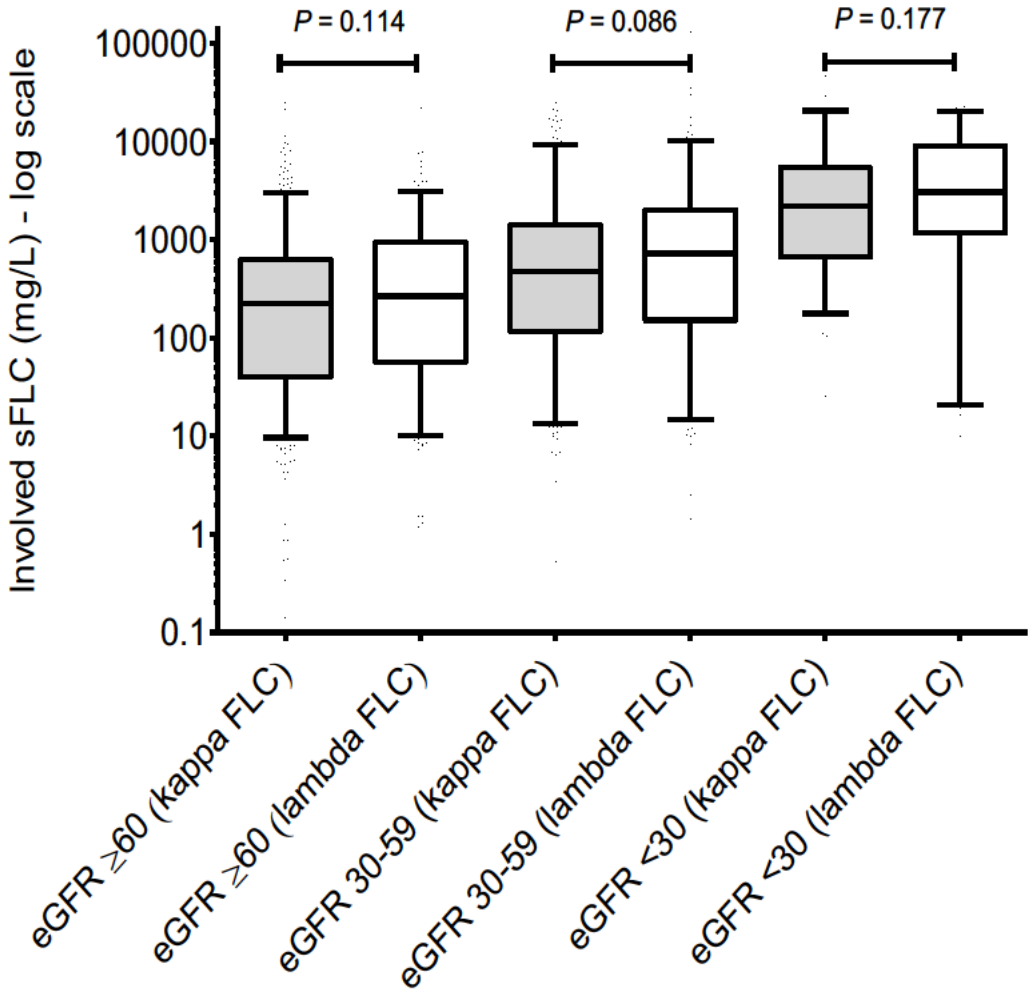
IgG myeloma (61.2%) was the predominant MM type followed by IgA myeloma (21.7%), light chain only myeloma (LCO) (13.5%), IgD myeloma (1.8%), non-secretory MM (1.1%), and IgM myeloma (0.5%) (Table 3.1).

The proportion of patients with LCO myeloma increased with worsening eGFR category, from 9.8% in patients with no RI to 35.6% in patients with severe RI (Table 3.1). The median eGFR was lower for patients with LCO myeloma and IgD MM compared to those with other paraprotein types (LCO myeloma 49.0 [IQR 28.0 80.0]; IgD MM 49.0 [IQR 36.7 83.0]; IgG MM 62.0 [IQR 47.0 79.0]; IgA MM 64.0 [IQR 49.0 80.0]; and IgM MM 65.0 [IQR 60.5 84.5]) (P <0.0001). There was no significant difference in the median age of patients between the paraprotein types (P = 0.220). An involved kappa FLC isotype (65.2%) was more common than an involved lambda FLC (34.8%) (Table 3.1). The median eGFR in patients with an involved lambda FLC paraprotein (58 [IQR 42 77]) was lower at diagnosis compared to patients with an involved kappa FLC (63 [IQR 47 80]) (P =0.008)

3.4.3 Serum FLC level and eGFR

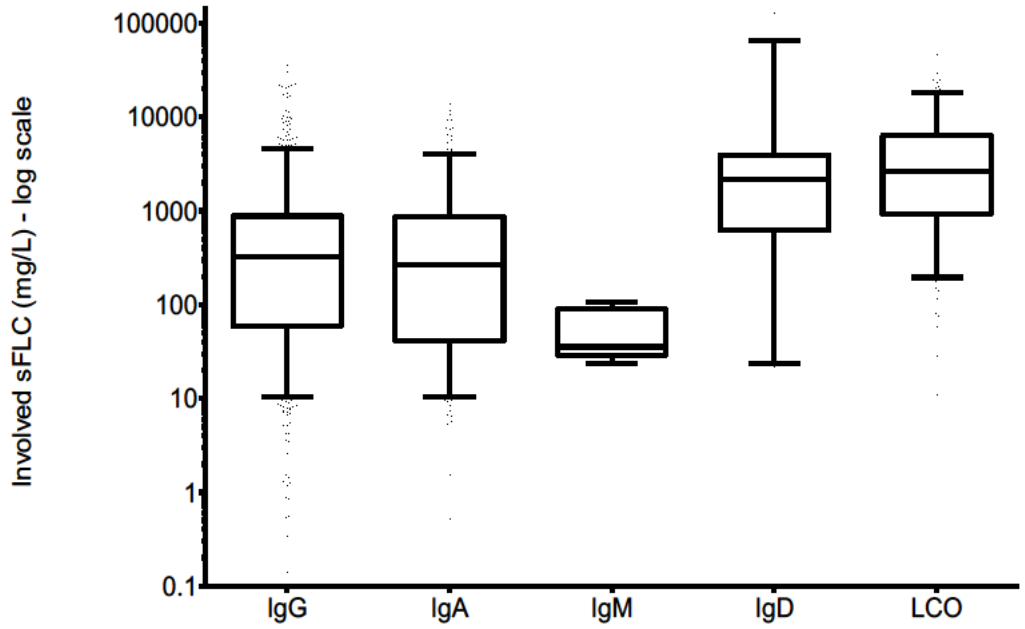
There was a sequential rise in the median involved serum FLC level by eGFR category, irrespective of the FLC isotype (Table 3.1). There was no significant difference in the median involved FLC level at diagnosis between the FLC isotypes for any of the three eGFR categories (Figure 3.2).

Figure 3.2 Serum FLC level distribution by eGFR - showing a progressive rise in serum FLC level with worsening of eGFR category irrespective of the FLC isotype



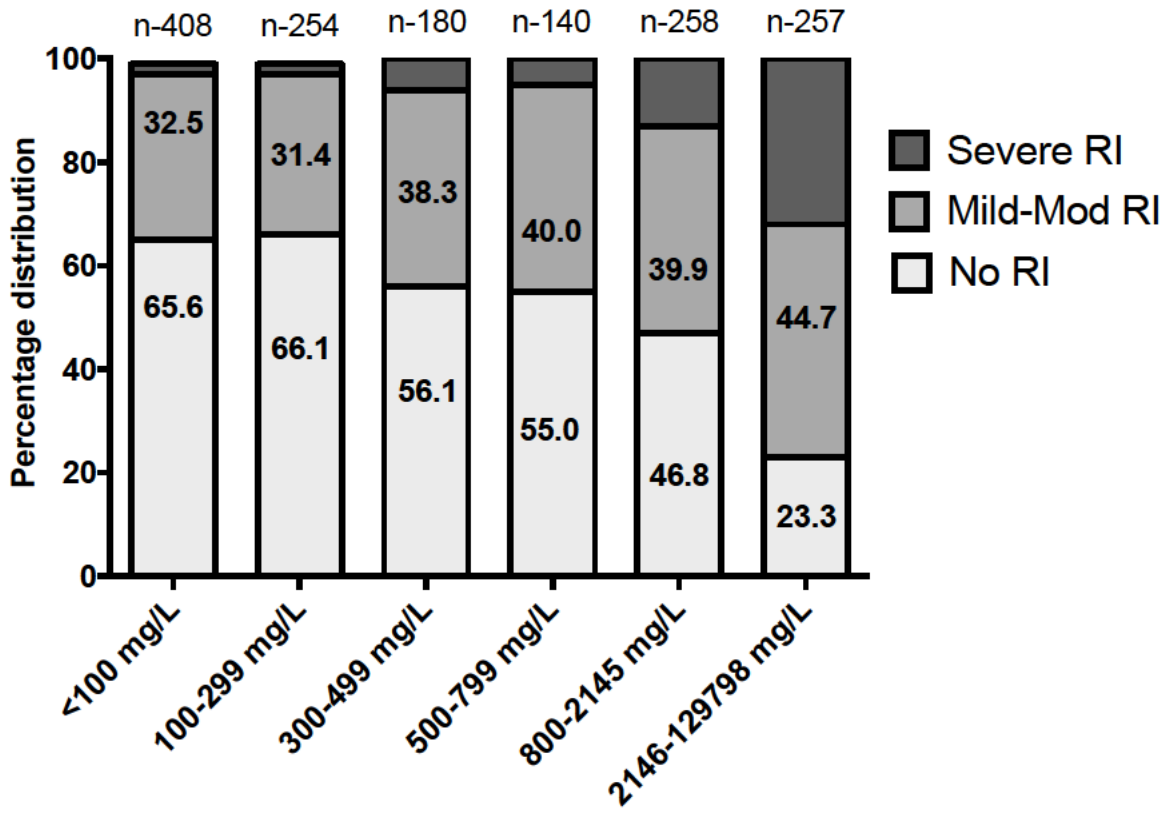
The median involved serum FLC level for patients with LCO myeloma and IgD MM was significantly higher compared to patients with other paraprotein types (Figure 3.3) (*P* <0.0001), consistent with the lower eGFR seen in these patients.

Figure 3.3 Involved serum FLC level by paraprotein isotype



In order to study the relationship of the varying levels of FLC in serum with renal function, patients were grouped on the basis of their eGFR at diagnosis into different serum FLC level categories (Figure 3.4).

Figure 3.4 eGFR distribution across serum FLC level categories



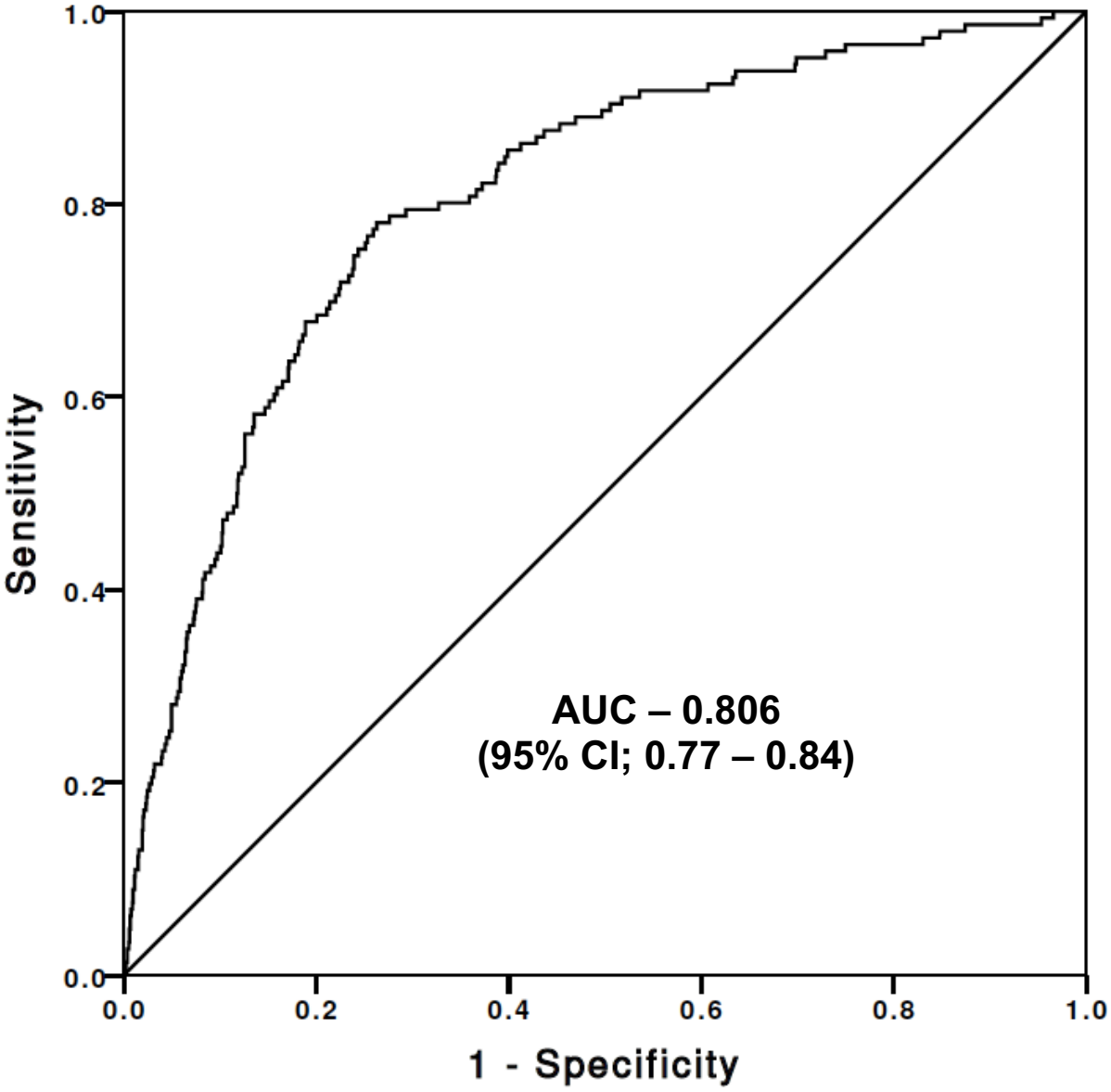
(Depicting increase in proportion of patients presenting with severe RI as serum FLC level at diagnosis rises above 800 mg/L)

On comparing the 408 patients with serum FLC level <100 mg/L with the 254 patients with serum FLC level between 100 299 mg/L, there was no difference in the proportion of patients that had mild to moderate RI (32.6% and 31.5% respectively) or severe RI (1.7% and 2.4% respectively) (P = 0.82). For the 180 patients with a serum FLC level between 300 499 mg/L the distribution of patients with mild to moderate RI increased by approximately 6% and for severe RI by approximately 4%. There was no significant further increase in the distribution of RI in the 140 patients with serum FLC level between 500 799 mg/L (P = 0.94). However, as the serum FLC level increased above 800 mg/L there was an exponential increment in the percentage of patients presenting with severe

RI in comparison to those with serum FLC level less than 800 mg/L (*P* <0.0001) (Figure 3.4).

