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Multiple myeloma can be accurately diagnosed in acute kidney injury patients using a rapid serum free light chain test

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Introduction

- Acute kidney injury (AKI) is a common complication of multiple myeloma and has been recommended to be treated as a medical emergency. Cast nephropathy is the most common cause of severe renal impairment in patients with myeloma. Nephrotoxic free light chains (FLCs) can cause renal impairment as an early feature of myeloma, prior to other disease-associated organ or tissue damage. Further, myeloma-related complications such as hypercalcaemia and dehydration can also cause or exacerbate renal injury
- The presence of elevated serum FLCs (sFLC) and a perturbed FLC κ:λ ratio is a key marker for detecting plasma cell malignancies and has been shown to be an important indicator of myeloma in the presence of AKI
- A κ:λ ratio range of 0.37–3.1 on the first commercially available sFLC assay (Freelite) has been demonstrated to provide 100% sensitivity and 99% specificity in identifying multiple myeloma in 41 patients who presented with AKI. AKI secondary to cast nephropathy is only likely when the sFLC level is ≥500 mg/L by Freelite
- Prompt identification and reduction of monoclonal FLCs by anti-myeloma therapy is vital for renal recovery and the prevention of irreversible damage. However, sFLCs assays run on nephelometric or turbidimetric analysers, such as Freelite and N Latex, often necessitate sending patient samples to specialist laboratories. This can lead to slow sample turn-around times and delays in receiving patient results
- Seralite is a lateral-flow test that rapidly quantitates serum κ and λ FLC levels simultaneously, which could be easily used as an urgent assay for small numbers of samples in routine hospital laboratories
- The aims of this study were to assess the utility of Seralite as a screening tool to distinguish between myeloma and non-myeloma related AKI, and provide a reference range for diagnostic purposes in patients presenting with AKI stage 3

Methods

- Patients diagnosed with AKI stage 3 as per the Kidney Disease: Improving Global Outcome (KDIGO) criteria (n = 99) with stored serum samples available at disease presentation were included in this retrospective analyses
- 45 of these patents were enrolled in the MyEloma Renal Impairment Trial (MERIT) for patients with newly diagnosed myeloma associated with acute renal failure (creatinine >500 µmol/L, urine output <400 mL/d or requiring dialysis)
- The other 54 patients presented with new dialysis-dependent renal failure to the University Hospital Birmingham, UK. These patients had AKI confirmed to be due to other causes through kidney biopsies and clinical investigation and were on haemodialysis. These patients were negative for monoclonal immunoglobulins using serum and urine immunofixation electrophoresis

	AKI stage 3 as per as per The Kidney Disease: Improving Global Outcome (KDIGO) criteria (n = 99)	
	Myeloma AKI (n = 45)	Non-myeloma related AKI (n = 54)
Mean age (± SD)	65 (± 10) years	63 (± 17) years
Aged ≥ 65 years	67%	56%
Male	56%	65%

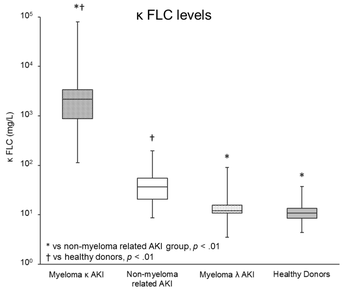
There was no significant difference in the age, the proportion of patients aged ≥ 65 years old or distribution of sex between AKI patient groups

- Healthy individuals (n = 91) were also included in the study, with serum creatinine levels ≤114 µmol/L (mean 81 ± 15 µmol/L)
- All serum samples underwent analysis for FLCs using Seralite - a portable lateral-flow test that utilises anti-FLC monoclonal antibodies (Abingdon Health Ltd, Oxford, UK). This test simultaneously quantitates κ and λ FLC levels in 10 minutes

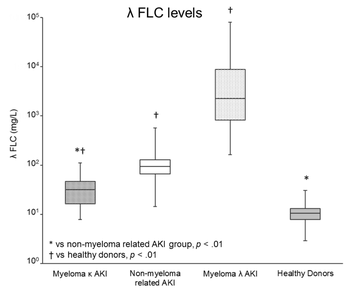
Results

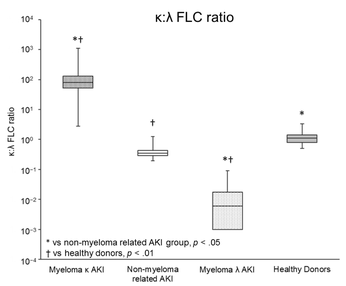
1. Seralite to differentiate between AKI with myeloma, AKI without myeloma and healthy donors

Myeloma patients (both κ and λ monoclonal isotype groups) had significantly different κ FLC compared to non-myeloma related AKI patients. Both myeloma κ patients and non-myeloma related AKI patients had κ FLC levels above healthy donors



κ and λ myeloma patient groups had significantly lower/higher λ FLCs levels compared to non-myeloma related AKI patients, respectively. All patient groups had higher λ FLC levels compared with healthy donors





The κ:λ ratio revealed significant differences between patient groups. All myeloma patients exhibited a perturbed ratio outside the healthy diagnostic range of Seralite (0.5–2.5). There was no overlap in κ:λ ratios between myeloma κ AKI patients (ratio ≥2.8) and myeloma λ patients (ratio ≤0.009) and non-myeloma AKI patients (ratio 0.2–1.3). All patient groups had significantly different ratios compared with healthy donors

Patient groups had significantly different FLC sum (κ + λ FLC levels) and FLC difference (maximum FLC minus the minimum FLC level). However, unlike the κ:λ ratio, there was an overlay in the distribution of FLC sums and dFLC values and complete differentiation between groups was not seen with these FLC parameters. All patients had higher FLC sums and dFLC values compared with healthy donors.