The association between serum FLC level at diagnosis and severe RI was tested by calculating the composite score for sensitivity and specificity as determined by the ROC curve analysis. The AUC was 0.80 (95% CI 0.77 0.84; *P* <0.001), indicating good predictive value for an eGFR <30 ml/min/1.73 m^2 (Figure 3.5).

Figure 3.5 Receiver operating characteristic (ROC) curve testing the association between serum FLC and eGFR <30 ml/min/1.73 m²



A serum FLC level of 500 mg/L, the level recommended by consensus for the consideration of AKI associated with MCN (Hutchison et al., 2011a) was associated with a sensitivity of 84% and specificity of 60%. However; the optimal FLC cut-off for prediction of eGFR <30 ml/min/1.73 m^2 was 800 mg/L which had a sensitivity of 80% and a specificity of 70%.

3.4.4 Correlations and regression modelling

There were significant correlations between age (r_s -0.174; *P* <0.0001) and log10 transformed serum FLC level (r_s -0.328; *P* <0.0001) with eGFR at diagnosis. Multivariable linear regression modelling incorporating all factors that were associated with eGFR at diagnosis showed a significant independent association with log10 transformed serum FLC level, age and female gender compared to male and not for the paraprotein type or the FLC isotype (Table 3.2).

Table 3.2 Factors associated with eGFR at diagnosis

Factors	Univariable correlation		Multivariable linear regression			
				95% confidence intervals		
	r_s	P value	Beta	Lower	Upper	*P* value
Age	-0.174	0.0001*	-0.277	-0.478	-0.077	0.007
Log10 serum FLC level	-0.328	0.0001*	-13.305	-15.449	-11.162	0.0001
Female gender	-	-	-3.271	0.523	6.019	0.020
IgA Myeloma	-	-	0.406	-2.881	3.693	0.809
IgM Myeloma	-	-	7.802	-13.357	28.961	0.470
IgD Myeloma	-	-	-0.359	-10.203	9.486	0.943
LCO Myeloma	-	-	1.855	-1.663	5.373	0.301
Kappa FLC isotype	-	-	1.198	-1.634	4.029	0.407
Intensive arm	-	-	3.136	-1.023	7.295	0.139

3.5 Discussion

The purpose of this study was to report the relationship between renal function, demographic and myeloma characteristics, with a focus on serum FLC levels, in newly diagnosed patients with MM. An inverse relationship between serum FLC level and eGFR is not surprising; however, the threshold at which the involved FLC clone causes nephrotoxicity is not known. Both the International Myeloma Working Group and the International Kidney Monoclonal Gammopathy research group, propose by means of consensus, a threshold of 1500 mg/L and 500 mg/L respectively to be the level of FLC in serum that is associated with myeloma cast nephropathy (Rajkumar et al., 2014, Hutchison et al., 2011a). Using data collected for the MRC Myeloma IX trial, and perhaps for the first time this association was explored in a large population based study which showed that the risk of severe RI as defined by an eGFR <30 ml/min/1.73 m^2 at diagnosis, became substantial when the serum FLC were >800mg/L.

It is however important to understand that it is beyond the scope of this study to tease the threshold of FLC associated nephrotoxicity in patients with MM from the prolonged FLC half-life that can otherwise occur in patients with either an acute or a slow decline in GFR. The Myeloma IX trial recruited patients with MM and RI irrespective of their presenting with either an AKI or an acute on CKD.

RI at diagnosis is an important, potentially modifiable risk factor in patients with MM. In the MRC Myeloma IX trial, patients requiring dialysis or at a high-risk of requiring dialysis were excluded from recruitment. Despite this 47% of patients had an eGFR <60

ml/min/1.73m^2, that included 37.3% of patients with an eGFR 30 59 ml/min/1.73 m^2 (mild to moderate RI) and 9.8% with an eGFR <30 ml/min/1.73 m^2 (severe RI).

There are no kidney biopsy series that have systematically reported findings from newly diagnosed MM patients with mild to moderate RI. Thus, in most patients with MM it is not known to what proportion the mild to moderate RI at diagnosis is attributable to: a) nephrotoxicity of the excess monoclonal FLC clone, b) other myeloma-related causes of RI, and/or c) longstanding and largely irreversible RI due to unrelated comorbidities.

In this study, the proportion of patients with mild to moderate RI at diagnosis was 37.3%, which compared to a CKD prevalence of 25% for age- and gender-matched populations from which these MM patients were recruited (Hoerger et al., 2015, Zoccali et al., 2010). This is consistent with two-thirds of the mild to moderate RI in this cohort being of longstanding origin and unrelated to the new diagnosis of MM. The elevated FLC level in these patients is partly due to the prolonged FLC half-life that occurs due a reduction in GFR and from the increased FLC secretion by the neoplastic clone. In the remaining one-third of patients presenting with mild to moderate RI the cause for renal dysfunction could either be from: nephrotoxicity of the secreted FLC clone; other myeloma-associated causes of RI such as hypercalcaemia, use of non-steroidal anti-inflammatory drugs, and intercurrent infection. The median serum FLC level irrespective of the light chain isotype amongst patients presenting with mild to moderate RI was 494 mg/L (IQR 128 1703).

On assessing patients with mild to moderate RI for serum FLC level at diagnosis we found mild to moderate RI in: 32.5% of patients with a serum FLC level <100 mg/L, 31.4% with a serum FLC level 100 299 mg/L and 38.3% with a serum FLC level 300 499 mg/L. Only

at a serum FLC level >2146 mg/L was there a significant increment in the proportion of patients (44.7%) with mild to moderate RI (P <0.001) (Figure 3.4). These findings indicate that only around 12% of MM patients with mild to moderate RI may have had RI secondary to FLC nephrotoxicity and in the remaining patients RI was most likely due to other causes.

In patients with MM and severe RI at diagnosis, renal biopsy studies have shown that the predominant lesion in up to 90% of patients is MCN, which is a direct consequence of excess monoclonal FLC production (Hutchison et al., 2012b). The percentage of patients presenting with severe RI in this study that excluded patients close to requiring or on dialysis, was approximately five-fold the reported prevalence of RI in an age- and gender-matched adult population (Jain et al., 2014, Zoccali et al., 2010). This is consistent with most of the severe RI observed in this study being attributable to the nephrotoxic FLC secreted in large quantities rather than any pre-existing unrelated comorbidities. Also all patients presenting with RI at MM diagnosis were investigated and treated for any myeloma-related causes of RI, such as dehydration and hypercalcaemia, prior to their recruitment in the MRC Myeloma IX trial.

FLC have differential nephrotoxicity. In studies that have reported on MCN, the FLC level in serum associated with the lesion can range by 100-fold; conversely some patients have no RI despite very high levels of FLC. The current study reinforces this observation; 19 (2.2%) of the 843 patients with no RI had levels of serum FLC above 5000 mg/L. Animal models and some previous clinical reports indicate that MCN can develop in some patients at far lower serum FLC levels than are present in many patients with normal

renal function (Sanders and Booker, 1992), indicating that nephrotoxicity of FLC varies greatly between patients.

LCO myeloma in the current study was associated with a lower eGFR compared to other paraprotein isotypes; this was specifically related to the serum FLC level and is not a function of the myeloma isotype. This finding is consistent with a previous study, which reported higher urinary FLC levels in patients with LCO MM compared to patients with IgG MM and IgA MM (Drayson et al., 2006); in that study RI was directly related to the urinary FLC levels. IgD MM was found in 1.8% of patients in the current study and the association of RI with elevated serum FLC levels at diagnosis was present in this group of patients as well. This and the possibility that IgD myeloma may still be diagnosed later than other myeloma types is under investigation in a larger cohort of patients.

78.4% of patients with LCO MM had a FLC ≥800 mg/L and 68.2% of these had RI. In comparison, only 27.2% of patients with an intact paraprotein myeloma had a serum FLC ≥800 mg/L and 63.2% of these patients had RI, further illustrating that the relationship with renal function is related to the FLC level in serum and not the paraprotein type. This finding was confirmed in a multivariable linear regression model where serum FLC level was the factor with the strongest association with eGFR; this relationship was independent of age and gender at diagnosis.

3.6 Study limitations

It is an analysis of the MRC Myeloma IX trial that relied on data collected by the study centres at the time of recruitment. In 371 patients, no samples for renal function test were

sent for central laboratory analysis and hence these patients had to be excluded from this study. Also patients receiving or at high risk of requiring dialysis were not recruited, as a result the association between FLC induced nephrotoxicity and serum FLC level could not be evaluated in dialysis patients. Renal biopsy data were unavailable and hence relationship between serum FLC levels with MCN or other well-defined histological pattern of renal injury seen in patients with MM could not be studied. Lastly, these results are only applicable to the Freelite® assay and have not been validated in the other available FLC assays (te Velthuis et al., 2011, Campbell et al., 2013)

3.7 Relevance to clinical practice

A serum FLC level >500 mg/L was thought to be associated with nephrotoxicity in patients with MM for some time; however, it is for the first time that this association has been studied in such a large population based study. Severe RI defined as estimated GFR <30 ml/min/1.73 m^2 best correlated with serum FLC levels >800 mg/L above finding re-affirms the link between FLC level in serum and nephrotoxicity and sets a threshold that informs both clinicians and patients of the risk of nephrotoxicity in patients with a new diagnosis of MM. Associations between serum FLC level and well-defined typical histological pattern namely myeloma cast nephropathy has not been evaluated in this study and will be addressed in the chapter 5.

3.8 Conclusion

In conclusion, in this study that included patients with RI but excluded those who were dialysis dependent, there was a strong relationship between higher serum FLC levels at diagnosis and the severity of RI, with a greater sensitivity and specificity for a FLC level

>800 mg/L with severe RI irrespective of the paraprotein type. Further studies are now required to more accurately evaluate the impact of the early reduction of high serum FLC levels on RI in patients with MM, and to assess if this is associated with better long-term renal function and overall survival.

CHAPTER FOUR: ASSOCIATION BETWEEN SERUM FLC RESPONSE AND RENAL RESPONSE POST-INDUCTION – A MYELOMA IX TRIAL ANALYSIS

4.1 Introduction

Outcomes in MM have significantly improved over the last 10-15 years. With rising number of patients achieving a deep haematological response, more stringent definitions have been developed to classify response in patients with MM (Kumar et al., 2016). Renal impairment at presentation is a marker of aggressive disease and is associated with poor outcome. Achieving disease response (especially complete response) has been widely accepted as a marker of favourable overall and disease free survival (Gay et al., 2011). Similar findings have also been linked to renal function recovery albeit in smaller studies (Hutchison et al., 2011b, Hutchison et al., 2009).

4.2 Aim

The aim of this study was to assess the relationship between disease response using the serum FLC response criteria and renal response post-induction (PI) by eGFR category in newly diagnosed patients with MM.

4.3 Methods

The study design and the protocol for the MRC Myeloma IX trial have already been explained in chapter 3.

4.3.1 Patients

All newly diagnosed patients with MM recruited in the intensive and non-intensive treatment arms of the Myeloma IX trial, who had blood samples sent for central laboratory analysis both at entry to the trial as well as in the post-induction (PI) period were eligible to participate in this study. Ethical approval for secondary analyses of data

from the Myeloma IX trial was already available and hence no further approval was sought for this study.

4.3.2 Data collection

Following data were collected:

(a) Age

(b) Gender

(c) Paraprotein type

(d) M-protein level

(e) Serum FLC level at presentation and PI

(f) Serum creatinine level at presentation and PI

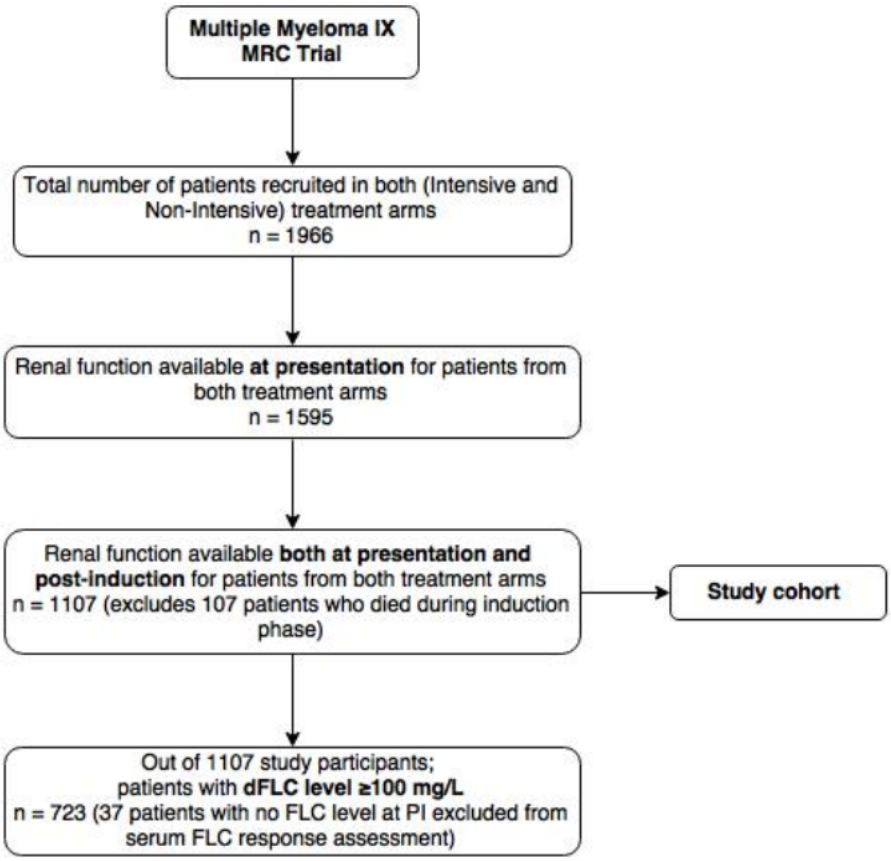
The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula: eGFR (ml/min/1.73 m^2) = 186 x (Serum creatinine / 88.4) $^{1.154}$ x (Age) $^{0.203}$ x (0.742 if female) x (1.210 if black) both at presentation and PI.

4.3.3 Serum FLC response at PI

A haematological disease response in the Myeloma IX trial was reported based on the reduction in M-protein level or serum FLC level if the serum or urine M-protein was undetected. However in this study, in order to maintain uniformity in the assessment of the disease response serum FLC response criteria was used to measure haematological response for all patients (Durie et al., 2006). As a result, only those patients with a difference between involved and uninvolved FLC level (dFLC) of greater than 100 mg/L at presentation were included in the study for the measurement of the serum FLC response. Patients were grouped into the following two haematological response

categories: very good partial response and greater (≥VGPR), if they demonstrated >90% decrease in the difference between the involved and uninvolved serum FLC levels; or partial response and below (≤PR), if they achieved ≥ 50% reduction in the difference between the involved and uninvolved serum FLC level (Figure 4.1).

Figure 4.1 CONSORT diagram showing distribution of patients



4.3.4 Renal response at PI

Patients were divided into three categories based on their presentation eGFR (ml/min/1.73 m^2) to provide a renal impairment (RI) category based on those used in clinical practice for the classification of chronic kidney disease (CKD): no RI (eGFR ≥60

ml/min/1.73 m^2), mild to moderate RI (eGFR 30 59 ml/min/1.73 m^2) and severe RI (eGFR <30 ml/min/1.73 m^2).

In patients presenting with an eGFR <60 ml/min/1.73 m^2 a favourable renal response at PI was defined as an improvement in eGFR either above ≥60 ml/min/1.73 m^2 or an eGFR <60 ml/min/1.73 m^2 but above ≥30 ml/min/1.73 m^2 for patients presenting with eGFR <30 ml/min/1.73 m^2 i.e. *'renal responders'*. An unfavourable renal response was defined as worsening of eGFR category at PI relative to the renal function at presentation i.e. *'deteriorators'*. Those presenting with an eGFR <60 ml/min/1.73 m^2 and showing neither an improvement or worsening of renal function at PI were classified as having maintained renal function i.e. *'renal non-responders'*.

4.3.5 Statistical analysis

Statistical analysis was performed using SPSS® for Windows, version 21.0 (SPSS Inc, Chicago, IL) and GraphPad Prism 5.0 (GraphPad Software Inc, San Diego, CA). Categorical variables were summarised as frequencies and percentages. Comparisons for categorical variables among different groups were made with the chi-square test and Fisher's exact test where appropriate. Continuous variables were expressed as mean and standard deviation (SD) if the data was normally distributed or median with interquartile range (IQR) for non-normally distributed data. Kruskal-Wallis test was used to compare the differences in age, involved kappa (κ) FLC, involved lambda (λ) FLC level, and eGFR at presentation by eGFR categories for the baseline data. Mann-Whitney *U* test was used to compare the differences in age, presentation eGFR, presentation FLC level, and the PI eGFR in patients who achieved a renal response at PI. A multivariable logistic regression

analysis was performed to identify variables that are associated with RI (eGFR <60 ml/min/1.73 m^2) at PI. A two-tailed *P* value of <0.05 was considered statistically significant.

4.4 Results

4.4.1 Patient distribution

1107 patients who had renal function results available from samples that were sent for central laboratory analysis at presentation and at PI were included (107 patients had died during the induction period and renal function at PI was missing in 381 patients); 660 patients were from the intensive arm and 447 patients from the non-intensive arm (Figure 4.1).

Patient characteristics at presentation are shown in Table 4.1. The median age was 65 years (IQR 58 72), and 685 (61.8%) patients were of male gender. At presentation, 612 (55.3%) patients had an eGFR ≥60 ml/min/1.73 m^2 (no RI); 389 (35.1%) an eGFR 30 59 ml/min/1.73 m^2 (mild to moderate RI); and 106 (9.5%) an eGFR <30 ml/min/1.73 m^2 (severe RI). Patients with RI were older compared to those with no RI (*P* <0.0001).

Table 4.1 Patient demographics

Variables	All patients (n – 1107)	Patients with eGFR ≥60 ml/min (n – 612)	Patients with eGFR 30 - 59 ml/min (n – 389)	Patients with eGFR <30 ml/min (n – 106)	*P* value	Missing data (n – 381)
Median age - years (IQR)	65 (58 – 72)	63 (57 – 70)	67 (59 – 75)	65 (59 – 71)	<0.0001	67 (58 – 73)
Gender						
Male (%)	685 (61.8)	390 (63.7)	234 (60.1)	61 (57.5)	0.330	217 (56.9)
Female (%)	422 (38.1)	222 (36.2)	155 (39.8)	45 (42.4)		164 (43.0)
Myeloma Type						
IgG (%)	688 (62.1)	388 (63.3)	252 (64.7)	48 (45.2)	<0.0001	227 (59.5)
IgA (%)	238 (21.4)	140 (22.8)	83 (21.3)	15 (14.1)		86 (22.5)
IgM (%)	7 (0.6)	6 (0.9)	-	1 (0.9)		2 (0.5)
IgD (%)	24 (2.1)	10 (1.6)	10 (2.5)	4 (3.7)		5 (1.3)
LCO (%)	140 (12.6)	60 (9.8)	42 (10.7)	38 (35.8)		56 (14.6)
Non-secretory MM (%)	10 (0.9)	8 (1.3)	2 (0.5)	-		5 (1.3)

FLC type						
Kappa (κ) (%)	731 (66.6)	417 (69.0)	256 (66.1)	58 (54.7)	0.015	239 (63.5)
Lambda (λ) (%)	366 (33.3)	187 (30.9)	131 (33.8)	48 (45.2)		137 (35.9)
Involved FLC level (mg/L)						
Median κFLC (IQR)	376.00 (78.00 – 1077.00)	241.08 (42.32 – 582.56)	468.00 (132.22 – 1218.00)	2420.00 (1003.50 – 5443.50)	<0.0001	406.84 (68.53 – 1297.50)
Median λFLC (IQR)	493.48 (74.74 – 1844.50)	255.06 (52.70 – 988.50)	705.94 (173.20 – 2543.50)	2780.00 (1054.75 – 6593.00)	<0.0001	435.96 (126.45 – 1552.75)
Median eGFR at presentation (ml/min/1.73 m²)	63.00 (46.00 – 81.00)	78.00 (68.08 – 90.00)	48.00 (40.94 – 54.13)	20.00 (16.00 – 24.74)	<0.0001	59 (43.79 – 76.89)
Treatment arm						
Intensive (%)	660 (59.6)	399 (65.1)	195 (50.1)	66 (62.2)	<0.0001	204 (54.1)
Non-intensive (%)	447 (40.3)	213 (34.8)	194 (49.8)	40 (37.7)		173 (45.8)

IgG myeloma (62.1%) was the commonest paraprotein type, followed by IgA myeloma (21.4%), light chain only myeloma (LCO) (12.6%), IgD myeloma (2.1%), non-secretory myeloma (0.9%), and IgM myeloma (0.6%). An involved κFLC isotype was more common than a λFLC isotype in patients with no RI and in those with mild to moderate RI; however, there was a skew from the normal 2:1 κ-λ FLC ratio to a near equal distribution between the two involved light chain isotypes in patients with severe RI.

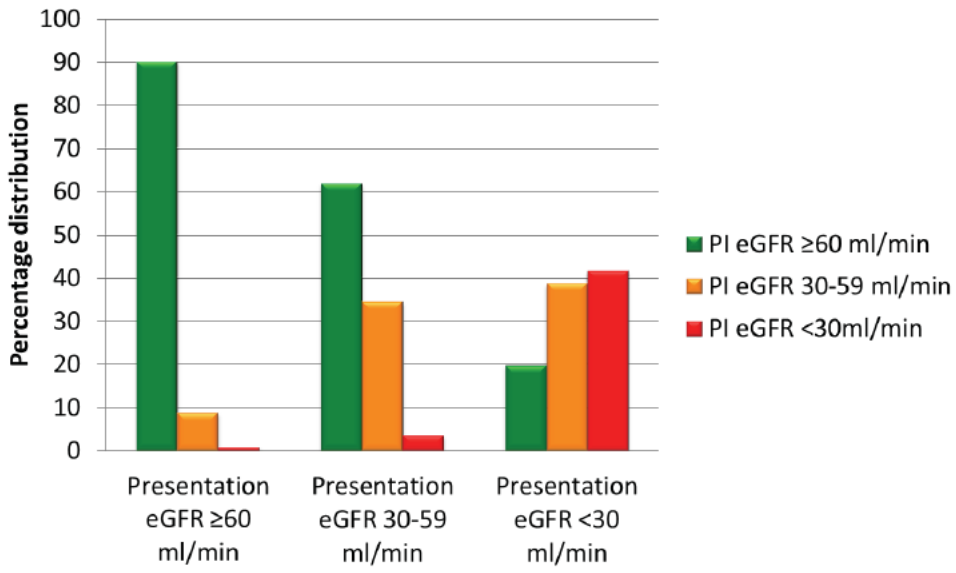
Patients recruited from the intensive arm and those with an eGFR ≥60 ml/min/1.73 m^2 at presentation had a higher eGFR (median 80.00 [IQR 70.00 90.00] ml/min/1.73 m^2) compared to those from the non-intensive arm (median 75.00 [66.00 88.50] ml/min/1.73 m^2 (P = 0.002); there was no significant difference in the eGFR at presentation between the two treatment arms for patients with mild to moderate RI and severe RI. There was also no significant difference in the involved serum FLC levels at presentation for the two FLC isotypes for the corresponding eGFR category.

4.4.2 Response at PI

4.4.2.1 Overall renal response

Four hundred and ninety-five (44.7%) of the total 1107 patients presented with an eGFR ≤60ml/min/1.73 m^2 and 303 (61.2%) of these patients had improved renal function by at least one stage by the PI period (Figure 4.2). Two hundred and fifty-two (22.7%) of the total 1107 patients with presentation eGFR <60 ml/min/1.73 m^2 had either sustained a drop in eGFR category or had no improvement in their eGFR between presentation and PI.

Figure 4.2 Renal response at PI



For each eGFR category and out of the 612 patients presenting with no RI at diagnosis, 552 (90.1%) patients maintained renal function at PI, 54 (8.8%) patients developed mild to moderate RI and 6 (0.9%) patients developed severe RI. For the 389 patients presenting with mild to moderate RI, 241 (61.9%) patients recovered normal renal function, 134 (34.4%) patients remained with mild to moderate RI, and 14 (3.5%) patients developed severe RI. For 106 patients presenting with severe RI, 21 (19.8%) patients recovered normal renal function, 41 (38.6%) patients had an improvement in renal function to mild to moderate RI, and 44 (41.5%) patients remained in severe RI.

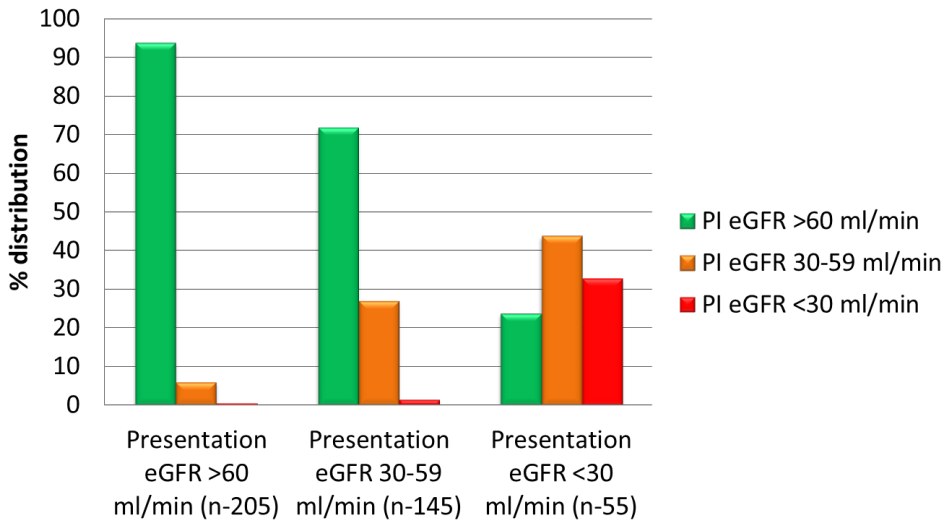
4.4.2.2 Renal response as per serum FLC response

A ≥VGPR was seen in 405 (56.0%) patients and a ≤PR in 318 (43.9%) patients. Patients who presented with RI and subsequently achieved recovery of renal function at PI were more likely to have demonstrated a ≥VGPR serum FLC response; conversely, a ≤PR

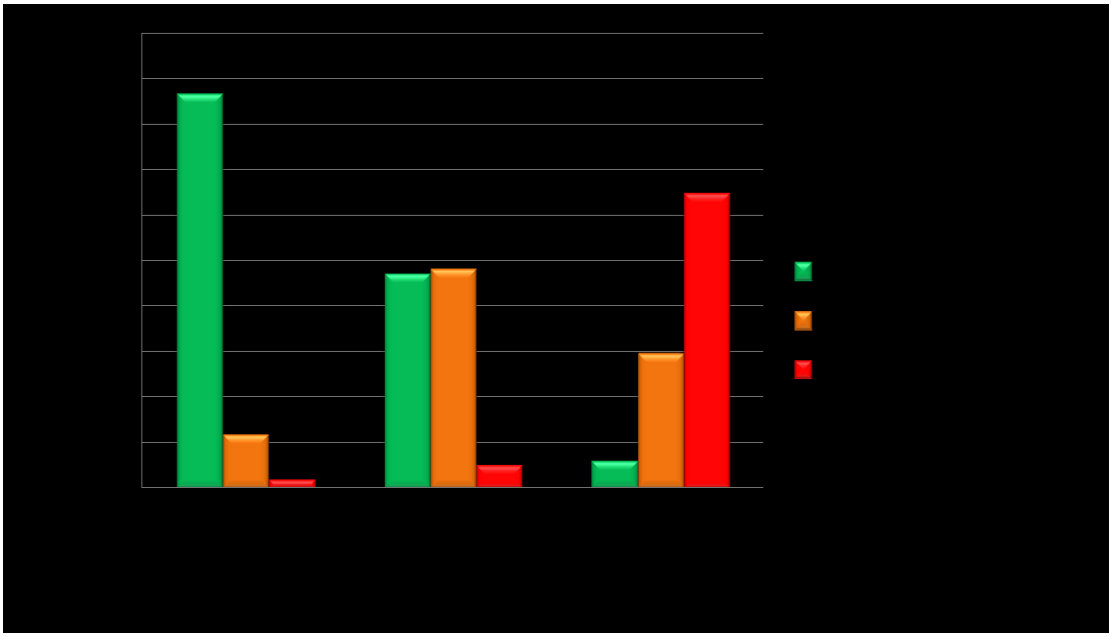
response was more common in patients who had deterioration in renal function at PI (Figure 4.3).