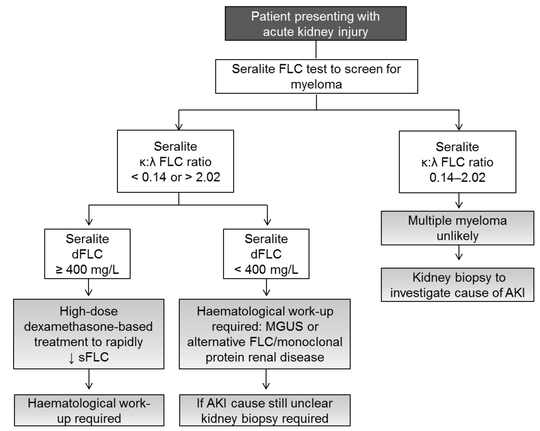
2. Seralite sFLC cut-offs to differentiate between AKI patients with myeloma and AKI patients without myeloma

The κ:λ ratio was able to classify myeloma from non-myeloma AKI patients with perfect accuracy. This was due to no overlap in the distribution of κ:λ ratios between the patient groups (myeloma κ patients always had higher ratios and myeloma λ always lower) resulting in no false positives/false negatives. Optimal cut-offs were 0.14 to identify λ myeloma patients and 2.02 to distinguish κ myeloma patients, providing 100% sensitivity and 100% specificity for differentiating between myeloma and non-myeloma related AKI. The FLC sum and dFLC also provided a high level of accuracy for identifying myeloma from non-myeloma patients

	Area under curve (95% confidence interval)	Best cut-off	Sensitivity	Specificity
Ratio: myeloma κ	1.0 (95% CI 1–1, *p* <.001)	2.02	100%	100%
Ratio: myeloma λ	1.0 (95% CI 1–1, *p* <.001)	0.14	100%	100%
FLC sum	0.97 (95% CI .94–.1.0, *p* < .001)	528 mg/L	89%	94%
dFLC	0.99 (95% CI .97–1.0, *p* < .001)	399 mg/L	91%	100%

3. Proposed screening pathway for myeloma in unexplained AKI using Seralite to quantitate serum FLCs

In the diagram below we propose guidelines for the use of Seralite in clinical practice for patient screening and stratification in patients with unexplained AKI. The κ:λ ratio can be used to diagnose multiple myeloma using the renal reference range of 0.14–2.02. If an abnormal κ:λ ratio is identified, a dFLC threshold of ≥400 mg/L could be used to confirm a high likelihood of myeloma cast neuropathy. We recommend patients with an abnormal ratio and a dFLC level of ≥400 mg/L should be considered for treatment with high-dose dexamethasone immediately, prior to awaiting additional laboratory results, and a renal biopsy is not indicated. Due to the high specificity observed in this study, it is extremely unlikely that using these criteria would result in an AKI patient without myeloma being administered high-dose dexamethasone. Irrespective of the sFLC level, where an abnormal ratio is identified a full haematological work-up is required urgently



Conclusions

- This study demonstrated that serum FLC quantitation using Seralite can be used as an effective screening tool for diagnosing myeloma in patients presenting with AKI stage 3
- The FLC ratio sensitively and specifically distinguishes between patients with AKI and myeloma or AKI attributable to other causes. The κ:λ ratio can be used to diagnose myeloma and the dFLC can be used to aid subsequent decisions for clinical management
- The portable device offered the same level of diagnostic performance previously reported for conventional laboratory-based testing. sFLC assays reliant on nephelometric or turbidimetric analysers are routinely run in batches and thus testing may not be carried out every day. Further, these assays are not available in all hospitals, often requiring sample dispatch to specialised laboratories. These delays in sample processing may defer patient results for days to weeks
- Speed is critical in diagnosing the underlying pathology in AKI. Prompt identification and reduction of monoclonal FLCs by anti-myeloma therapy is vital to enable renal recovery and improve patient prognosis. In addition, by rapidly identifying a high probability of cast nephropathy patients may be spared the risk of a renal biopsy. Similarly, in cases where myeloma is not the cause of AKI, it is important to rule this out quickly so that patients can be referred for a kidney biopsy and further clinical investigation
- Seralite is easily applicable to testing urgent samples by any hospital that operates a 24h laboratory service and therefore could be used to speed up the diagnosis of myeloma in AKI patients and help inform early treatment intervention

Disclosures: UoB, MD and JC own shares in Abingdon Health Ltd, who manufacture Seralite and MD advises AH Ltd