Figure 4.3 Renal response at PI by serum FLC response category; (a) more than or equal to VGPR, and (b) less than or equal to PR

(a)



(b)

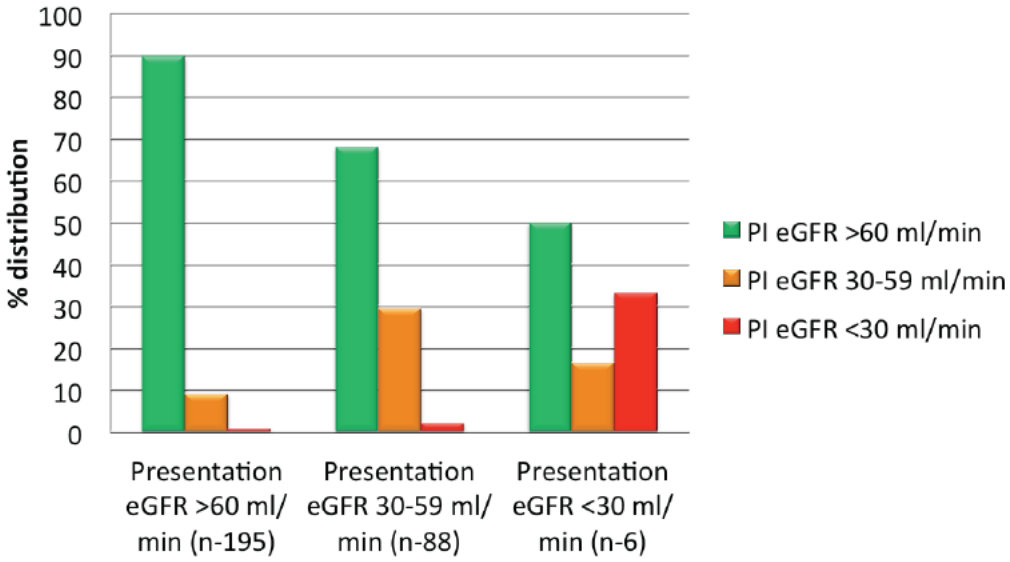


There was no significant difference in the eGFR at diagnosis for patients who attained either a ≥VGPR or a ≤PR serum FLC response at PI (*P* = 0.925); however patients who achieved a ≥VGPR serum FLC response were younger compared to those with a ≤PR (62 years, IQR [56 69] vs 69 years, IQR [61 75] respectively; *P* value <0.0001) and had a higher presentation FLC levels at diagnosis (765.5 mg/L, IQR [362.3 2617.0] vs 630.7 mg/L, IQR [245.4 1581.0]; *P* value 0.0004). Following anti-myeloma treatment, patients who achieved a ≥VGPR serum FLC response had a better eGFR at PI compared to those with ≤PR (median 78.00 ml/min/1.73 m^2, IQR [60.50 90.00] vs median 69 ml/min/1.73 m^2; IQR [51.00 90] respectively; *P* <0.0001).

4.4.2.3 Patients with dFLC level <100 mg/L

Two hundred and eighty-nine patients at diagnosis had a dFLC level <100 mg/L; of these 195 (67.5%) patients presented with eGFR ≥60 ml/min/1.73 m^2, 88 (30.4%) patients with an eGFR 30 59 ml/min/1.73 m^2 and 6 (2%) patients with eGFR <30 ml/min/1.73 m^2. Amongst those presenting with RI at presentation, an improvement in renal function by at least one stage at PI was noted in 64 (68.1%) patients, whilst only 2 (2.1%) patients had worsening of renal function, one of whom had a significant rise in serum FLC levels at PI. For patients who had no RI at presentation, only 20 (10.2%) patients exhibited worsening of renal function at PI (Figure 4.4)

Figure 4.4 Renal Response at PI in patients with dFLC <100 mg/L



4.4.3 Renal responders' vs Renal non-responders and/or deteriorators

Of 723 patients with dFLC levels above 100 mg/L and following exclusion of 349 patients who both presented and maintained an eGFR ≥60 ml/min/1.73 m^2 at PI, an improvement in renal function at PI was noted in 222 patients. The characteristics of patients who achieved an improvement in renal function at PI compared to those who developed worsening or demonstrated no change in renal function is shown in Table 4.2.

Table 4.2 Characteristics of renal responders vs renal non-responders and deterioraters as per serum FLC response criteria

Variables	Renal responders n – 222	Renal non-responders and deteriorators n – 189	*P* value
Age (years) [IQR]	64 [57 71]	70 [62 76]	<0.0001*
Male gender (%)	132 (59.5)	107 (56.6)	0.560
Female gender (%)	90 (40.5)	82 (43.4)	
Presentation eGFR (ml/min/1.73 m^2) [IQR]	45.00 [31.00 53.25]	43.00 [33.00 55.00]	0.689
Presentation FLC (mg/L) [IQR]	1036.00 [443.60 3244.00]	1037.00 [349.90 3254.00]	0.554
Whole Ig MM (%)	181 (81.5)	146 (77.2)	0.283
LCO MM (%)	41 (18.5)	43 (22.8)	
κFLC isotype (%)	147 (66.2)	115 (60.8)	0.259
λFLC isotype (%)	75 (33.8)	74 (39.2)	
Intensive arm (%)	142 (64.0)	72 (38.1)	<0.0001*
Non-intensive arm (%)	80 (36.0)	117 (61.9)	
PI eGFR (ml/min/1.73 m^2) [IQR]	73.00 [62.00 90.00]	47.00 [29.00 54.50]	<0.0001*
≥VGPR	141 (67.1)	72 (40.0)	<0.0001*
≤PR	69 (32.9)	108 (60.0)	

Although renal responders were younger at diagnosis (*P* <0.0001), there was no significant difference in eGFR at presentation between the two-groups (*P* = 0.689). Serum FLC levels at presentation was also not significantly different between patients who exhibited an improvement in renal function at PI compared to those who did not (*P* = 0.554). There was no association between the paraprotein types or the involved FLC light chain isotypes at diagnosis in patients who achieved a renal response compared to those who did not. Patients who achieved an improvement in renal function at PI were more likely to have been in the intensive treatment arm than the non-intensive treatment arm

(*P* <0.0001) and demonstrated a ≥VGPR disease response compared to ≤PR response (*P* <0.0001).

4.4.4 Predictors of renal impairment (eGFR <60 ml/min/1.73 m^2) at PI

A multivariable logistic regression model was fitted to identify factors that were associated with RI at PI (Table 4.3). eGFR at presentation was the most important variable that predicted RI; there was a 7% reduction in the probability of RI at PI in patients who had a higher eGFR at diagnosis (OR 0.93, 95% CI 0.924 0.946; *P* <0.0001). Higher age at presentation was associated with an increased likelihood of RI at PI (OR 1.036, 95% CI 1.005 1.068; *P* = 0.024) and achievement of a ≥VGPR haematological response compared to ≤PR was associated with a decreased likelihood of RI at PI (OR 0.501, 95% CI 0.325 0.771; *P* = 0.002).

Table 4.3 Predictors of RI at PI as per serum FLC response criteria

Factors	**Logistic regression**			
		95% confidence interval		
	Odds ratio	**Lower**	**Upper**	***P* value**
Age	1.036	1.005	1.068	0.024*
Male vs Female	0.877	0.582	1.323	0.533
LC MM vs *Whole Ig MM*	1.502	0.876	2.575	0.139
λFLC vs κFLC	1.323	0.862	2.031	0.200
Presentation FLC	1.000	1.000	1.000	0.655
Presentation eGFR	0.935	0.924	0.946	<0.0001*
≥VGPR vs ≤PR	0.501	0.325	0.771	0.002*
Intensive arm vs Non-intensive arm	0.578	0.310	1.080	0.086

(Underlined factors are reference value)

4.5 Discussion

This study emphasises the association between RI at presentation and at PI in patients presenting with newly diagnosed MM as well as the importance of achieving an optimal disease response in achieving a favourable renal response. Patients with RI (<60 ml/min/1.73 m^2) at PI were more likely to have also presented with RI at diagnosis.

Several studies have stressed the importance of achieving an optimal disease response in patients with MM (Gay et al., 2011, Harousseau et al., 2009, Niesvizky et al., 2008, Moreau et al., 2011a, van de Velde et al., 2007). Disease response may also be linked to renal function recovery, which may contribute to a better OS in patients with MM (Hutchison et al., 2009, Hutchison et al., 2011b). There have been tremendous advances in the understanding of pathobiology of MM over the last 15 years which has led to the development of more stringent diagnostic criteria in assessing disease response in patient with MM and also risk-stratification of patients at presentation and in the post-treatment phase. In a recent retrospective analyses of 609 newly diagnosed MM patients, those achieving a CR showed significantly longer OS (median 128 months) compared to those in PR (75 months) or less than PR (28 months) (Lahuerta et al., 2017). They also found that the survival benefit in those attaining CR was specifically attributed to the achievement of a minimal residual disease (MRD) negative state. One mechanistic finding in this current study that supports this report is that patients who achieved ≥VGPR at PI were more likely to demonstrate an improvement in kidney function compared to those who achieved ≤PR (Figure 4.3). This finding was not related to serum FLC level at presentation (Table 4.2 and Table 4.3).

Conversely, in patients with eGFR ≥60 ml/min/1.73 m^2 at diagnosis and at PI, disease response appeared to play a minor role in the maintenance of renal function recovery. A plausible explanation of the above finding could be the low level of serum FLC that was seen in this group of patients. This finding again leads to a probable link to a level of FLC in serum beyond which the involved FLC has the potential of causing nephrotoxicity.

Renal impairment was present in 94 of 289 patients who presented with dFLC levels below 100 mg/L. These patients were excluded from serum FLC response assessment at PI. In the absence of any additional data in this group of patient, contributors to cause of RI at presentation may have variably included concomitant use of nephrotoxic medications at time of diagnosis, intercurrent illness, hypercalcaemia, and chronic kidney disease.

4.6 Study Limitation

Renal function at PI was missing in 381 patients, 58 patients had no serum FLC level available at presentation, and they were hence excluded from analysis. Disease response was measured using serum FLC response criteria hence 289 patients with dFLC less than 100 mg/L did not have a disease response assessment. Patients from both the intensive and non-intensive groups were included in this study and there may have been an inherent bias as patients from the intensive arm may have demonstrated better disease response and hence renal response compared to those who were deemed to be unfit to receive intensive arm chemotherapy. In patients presenting with dFLC <100 mg/L and RI, the cause of nephrotoxicity at presentation in these patients although unclear but

could be related to additional external factors such as nephrotoxic medications, intercurrent illness, and or hypercalcaemia.

4.7 Relevance to clinical practice

This is the first time that an association between kidney function (eGFR) both at presentation and at PI has been linked to disease response in a large multicentre study. It does however pose certain relevant questions that are perhaps beyond the scope of this study.

1. Renal function recovery in patients presenting with severe RI is associated with survival outcome and so is achieving an optimum haematological disease response. In patients where the RI may be secondary to the nephrotoxic FLC and in absence of any other factors responsible for the RI should adjustment of chemotherapy be considered?
2. Should serum FLC response criteria be used for measurement of disease response for all patients irrespective of paraprotein type? Serum FLC has a short half-life compared to intact immunoglobulin and may direct early changes in therapy. The optimal time point for switching therapy for patients who fail to demonstrate both a favourable disease response and/or renal response may require investigation.

4.8 Conclusion

In conclusion, renal function at presentation is a determinant of RI post induction; this was irrespective of age and serum FLC level at presentation. Patients who attained a VGPR or above were more likely to achieve renal function recovery at PI compared to those who achieve a PR or below disease response. More research needs to be

undertaken to ascertain the optimum time for treatment switch in patients who present with RI and fail to achieve an optimal haematological disease response.

The relationship of disease response and clinical outcomes will be explored again in Chapter 6 of the thesis.

CHAPTER FIVE: SERUM FLC LEVEL AT DIAGNOSIS IN MYELOMA CAST NEPHROPATHY – A MULTICENTRE STUDY

5.1 Introduction

Renal impairment (RI) is reported in up to 50% of patients with multiple myeloma (MM) at presentation (Augustson et al., 2005, Blade et al., 1998, Knudsen et al., 2000, Kyle et al., 2003, Knudsen et al., 1994). Severe RI as defined by an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 is present in up to 20% (Dimopoulos et al., 2014a) of MM patients at diagnosis, this approximates to the level of renal function defined in the CRAB classification system (International Myeloma Working, 2003). The predominant cause for severe RI is the pathognomonic distal tubular lesion, myeloma cast nephropathy (MCN), a direct consequence of the secreted monoclonal immunoglobulin (Ig) free light chain (FLC) (Hutchison et al., 2012b). The level of pathogenic FLC that causes MCN varies substantially and there is uncertainty about the threshold level that should be used to inform clinical practice (Sanders and Booker, 1992).

A paradigm shift in the management of patients with MM has been the development of the serum FLC assay (Bradwell et al., 2001), which is also the test recommended by the International Myeloma Working Group (IMWG) for the screening of patients with a suspected paraproteinemia (Dispenzieri et al., 2009). The IMWG recently revised the criteria for the diagnosis of MM and included a serum FLC ratio >100 in association with an involved FLC level above 100 mg/L as one of the myeloma defining factors which, along with a clonal bone marrow plasma cell concentration of ≥10%, or biopsy confirmed bony or extramedullary plasmacytoma, aids the diagnosis of MM (Rajkumar et al., 2014).

The serum FLC assay can also be used in patients with unexplained acute kidney injury (AKI) to screen for potential MCN. However the range of FLC at which MCN can occur is uncertain. The IMWG associated RI as a consequence of MCN to a serum FLC level above 1500 mg/L (Rajkumar et al., 2014), whereas the International Kidney and Monoclonal Gammopathy (IKMG) Research Group proposed a serum FLC level above 500 mg/L (Hutchison et al., 2011a). Additionally, it has also been unclear if the level of FLC in serum at presentation is an independent determinant of outcome in patients with AKI and MCN.

5.2 Aims

The aims of this study that provides the basis for this chapter were:

1. To report the range of FLC levels in serum in newly diagnosed MM patients who had RI from renal biopsy-confirmed MCN and,
2. To report renal outcome and overall survival (OS) relative to serum FLC level at presentation.

5.3 Methods

5.3.1 Study design and patients

An observational study of newly diagnosed patients with MM presenting with renal biopsy confirmed MCN between 2002 and 2014. Patients had presented at three tertiary centres: University Hospital Birmingham NHS Foundation Trust (UHB), Birmingham, UK; Mayo Clinic, Rochester, Minnesota, USA and, University of Alabama at Birmingham, Alabama, USA. Prospectively measured levels of involved FLC in serum using a single nephelometric assay (Freelite®, The Binding Site, Birmingham, UK) were evaluated. Approval for conduct of this study was obtained from the local ethics committee or the

Institutional Review Board from the three centres in accordance with the Declaration of Helsinki.

Figure 5.1 CONSORT diagram showing patients included in study

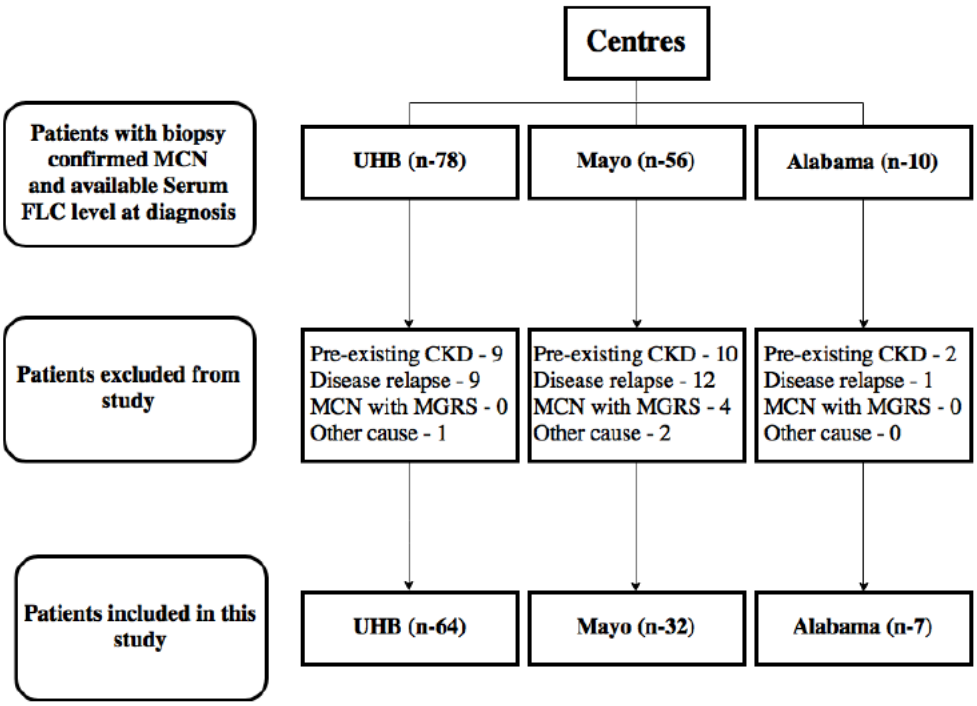


Figure 5.1 is a CONSORT diagram showing the characteristics of patients included in the study. Patients that were excluded from analysis comprised: (i) those with relapsing/remitting MM, (ii) those known to have chronic kidney disease (CKD), (iii) renal transplant recipients, (iv) those with a histological diagnosis of MCN and other paraproteinemia e.g. amyloidosis, renal monoclonal Ig deposition diseases, or any other monoclonal gammopathy of renal significance (MGRS) (Leung et al., 2012), and (v) patients in whom serum FLC levels were measured after commencement of anti-myeloma therapy.

5.3.2 Data collection

Data that were collected for the study included:

(a) Age

(b) Gender

(c) Date of presentation with RI

(d) Modification of Diet in Renal Disease study equation (MDRD) eGFR (ml/min/1.73 m^2)

(e) Corrected calcium

(f) Haemoglobin

(g) Paraprotein and FLC isotype

(h) Serum FLC level at presentation

(i) Date of renal biopsy

(j) Days from presentation to renal biopsy

(k) Days from presentation to receipt of first dialysis

(l) Date of dialysis independence

(m) Duration on dialysis

(n) Percentage of plasma cell infiltrate in bone marrow

(o) Survival and time to death

5.3.3 Statistical analysis

Statistical analysis was performed using SPSS® for Windows, version 21.0 (SPSS Inc, Chicago, IL) and Graph Pad Prism 5.0 (GraphPad Software Inc, San Diego, CA). Categorical variables were summarised as frequencies and percentages. Comparisons for categorical variables among different groups were made with the chi-square test and Fisher's exact

test where appropriate. Continuous variables were expressed as mean and standard deviation (SD) if the data was normally distributed or median with range for non-normally distributed data. Non-parametric comparisons were performed by using the Mann-Whitney *U* test. Correlation analysis between patients presenting with eGFR <15 ml/min/1.73 m^2 irrespective of haemodialysis status at diagnosis and serum FLC levels was performed with Spearman's rank test.

In addition to reporting levels of FLC in serum that were associated with MCN, I examined variables collected at presentation that correlated with renal function recovery in patients on haemodialysis and overall patient survival. For patients on haemodialysis, renal function recovery was defined as a sustained independence from dialysis treatment for at least two months. Patients were followed until death from any cause or censored on 31st December 2014, if they were still alive at this date, for survival analysis. In order to reduce the possibility for lead-time bias, OS for patients who achieved independence from haemodialysis and were alive were compared with OS for patients who were haemodialysis dependent and alive in a landmark analysis at 3, 6, 9 and 12 months after presentation with a new diagnosis of MCN. Patients who died before the landmark time were excluded and OS for the landmark analysis was performed from the landmark time to death. Outcomes in patients with MM have progressively improved with time due to the advances in supportive care and introduction of novel anti-myeloma therapies. From 2008, the chemotherapy regimens based on the proteasome inhibitor bortezomib became the standard of care for MM and severe AKI, and hence differences in survival were compared between those diagnosed with MCN before and after this time-point. All statistical tests were two sided and a *P* value of <0.05 was considered as significant.

5.4 Results

5.4.1 Patient demographic and disease characteristics

103 patients with a new diagnosis of MM, no previous history of known CKD and with serum FLC level available at diagnosis presented with a renal biopsy-confirmed MCN. Table 5.1 summarises the baseline characteristics of patients in the study.

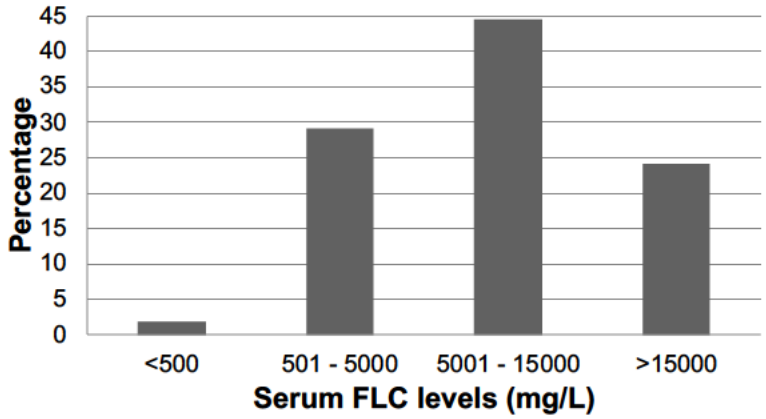
Table 5.1 Patient characteristics at diagnosis

	All patients (n=103)	Patients not requiring dialysis (n=34)	Patients requiring dialysis and recovering renal function (n=36)	Patients requiring dialysis and not recovering renal function (n=33)
Centres				
UHB	64 (62.1)	14 (41.1)	27 (75.0)	23 (69.7)
Mayo	32 (31.1)	17 (50.0)	7 (19.4)	8 (24.2)
UAB	7 (6.8)	3 (8.8)	2 (5.5)	2 (6.0)
Age (years)	63 (38 – 85)	64 (38 – 84)	60 (43 – 72)	65 (45 – 85)
Gender				
Male	59 (57.3)	19 (55.9)	25 (69.4)	15 (45.4)
Female	44 (42.7)	15 (44.1)	11 (30.5)	18 (54.5)
Ethnicity				
White	91 (88.3)	32 (94.1)	30 (83.3)	29 (87.8)
Non-white	12 (11.6)	2 (5.8)	6 (16.6)	4 (12.1)
Paraprotein type				
Light chain restricted MM	49 (47.6)	14 (41.1)	15 (41.6)	20 (60.6)
Whole Ig MM	54 (52.4)	20 (58.8)	21 (58.3)	13 (39.3)
FLC isotype				
Kappa (κ)	56 (54.4)	16 (47)	19 (52.7)	21 (63.6)
Lambda (λ)	47 (45.6)	18 (52.9)	17 (47.2)	12 (36.3)
FLC level (mg/L)				
FLC level irrespective of isotype	7531 (107 – 114600)	6724 (107 – 32294)	7960 (580 – 43161)	10134 (1620 – 114600)
κFLC level	6965 (201 – 46000)	6474 (201 – 32294)	7844 (580 – 28622)	9302 (1620 – 46000)
λFLC level	8220 (107 – 114600)	6853 (107 – 20000)	8108 (1971 – 43161)	12667 (1760 – 114600)

Serum creatinine (µmol/L)	535 (168 – 2993)	349 (168 – 1141)	685 (329 – 2210)	778 (265 – 2993)
eGFR (ml/min/1.73 m²)	7 (1 – 34)	12 (3 – 34)	6 (2 – 15)	5 (1 – 17)
Haemoglobin (g/L)	90 (46 – 131)	99 (54 – 129)	86 (56 – 131)	86 (46 – 126)
Corrected calcium (mmol/L)	2.35 (1.65 – 4.25)	2.38 (1.96 – 4.25)	2.32 (1.65 – 3.27)	2.43 (1.97 – 4.23)
Percentage plasma cell infiltrate on bone marrow	55 (1 – 90)	60 (1 – 85)	50 (10 – 90)	55 (20 – 90)

The median age at presentation was 63 years (range 38 – 85), 57.3% were of male gender and 88.3% of white ethnicity. Light chain-only (LCO) MM (47.6%) was the predominant paraprotein type followed by IgG MM (24.3%), IgA MM (22.3%), IgD MM (3.9%) and IgM MM (1.9%). An involved monoclonal kappa (κ) FLC isotype was present in 54.4% and an involved lambda (λ) FLC in 45.6% of patients. The median involved serum FLC level at presentation was 7531 mg/L (range 107 – 114600). Distribution of FLC levels in serum for the entire cohort is presented in figure 5.2.

Figure 5.2 Distribution of FLC level in serum



There was no significant difference in the levels of FLC in serum for patients presenting with involved κFLC (median 6965 mg/L [range 201 – 46000]) or involved λFLC (median 8220 mg/L [range 107 – 114600]) isotypes ($P = 0.211$). The median haemoglobin was 90 g/L (range 46 – 131) and the median serum corrected calcium level was 2.35 mmol/L (range 1.65 – 4.25). Two (1.9%) patients presented with an involved serum FLC level that was less than 500 mg/L at diagnosis; one patient was hypercalcaemic and the other patient had a high-normal serum calcium level and was on a non-steroidal anti-inflammatory drug.

5.4.2 Renal characteristics at diagnosis

The median serum creatinine was 535 µmol/L (range 168 2993) and the MDRD eGFR was 7 ml/min/1.73 m^2 (range 1 34). Sixty-nine (66.9%) patients required haemodialysis at presentation. The median time from presentation to start of haemodialysis was 1-day (range 0 202). There was no significant difference in serum FLC levels in patients presenting with eGFR <15 ml/min/1.73 m^2 irrespective of haemodialysis status at diagnosis (median serum FLC level in patients not requiring haemodialysis 7444 mg/L [range 575 32294] and 8643 mg/L [range 580 114600] for those requiring haemodialysis) (Figure 5.3).

Figure 5.3 Box-plot of serum FLC levels at diagnosis in patients presenting with eGFR <15 ml/min



5.4.3 Renal outcomes and patient survival

Thirty-four (33%) patients had no requirement for haemodialysis treatment at diagnosis. For the 69 (67%) patients who required haemodialysis at diagnosis, 36 (52.1%) achieved recovery of renal function. The median duration on haemodialysis was 36 days (range 10 701).

There was no significant difference in age, eGFR, corrected calcium, haemoglobin, and involved serum FLC level at presentation between patients who required haemodialysis and recovered renal function compared to those who remained dialysis-dependent. Patients who did not require dialysis had higher haemoglobin concentration (median 98 g/L [range 54 129] vs 86 g/L [range 46 126] respectively, P = 0.010), and lower involved serum FLC level (median 6724 mg/L [range 107 32294] vs 10134 mg/L [range 1620 114600], P = 0.044) compared to those who remained dialysis-dependent.

At the end of the follow-up period, 66 (64%) patients had died. The median OS from diagnosis was 2.5 years (95% CI 1.8 3.3). There was no significant difference in OS between patients who received haemodialysis at presentation (median 2.0 years; 95% CI 0.9 3.1) compared to those who had no requirement for dialysis (median 3.5 years; 95% CI 1.6 5.5) (P = 0.248). Patients who received haemodialysis at diagnosis, and subsequently recovered renal function showed a significantly improved OS (median 3.3 years, 95% CI 1.6 5.0) compared to those who remained dialysis-dependent (median 0.8 years, 95% CI 0.6 1.0) (P <0.0001).

On performing a landmark analysis, independence from dialysis at 3-months (P = 0.003), 6-months (P = 0.035) and 9-months (P = 0.014) time points were associated with improved survival whereas no such survival benefit was observed beyond 12 months (P = 0.146) (Table 5.2). The median OS amongst patients who presented after 2008 was 3.8 years (95% CI 2.5 5.1) and was significantly better compared to those who presented before 2008 (median 1.7 years, 95% CI 0.6 2.9) (P <0.006). We found no statistically significant change in the rates of renal function recovery (P = 0.151) between those presenting before or after 2008.

Table 5.2 Landmark analysis of associations between haemodialysis independence and overall survival at 3, 6, 9 and 12 months in patients with MCN (n=69)

		HD independent			HD dependent			
Landmark time	**Pts excluded (n)**	**Patients (n)**	**Deaths after landmark time (n)**	**Median OS (years)**	**Patients (n)**	**Deaths after landmark time (n)**	**Median OS (years)**	***P* value**
3 months	9	35	22	3.85	25	21	1.12	0.003
6 months	17	34	21	3.85	18	15	1.73	0.035
9 months	19	32	19	4.23	18	15	1.72	0.014
12 months	25	31	18	4.23	13	10	2.93	0.146

5.5 Discussion

In this multicentre study the principal findings were 1) the variable range of FLC levels in serum that were observed in patients presenting with biopsy-confirmed MCN; 2) only two of the 103 patients presented with FLC levels below 500 mg/L; 3) dialysis independence within 12 months was associated with better OS; and 4) the serum FLC level at presentation was not associated with renal function recovery or with patient survival.

This study is the largest analysis to date of the relationship between FLC level in serum and biopsy-confirmed MCN. Only thirty-five studies to date have reported on serum FLC level in patients with biopsy-confirmed MCN (Hutchison et al., 2009, Hasegawa et al., 2010, Hutchison et al., 2012b, Sinisalo et al., 2012, Khalafallah et al., 2013, Kourelis et al., 2013, Tan et al., 2014, Buus et al., 2015, Rousseau-Gagnon et al., 2015, Decourt et al., 2016, Borrego-Hinojosa et al., 2013, Ecotiere et al., 2016, Curti et al., 2016, Jayaballa et al., 2016, Pradhan et al., 2015, Pasquali et al., 2015, Weinstein et al., 2014, Hada et al., 2012, Mehta et al., 2012, Ward et al., 2012, Dahal et al., 2013, Susantitaphong et al., 2012, Peters et al., 2011, Basnayake et al., 2008, Leung et al., 2008, Basnayake et al., 2010, Rassner et al., 2018, Snozek et al., 2018, Kawabe et al., 2016, Sethi et al., 2017, Bridoux et al., 2017). The median numbers of patients reported in these studies were 5 (range 1 98) and the median serum FLC levels at diagnosis where available were: involved κFLC 14100 mg/L (range 80 42000) and involved λFLC 4267 mg/L (range 855 69430).

Immunoassays for serum FLC have only entered widespread clinical practice in the last decade and there is limited data on the relationship between serum FLC level and MCN.

The IMWG in their recent revised diagnostic criteria for MM included RI caused by MCN as a myeloma defining event, where MCN was characterised by the presence of typical histological features or an involved serum FLC level above 1500 mg/L (Rajkumar et al., 2014). The IKMG research group recommended an involved serum FLC level above 500 mg/L in patients with AKI as a threshold level for suspecting MCN and for consideration of an urgent haemato-oncological work up (Hutchison et al., 2011a). The results in the present study supports the IKMG threshold for MCN, as 6% of patients presented with a serum FLC level below 1500 mg/L; these patients would have been at risk of misdiagnosis if using the IMWG threshold for MCN.

There is great interest in improving the time to diagnosis and commencement of treatment for MCN. Hence, defining the serum FLC levels associated with MCN using the above threshold is an important component of achieving this aim. This would help by averting the need, delays, and risks associated with renal biopsy and consequent delay in initiation of life and organ saving anti-myeloma treatment. In addition, knowledge of early changes in serum FLC levels from baseline after commencement of chemotherapy in patients with MCN may also direct early changes in therapy. There is evidence that early disease response defined by a reduction in serum FLC is associated with an increased probability of renal recovery (Hutchison et al., 2011b).

A secondary aim of this study was to assess the association between serum FLC levels at presentation with renal recovery and OS in this population of patients who presented with severe RI. This analysis was limited by the change in time frame over which the study was performed and missing details of the chemotherapy regimens used for these patients. To date there are no studies that have reported on the relationship between

serum FLC levels at diagnosis in patients presenting with MCN and subsequent renal recovery. We found that the level of serum FLC level at presentation had no influence on whether or not patients who required dialysis subsequently recovered independent renal function or remained dialysis-dependent.

There is however growing evidence that OS is improving substantially in patients with MM who require dialysis for AKI (Evison et al., 2016); this improvement may be associated with increasing use of bortezomib-based regimens (Uttervall et al., 2014). I did not have sufficient information on chemotherapy to perform an assessment of the impact of use of bortezomib, but by time-period I found a significantly better OS in patients who presented after 2008, compared to patients who presented before 2008 (P = 0.006). Treatment of MM with bortezomib-based regimens became increasingly common after 2008.

5.6 Study limitations

This study does have some limitations. Being an observational study, only associations could be made between the levels of FLC in serum in patients with renal biopsy confirmed MCN. Patients with known CKD and/or relapsing MM were excluded from this study and these observations cannot be translated in these patients. MCN can occur in patients with monoclonal gammopathy of renal significance such as AL amyloidosis and light/heavy chain deposition disease and these patients too were excluded from this study. Chemotherapy data was not available hence, impact of novel agents in renal and OS outcomes could only be estimated.

5.7 Relevance to clinical practice

This study provides the range of serum FLC levels in one of the largest cohort of patients with biopsy confirmed MCN. It offers credence to the guidance offered by the IKMG research group that advises urgent haemato-oncological assessment in patients with AKI and serum FLC levels >500 mg/L, as the underlying pathology in these patients is most likely to be MCN. All efforts should thereafter be directed towards reduction of the elevated serum FLC levels with anti-myeloma therapy than to delay treatment whilst awaiting a renal biopsy.

Renal biopsy does however have a role irrespective of the serum FLC level especially in patients where there is a high clinical suspicion of MGRS. Those with predominant glomerular pathology e.g. Ig-related amyloidosis and monoclonal Ig deposition disease are more likely to present with nephrotic range proteinuria with predominant albuminuria and renal biopsy should be considered in these cases. Other situation where renal biopsy may be considered is in patients with predominant tubular lesions e.g. light chain Fanconi syndrome or crystal storing histiocytosis.

5.8 Conclusion

In conclusion, this is the largest study of the relationship between serum FLC levels and biopsy-confirmed MCN in patients with MM. 98% of patients with MCN at diagnosis presented with a serum FLC level >500 mg/L. Based on the findings from this study one could propose that a serum FLC level >500 mg/L should be considered for future diagnostic criteria for MCN. This recommendation is only valid for the Freelite® FLC assay (The Binding Site, Birmingham) and validation with other FLC assays have not been

performed. Serum FLC level at diagnosis was not associated with patient outcomes in MCN. Renal function recovery within 12 months was associated with improved survival in patients with MCN when compared to those who remained dialysis-dependent, no such benefit was observed after 12 months.

CHAPTER SIX: PATIENTS WITH MULTIPLE MYELOMA HAVE EXCELLENT LONG TERM OUTCOMES AFTER RECOVERY FROM DIALYSIS DEPENDENT ACUTE KIDNEY INJURY

I have published a paper related to this chapter. Yadav P, Hutchison CA, Basanayake K, Stringer S, Jesky M, Fifer L, Snell K, Pinney J, Drayson MT, Cook M, Cockwell P. Patients with multiple myeloma have excellent long-term outcomes after recovery from dialysis dependent acute kidney injury. Eur J Haematol. 2016 Jun;96(6):610-7. doi: 10.1111/ejh.12644. Epub 2015 Sep 16.

6.1 Introduction

Up to 50% of patients with multiple myeloma (MM) at diagnosis have renal impairment (Knudsen et al., 2000, Dimopoulos et al., 2008) and up to 5% of patients have severe acute kidney injury (AKI) requiring or progressing to dialysis treatment (Torra et al., 1995). Up to 90% of cases of severe AKI in MM are secondary to myeloma cast nephropathy. The need for dialysis treatment stratifies patients with MM into a group with a median survival of between 4 months and 20 months (Torra et al., 1995, Haynes et al., 2010, Tsakiris et al., 2010), less than 20% of the median overall survival (OS) that is now being reported for all patients with MM (Kumar et al., 2014). These very poor outcomes are associated with failure to recover independent renal function in the large majority of cases (Haynes et al., 2010).

The introduction of novel therapies has probably contributed to reports of better overall outcomes for people with MM and severe kidney disease (defined as an estimated glomerular filtration rate (eGFR) at presentation of <30 ml/min/1.73 m^2) (Dimopoulos et al., 2014a, Gonsalves et al., 2015, Uttervall et al., 2014). For patients with MM and

severe AKI requiring dialysis recent studies report better renal recovery rates; these are associated with improved survival in the first 12 months (Hutchison et al., 2009). However there is no published data on the long-term survival of patients with MM and dialysis-dependent AKI who recover renal function.

6.2 Aims

The aims of this study that provides the basis for this chapter were:

1. To report the long-term outcomes of patients who recover renal function from dialysis-dependent AKI due to myeloma cast nephropathy.
2. To analyse determinants of survival for patients in this group, including the impact of the kidney biopsy findings and serum free light chain (FLC) responses.

6.3 Methods

6.3.1 Study design and patients

This single centre study used data collected prospectively from 1 January 2005 until 31 December 2012. All patients who underwent kidney biopsy and required dialysis treatment at University Hospitals Birmingham (UHB) for the time-period of the study had information entered into prospective clinical databases. The study was approved by local Research Ethics Committees and the Research and Development Department and Clinical Governance department of UHB National Health Service Foundation Trust.

Sixty one patients with MM and dialysis-dependent AKI were managed at the centre during the study period: 32 patients presented with MM and dialysis-dependent AKI and

subsequently recovered independent renal function; 28 of the 29 patients who remained dialysis-dependent and were not included in the study also had myeloma cast nephropathy. The median time to death in patients with myeloma cast nephropathy and those who failed to recover independent renal function was 5.10 months (95% CI 3.68 6.52). Individuals with a histological and/or clinical diagnosis of amyloidosis or light or heavy chain deposition disease with MM were excluded from this study. For the patients who recovered kidney function, five had no bio-clinical data available from three months after presentation and were not included in the analysis; these patients had returned to other centres for further management. Twenty four patients with a histological diagnosis of myeloma cast nephropathy were included in the study, the three patients under long term follow-up at the centre that were not included in the analysis comprised two patients in whom the renal biopsy core was inadequate for a histological diagnosis and one patient with a histological diagnosis of acute tubular necrosis. Both renal and haematological parameters were collected at multiple time-points for patients who were included in the study as part of routine clinical practice.

The diagnosis of MM required the following diagnostic criteria: (a) clonal bone marrow plasma cells ≥ 10%, (b) presence of serum and/or urinary monoclonal protein (except in cases of non-secretory MM) and (c) evidence of end organ damage that could be attributed to the underlying plasma cell proliferative disorder (Rajkumar et al., 2014).

6.3.2 Data collection

The following data were collected for the study:

(a) Age

(b) Gender

(c) Date of first presentation with dialysis-dependent AKI

(d) Dialysis modality at presentation [high flux haemodialysis (HF-HD) or standard high cut off haemodialysis (HCO-HD)]

(e) Number of days from presentation to a percutaneous kidney biopsy

(f) Numbers of days on dialysis

(g) New or relapsing MM

(h) Paraprotein and FLC type

(i) Knowledge of pre-existing chronic kidney disease (CKD)

(j) Serum creatinine

(k) eGFR

(l) Serum FLC concentrations at presentation

(m) Percentage FLC reduction from baseline at follow-up (day 12, day 21, day 42, month 3, month 6, month 12 and month 24)

(n) Corrected serum calcium; serum albumin

(o) Haemoglobin

(p) Chemotherapy regimen at presentation and

(q) Date of death

(r) Kidney biopsy was assessed for chronic damage by estimating cortical atrophy and interstitial fibrosis on a semi-quantitative scale by the reporting histopathologist based on the percentage involvement of the renal cortex and recorded as: none (0%), mild (1% - 25%), moderate (26% - 49%) or severe (≥50%).

Serum FLC levels were measured using the nephelometric assay (Freelite®, Birmingham, UK). eGFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation. Response to treatment was assessed based on changes in serum FLC

levels according to the International Myeloma Working Group (IMWG) consensus recommendations (Durie et al., 2006). Renal recovery was defined as sustained independence of dialysis of at least two months. All patients were followed up until death from any cause or censored on 30 December 2013 if they were still alive at this date.

6.3.3 Statistical analysis

Statistical analysis was performed using SPSS® for Windows, version 21.0 (SPSS Inc, Chicago, IL). Continuous variables were summarised as mean ± standard deviation (SD) if normally distributed or median with inter-quartile range (IQR) if not normally distributed. Categorical variables were summarised as frequencies and percentages. Mann-Whitney U test for non-normally distributed data were used to compare: differences in the FLC concentration at presentation between the FLC isotypes; differences in the FLC concentration at presentation in individuals presenting with intact immunoglobulin (Ig) myeloma and light chain only myeloma (LCO); to assess differences in the renal recovery rate between HCO-HD and HF-HD and to assess the differences in eGFR achieved following renal function recovery in individuals treated with HCO-HD and standard HF-HD. Friedman test was used to compare the difference in non-normally distributed eGFR at the specified time-points. Univariable linear regression was performed to evaluate the association between eGFR at six-months and demographic, clinical and biochemical variables. Due to a small number of patients, we included variables with a P value ≤0.1 from the univariable analysis in the multivariable regression model. The endpoint of the study was OS, defined as the time from presentation with dialysis-dependent AKI from MM to death from any cause. Survival curves were plotted from the time of presentation to the renal unit using the Kaplan-Meier method and

differences in survival were statistically compared using the log-rank test. Univariable analysis of survival was performed using Cox proportional hazards model.

6.4 Results

6.4.1 Patient and baseline disease characteristics

The baseline demographic, laboratory, paraprotein and renal specific characteristics of the study population are presented in Table 6.1. The chemotherapy regimens that were used are presented in Table 6.2.

Table 6.1 Patient characteristics

Variable	Summary statistic* (n = 24)
Demographic data	
Age (years)	62.1 ± 8.1
Gender	
Male	18 (75)
Female	6 (25)
Ethnicity	
White	18 (75.0)
South Asian	5 (20.8)
Afro-Caribbean	1 (4.1)
Myeloma data	
New MM	22 (91.7)
Relapsing MM	2 (8.3)
Myeloma type	
IgG	9 (37.5)
IgA	4 (16.7)
IgM	1 (4.2)
IgD	2 (8.3)
Light Chain only	8 (33.3)
FLC type	
Kappa	11 (45.8)
Lambda	13 (54.2)
FLC concentration	
Kappa (mg/L)	8076.00 [2254.00 10387.00]
Lambda (mg/L)	6407.00 [4267.50 10568.50]
Renal data	
Pre-existing CKD	3 (12.5)
Serum creatinine (μmol/L)	685.00 [486.25 948.75]
eGFR (ml/min/1.73 m^2)	6.0 [4.0 7.7]
Dialysis modality	
High Cut Off haemodialysis	14 (58.3)
Standard haemodialysis	10 (41.7)
Days on dialysis	28.0 [16.2 51.7]
Other laboratory data	
Serum corrected calcium (mmol/L)	2.38 (2.23 2.64)
Serum albumin (g/L)	35.50 (29.25 42.00)

Haemoglobin (g/L)	89.00 ± 2.08

*Mean ± standard deviation or median [interquartile range] reported for continuous variables and frequency (percentage) reported for categorical variables.
MM, multiple myeloma; Ig, immunoglobulin; FLC, free light chain; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Table 6.2 Chemotherapy regimens at presentation

Chemotherapy	Regimen	Number (%)
Bortezomib-based	Bortezomib, Adriamycin and Dexamethasone (PAD)	12 (50)
Thalidomide-based	Cyclophosphamide, Thalidomide and Dexamethasone (CTD)	6 (25)
	Thalidomide and Dexamethasone (TD)	4 (16.7)
Others	Vincristine, Adriamycin and Dexamethasone (VAD)	1 (4.2)
	Cyclophosphamide and Dexamethasone (CD)	1(4.2)

Mean age at presentation was 62.1 years; 75% were men. The majority of individuals were of white ethnicity (75%); 20.8% were of South-Asian ethnicity and 4.2% of Afro-Caribbean ethnicity. Twenty two (91.7%) patients were at their first presentation of MM; two (8.3%) patients were at first relapse. IgG MM (37.5%) was the commonest paraprotein type, followed by LCO (33.3%), IgA (16.7%), IgD (8.3%) and IgM (4.2%) MM.

The serum FLC levels were quantified in all individuals at presentation; a monoclonal kappa (κ) FLC isotype was present in 11 (45.8%) patients and lambda (λ) FLC isotype in 13 (54.2%) patients. The median monoclonal κFLC concentration at presentation was 8,076 mg/L [IQR 2,254 10,387] and the median monoclonal λFLC concentration was

6,407.0 mg/L [IQR 4,267.5 10,568.5]. There was no significant difference in the FLC concentration between the involved FLC isotypes (P = 0.953) and there was no significant difference between the monoclonal FLC concentration at presentation between individuals presenting with LCO MM (median 7,960.0 mg/L [IQR 6023.2 8594.0] or intact Ig MM (median 7,376.5 mg/L [IQR 2,219.0 10,528.0]; P = 0.736).

6.4.2 Baseline renal characteristics

Median eGFR at presentation was 6.0 ml/min/1.73 m^2 [IQR 4.0 7.7]. Three (12.5%) patients were known to have pre-existing excretory CKD, as defined by an eGFR <60 ml/min/1.73 m^2 at least three months prior to their presentation with dialysis-dependent AKI.

Fourteen (58.3%) patients received extended haemodialysis from presentation using a HCO-HD protocol (Hutchison et al., 2009); the remaining 10 (41.7%) patients received a standard HF-HD prescription. Individuals who received HCO-HD recovered renal function at a median of 21.0 days [IQR 16.2 29.0] compared to a median of 56.0 days [IQR 27.5 56.0] for those who received standard HF-HD (P = 0.108).

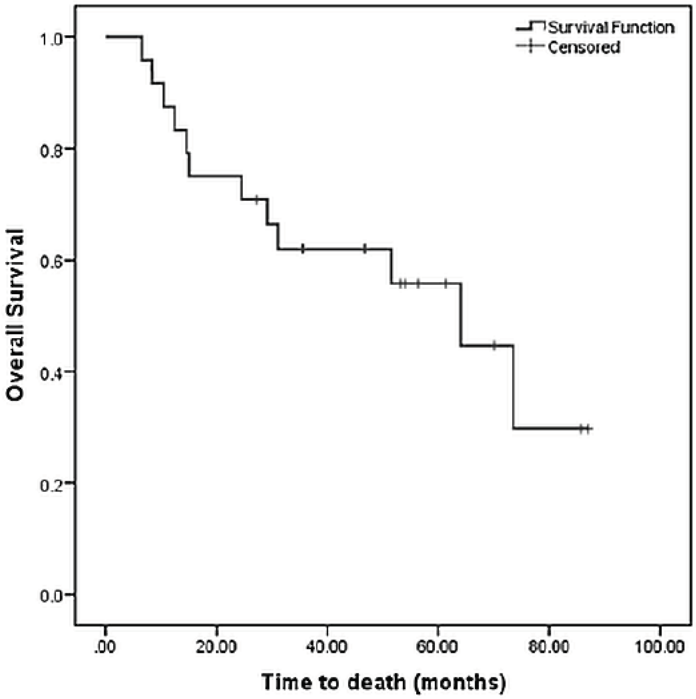
All patients had a kidney biopsy performed. The median time from admission to having a kidney biopsy was 3 days [IQR 2 5]. Amongst those where an adequate kidney biopsy was available locally (n=13), cortical atrophy was absent in 41.7%, mild in 16.7%, and severe in 16.7% of cases. Interstitial fibrosis was absent in 45.8%, mild in 12.5%, moderate in 4.2%, and severe in 12.5% of cases.

6.4.3 Survival Outcome

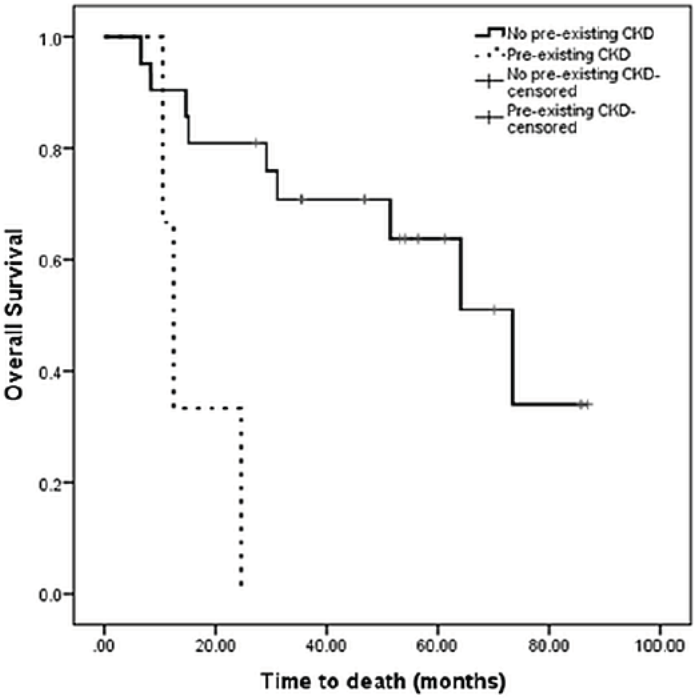
After a median follow-up of 56.4 months, 12 (50%) patients were alive and 12 (50%) patients had died. The median OS for the population was 64.1 months (Figure 6.1a). Twenty three (95.8%) patients remained dialysis-independent until death or end of follow-up and one patient subsequently required recommencement of haemodialysis treatment, with a time from renal recovery to recommencing dialysis treatment of 8 months and from restarting dialysis to death of 3.7 months. This patient had a relapsing-remitting disease course and was subsequently refractory to further treatment.

Figure 6.1 Patient survival

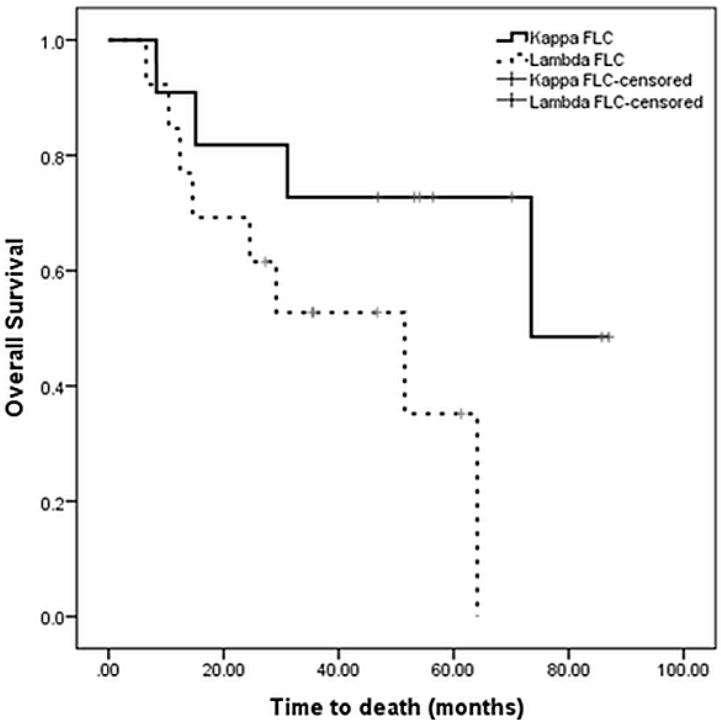
(A) Overall survival



(B) Survival curves of patients based on presence of pre-existing chronic kidney disease



(C) Survival curves of patients based on free light chain isotype at presentation



On fitting univariable Cox models, presence of pre-existing CKD compared with no pre-existing CKD (Hazards ratio (HR) 7.9; P = 0.008) was significantly associated with poor survival (Figure 6.1b). Other factors that had an indication of association with survival were presence of λFLC isotype compared to κFLC (Figure 6.1c), male gender, presence of severe cortical atrophy and severe interstitial fibrosis on renal biopsy at presentation, serum corrected calcium and eGFR levels at presentation (Table 6.3); however none of these variables achieved statistical significance; this is likely due to the small sample size. A multivariable model was not undertaken as there were insufficient events per variable in the study to fit the model.

Table 6.3 Univariable Cox model estimates

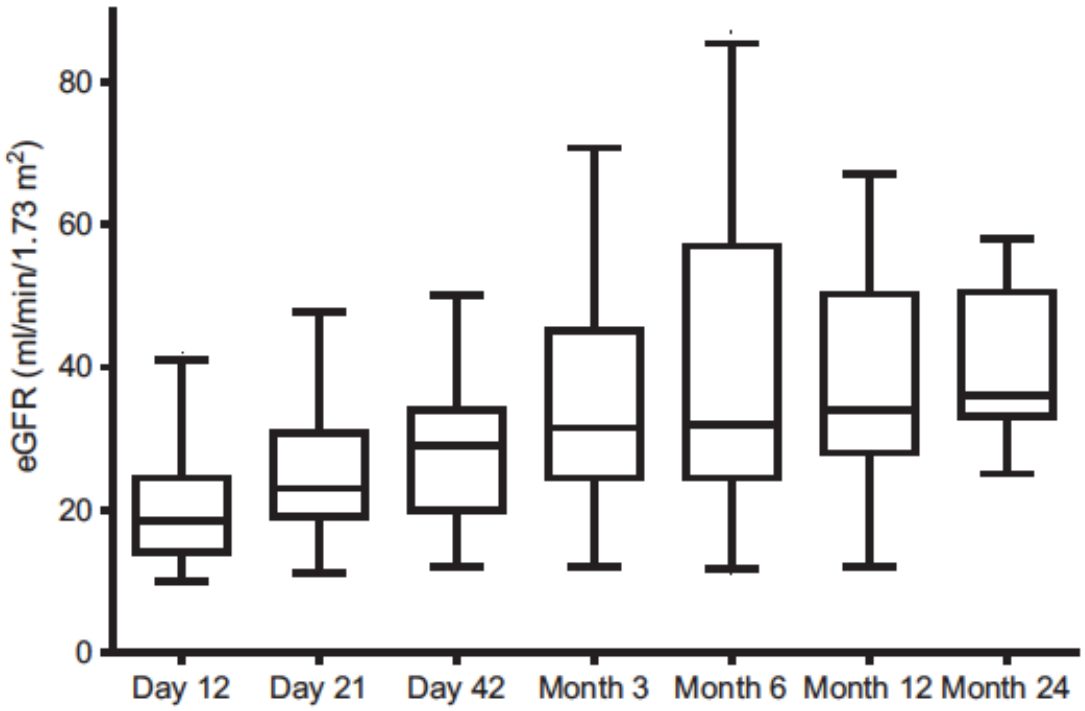
Variable	Beta	Hazards ratio	95% CI	P value
Age	0.019	1.019	0.936 1.109	0.662
Male gender	1.595	4.927	0.627 38.699	0.129
Severe Cortical atrophy	1.271	3.564	0.771 16.464	0.104
Severe Interstitial Fibrosis	0.670	1.954	0.367 10.412	0.433
Pre-existing CKD	2.068	7.912	1.703 36.754	0.008
eGFR at presentation	-0.250	0.779	0.590 1.027	0.077
Corrected Calcium	0.760	2.138	0.368 12.427	0.397
Lambda FLC type	1.247	3.480	0.891 13.593	0.073

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FLC, free light chain

6.4.4 Renal outcome

The median time from starting haemodialysis to recovery of independent renal function was 28.0 days [IQR 16.2 51.7]. Twenty (83.3%) patients recovered independent renal function by eight weeks from the day of admission to hospital; four (16.7%) individuals recovered independent renal function between 3 10 months. The median eGFR (ml/min/1.73 m^2) were as follows: day 12, 18.5 [IQR 14.0 24.5]; day 21, 23.0 [IQR 19.0 30.7]; day 42, 29 [IQR 20 34]; 3 months, 31.5 [IQR 24.5 45.0]; 6 months, 32.0 [IQR 24.5 57.0]; 12 months, 34.0 [IQR 28.0 50.2]; 24 months, 36.0 [IQR 33.0 50.5] (P <0.0001) (Figure 6.2). There was no significant difference in the median eGFR achieved following renal function recovery at the specified time points between the patients who received HF-HD and those who received HCO-HD.

Figure 6.2 Median eGFR (ml/min/1.73 m^2) at stated time interval from recovery of independent renal function



(day 12, 17 [IQR 12.00 21.75]; day 21, 20 [IQR 12.5 27.0]; day 42, 30.5 [IQR 17.75 35.00]; 3 months, 31.5 [IQR 26.25 43.50]; 6 months, 32 [IQR 24 45]; 12 months, 32 [IQR 29.75 45.00]; 24 months, 32 [IQR 24 46])

A linear regression model was fitted with eGFR at six-months as the dependent variable in order to identify factors that have the potential of predicting renal function at this time-point. In the univariable analysis, duration on dialysis (P = 0.02) and percentage FLC reduction on day 21 (P = 0.071) correlated with eGFR at six-months. Both these factors together also predicted the eGFR at six-months in a multivariable model (P = 0.035, adjusted R^2 0.33).

6.4.5 Haematological disease response

Twenty two (91.6%) patients received a chemotherapy regimen that included a novel chemotherapeutic agent; 12 (50%) received a bortezomib and 10 (41.6%) received a thalidomide-based regimen at presentation. The chemotherapy regimens are stated in Table 6.2. Where results of the serum FLC assay were available on follow-up at the specified time-points, disease response was calculated based on percentage reduction in the difference between the involved and the uninvolved pathologic FLC clone (dFLC) from baseline as per the IMWG guidance (Durie et al., 2006). Table 6.4 shows the measured disease response at various time-points.

Table 6.4 Disease response by time-point

Interval	Median FLC percentage reduction for all group [IQR]	Number responded/total at time-point (percentage)				
		Complete response (CR)	Very good partial response (VGPR)	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)
Day 12	81.95 [59.10 93.58]	0/20 -	5/20 (25)	12/20 (60)	3/20 (15)	0/20 -
Day 21	88.38 [77.47 96.20]	0/17 -	8/17 (47)	8/17 (47)	1/17 (6)	0/17 -
Day 42	92.00 [83.20 98.31]	0/18 -	10/18 (66.6)	8/18 (44.4)	0/18 -	0/18 -
3 months	92.18 [83.59 99.18]	3/19 (15.7)	7/19 (36.8)	8/19 (42.1)	0/19 -	1/19 (5.2)
6 months	95.28 [84.99 99.14]	2/19 (10.5)	9/19 (47.3)	6/19 (31.5)	0/19 -	2/19 (10.5)
12 months	98.92 [96.89 99.84]	4/14 (28.5)	9/14 (64.2)	0/14 -	1/14 (7.1)	0/14 -
24 months	98.68 [96.72 99.85]	3/11 (27.2)	7/11 (63.6)	1/11 (9.0)	0/11 -	0/11 -

6.5 Discussion

The study reports the long-term outcomes of patients who have recovered renal function following dialysis-dependent AKI secondary to myeloma cast nephropathy. Patients presenting between January 2005 and December 2012 were included, which meant that novel chemotherapy agents were components of routine clinical care for the large majority of patients and extra-corporeal FLC removal by HCO-HD was used in the majority of the cohort. The median OS in people who recovered renal function was 64.1

months. This compares well with the reported OS in newly diagnosed MM patients treated with novel agents between 2001 and 2010 (Kumar et al., 2014). The median OS for the entire cohort in the study by Kumar et al was 5.2 years (62.4 months); 4.6 years (55.2 months) for patients diagnosed between 2001 2005 and 6.1 years (73.2 months) for 2006 2010, illustrating the benefits of using novel agents as induction therapy (Kumar et al., 2014). The median time to death in patients who presented with myeloma cast nephropathy and dialysis-dependent AKI and did not recover renal function during the study-period was 5.10 months (95% CI 3.68 6.52), indicating the major benefit associated with recovery of independent renal function.

Long-term renal function following achievement of dialysis independence was also assessed in this study. Renal function did not recover to normal following recovery from MM and dialysis dependent AKI, with the majority of patients improving to a post-recovery baseline of stage 3b/4 CKD. This is compatible with the AKI being caused by a distinct pathogenic process (myeloma kidney/cast nephropathy) and indicates that this process is responsible for rapidly inducing CKD.

Recovery of independent renal function was associated with effective treatment of MM and a sustained reduction in the concentration of the involved FLC clone. Only one patient subsequently required further haemodialysis treatment. This patient experienced a relapsing-remitting disease course and was eventually refractory to further chemotherapy and died within four months of recovering renal function.

This study is in response to recent reports that indicate an increasing proportion of patients are recovering independent renal function following MM and severe dialysis-

dependent AKI (Hutchison et al., 2009, Zannetti et al., 2015b, Ludwig et al., 2015, Hutchison et al., 2012b). Zannetti et al recently reported a 76% renal recovery rate and a 67% three-year OS in 21 newly diagnosed MM patients all of whom were treated with bortezomib-based regimen and received HCO-HD (Zannetti et al., 2015b). A phase-II study which evaluated renal and myeloma response to lenalidomide-dexamethasone in individuals presenting with acute LC induced renal failure reported renal function recovery in five (38.5%) of the 13 patients who were dialysis-dependent at presentation (Ludwig et al., 2015). In one of the largest multicentre studies which included 67 dialysis-dependent MM patients treated with novel agents and HCO haemodialysis; a 63% renal recovery rate was noted with 76% of patients demonstrating a reduction in serum FLC levels by day 12 (Hutchison et al., 2012b). Ludwig et al reported reversal of renal failure in five out of eight patients, which included five haemodialysis patients, who were treated with bortezomib-based regimen (Ludwig et al., 2007). Roussou et al noted reversal of renal failure in 40% of patients with MM complicated by renal failure on a bortezomib-based chemotherapy that included five patients who required haemodialysis (Roussou et al., 2008). These findings are in sharp contrast to historic data that reported extremely poor renal recovery rate in dialysis-dependent MM patients when treated with conventional chemotherapeutic agents (Magee et al., 1998, Torra et al., 1995, Knudsen et al., 2000, Blade et al., 1998, Haynes et al., 2010).

The serum FLC assay has been a major advance in both the diagnosis and surveillance of patients with MM (Gertz, 2015). This study benefitted from FLC measurements at presentation and during follow-up. It has previously been shown that in patients who have dialysis-dependent AKI and MM each increment of 10% FLC reduction at day 21 was associated with a 60% increased likelihood of renal recovery and the odds of renal

function recovery is 13 times higher if the reduction is more than 50% (Hutchison et al., 2011b). This present study extended these observations by assessing serum FLC levels over a two-year period in individuals who recover renal function. In this study more than 80% median serum FLC reduction from day 12 and up to two-years from presentation was noted in majority of patients. The relationship between percentage FLC reduction at day 21 and eGFR at six-months was of borderline significance (P = 0.071); this may relate to the small number of patients in this study and the majority achieving an excellent early reduction in their FLC levels. When total duration of dialysis and serum FLC reduction at day 21 were included in a multi-variable model, both variables in combination could predict the eGFR at six-months (adjusted R^2 = 0.33; P = 0.035). Total duration spent on dialysis prior to renal function recovery was the most significant determinant of eGFR at six-months in the univariable analysis (P = 0.02).

Several studies have shown the importance of achieving a very good partial response (VGPR) in chemotherapy treated symptomatic MM patients (Harousseau et al., 2009, Niesvizky et al., 2008, van de Velde et al., 2007). In a post-hoc analysis performed by the Intergroupe Francophone du Myélome (IFM) 2005-01 study group, achievement of a response less than VGPR was associated with poor prognosis in patients who were randomised to a bortezomib-dexamethasone or a vincristine-adriamycin-dexamethasone chemotherapy regimen (Moreau et al., 2011a). In the present study, more than 50% of patients achieved a ≥VGPR disease response that was sustained throughout the follow-up period. There was no significant association between attaining a CR only or ≥VGPR disease response at the specified time points on the prediction of eGFR at six-months or long-term OS. The only factor that was associated with worse survival in the univariable analysis was the presence of pre-existing CKD at presentation.

6.6 Study Limitations

The main limitation of this study is the sample size. Therefore, the relationship between some variables and long-term outcomes may have been over-estimated; also due to the uncertainty in estimates and a lack of power weaker associations between variables may have gone undetected. A second limitation is centre bias; the reporting centre has a clinical and research interest in this area, hence the OS seen in our patients might not be representative of the general population.

6.7 Relevance to clinical practice

The present study extends on previous reports by showing that patients who recover independent renal function as a consequence of MM can have good long-term outcomes. This information is extremely important for discussing long-term outcomes with MM patients. Furthermore, it focuses clinicians on the importance of independence from dialysis as a very important treatment goal.

6.8 Conclusion

In summary, this is the first study to report long-term survival outcomes in individuals who recover renal function from dialysis-dependent AKI secondary to myeloma cast nephropathy. Early variables such as number of days on dialysis and serum FLC reduction on day 21 are associated with future renal function. The OS in MM patients who become dialysis-independent in this study is good and comparable to separate reports on the OS of patients with MM , however further studies with larger sample size would be required to validate these results. Finally, in the era of novel agents the large majority of patients who recover renal function have no future need for renal replacement therapy.

CHAPTER SEVEN: OVERALL CONCLUSION

Renal impairment (RI) in MM is a medical emergency. Renal function recovery is an important treatment goal in improving the long-term outcomes of patients presenting with severe RI as a consequence of MM. Availability of the serum FLC assay has not only helped in the diagnosis of patients with paraproteinemia but has also assisted in monitoring disease response in MM post treatment. However at the time of the work done in this thesis there was a lack of information on areas of major clinical relevance to patients with MM and RI. In this thesis I report studies that I did to address this shortfall: these comprised an assessment of the relationship between serum FLC levels and kidney function in a large prospective study; an analysis of the relationship between FLC and outcomes in the largest series to date of patients with myeloma cast nephropathy (MCN); and a study of the long-term outcomes of patients with MM and severe AKI in the era of novel chemotherapy.

The IMWG and IKMG have, through consensus, advised different threshold levels of serum FLC for the development of MCN. In a large study utilising data obtained from the Myeloma IX trial I demonstrated that the risk of severe RI was strongly associated with an involved serum FLC level above 800 mg/L. Knowledge of this finding will help clinicians channel their efforts towards an early diagnosis as well as management of this high-risk group of patients. It will also help in communication with patients around the interpretation of the test and the likelihood of the distinct pattern of renal damage seen in MCN.

I also found that patients with RI post-induction (PI) are primarily those with RI at diagnosis. Patients with a VGPR or above disease response post-induction had a greater likelihood of achieving an improvement in renal function; this indicates that the focus of treatment should be on the rapid reduction of FLC levels. Studies that identify whether an early switch in chemotherapy for patients who do not have a VGPR response may be indicated. Previous work has shown that disease response to chemotherapy in the first three weeks as identified by serum FLC response is a strong predictor of recovery of renal function. The work that I report extends this by showing that serum FLC response is also a determinant of subsequent kidney function for patients who do not require dialysis at presentation.

Myeloma cast nephropathy is the commonest pattern of renal injury that is seen in patients with MM presenting with severe RI. Renal biopsy findings were unavailable in the Myeloma IX trial hence in that study I was unable to identify if there was a specific level of FLC in the serum that was associated with the development of MCN. To address this I did the largest multicentre study to date of patients with a new diagnosis of MM and biopsy proven MCN. I found that 98% of patients had a serum FLC level above 500 mg/L at diagnosis. This finding is substantial as it indicates that patients with severe RI and a serum FLC above 500 mg/L should be referred urgently for a haematological work-up so that treatment is not delayed in patients who may have MCN. The finding I report is in line with the recommendations of the IKMG group; however until the study reported in this thesis there was limited data that could support this recommendation.

Overall survival in patients with MM is improving compared to historic data and survival benefits are more pronounced in those who achieve renal function recovery from a

dialysis-dependent state within the first 12 months of diagnosis. However there is a lack of very long-term data on the survival of patients with MM and dialysis dependent AKI, including those who recover independent kidney function, in the era of novel chemotherapy. I show that patients with MCN and dialysis dependent AKI, who recover renal function by becoming dialysis-independent through a good haematological disease response, can have an excellent long-term survival. This provides further evidence for focusing on this group of patients.

With the gratifying improvement in outcomes of patients with MM and RI, we are entering a different era of medical care for patients with this cancer. It is possible that MM may be reclassified as a chronic disease. Our experience with other chronic diseases is that kidney function is a major determinant of very long-term outcome. Therefore there will be an increasing need to better identify the relationship between kidney function and outcomes in patients with MM. A major focus of future diagnostic monitoring and therapy may be on sparing kidney function or the risk of kidney function decline to ensure that the patient has sufficient renal reserve over the course of their disease to ensure that they have a high chance of long-term survival.

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Publications arising from Thesis

The following is the list of publications arising from this thesis:

1. **Serum free light chain levels and renal function at diagnosis in patients with multiple myeloma.**

   Yadav P, Cockwell P, Cook M, Pinney J, Giles H, Aung YS, Cairns D, Owen RG, Davies FE, Jackson GH, Child JA, Morgan GJ, Drayson MT.

   BMC Nephrol. 2018 Jul 13;19(1):178. doi: 10.1186/s12882-018-0962-x.

2. **Current Trends of Renal Impairment in Multiple Myeloma.**

   Yadav P, Cook M, Cockwell P.

   Kidney Dis (Basel). 2016 Mar;1(4):241-57. doi: 10.1159/000442511. Epub 2016 Feb 3. Review.

3. **Patients with multiple myeloma have excellent long-term outcomes after recovery from dialysis-dependent acute kidney injury.**

   Yadav P, Hutchison CA, Basanayake K, Stringer S, Jesky M, Fifer L, Snell K, Pinney J, Drayson MT, Cook M, Cockwell P.

   Eur J Haematol. 2016 Jun;96(6):610-7. doi: 10.1111/ejh.12644. Epub 2015 Sep 16

4. **The use of immunoglobulin light chain assays in the diagnosis of paraprotein-related kidney disease.**

   Yadav P, Leung N, Sanders PW, Cockwell P.

   Kidney Int. 2015 Apr;87(4):692-7. doi: 10.1038/ki.2014.333. Epub 2014 Oct 8.

5. **Serum FLC level at diagnosis in myeloma cast nephropathy – A multicentre study.**

   Yadav P, Sathick IJ, Leung N, Brown EE, Cook M, Sanders PW, Cockwell P.

   Accepted for publication by Blood Cancer Journal (Nature) in August 2019.