Author's response to reviews

Title: Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure.

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Author's response to reviews: see over
Dear Dr Koutsos,

Re: MS: 1725228718196910

Thank you for you recent review of our manuscript entitled: Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure. The comments provided by the reviewers were insightful and very helpful. We believe we have addressed all of their comments in full. In the manuscript we have highlighted changes in red and below we provide point by point explanations to the reviewer’s comments.

Thank you again for considering our manuscript for publication in your journal.

Yours Sincerely

Colin Hutchison

Addressing reviewer’s comments:

Reviewer: Jill Tate

Thank you for your detailed review of our manuscript and in particular for highlighting the need for us to clarify certain aspects of the manuscript. We believe we have addressed all of your comments and placed them appropriately in the text.

Major compulsory revisions:

1. We have updated this reference to confirm that the manuscript is now in press with Clin J Am Soc Nephrol. We have expanded the introduction (page 5) to describe in more detail this population with chronic kidney disease. Details of the ranges of renal function (serum creatinine and estimated GFR) and serum FLC concentrations and ratios are given. The distributions were not Gaussian.

2. On page 5 of the introduction we have clarified the section introducing the influence of the production rates of kappa and lambda on the serum FLC ratio. First, we clarified that it is the plasma cells that are known to be at a ratio of 2:1 not the median ratio of FLCs being produced. Second, we agree that a ratio of 1.1 is not close to 2; therefore, we have rephrased the sentence to state the serum FLC ratio becomes ‘increasingly influenced by the underlying production’ rather than ‘representative of the underlying production rates’.

3. On page 11 we have added the median FLC ratio and range for Katzmann’s original reference population. We believe the likely reason the changes in the lower and upper reference levels of the ratio are disproportionate is that at the lower end will principally represent patients with relatively normal renal metabolism of FLCs; where as the upper end of the ratio represents those with more advance renal impairment and it is in these patients that we see greater increases in serum kappa concentrations than lambda.
4. This patient had a renal diagnosis of adult polycystic disease as the cause of his renal failure and to date not developed any further indications of a plasma cell dyscrasia. We will follow up this patient long term.
5. In the discussion (pages 11 and 12) we have revised our discussion of ratios in the range of 1.65 and 3.0 to take into account your comments. First, no state that a ratio in this range in a patient with normal renal function warrants further investigation for possible monoclonal protein. Second, we have added that a ratio in this range with abnormal renal function may require further investigation particularly if AL-amyloidosis is suspected.

Minor essential revisions:
1. We have removed ARF and now only use AKI through the manuscript.
2. We have followed your advice and use ‘K/L FLC ratio’.
3. Corrected
4. On page 7 we have now stated that the Tencer reference refers to the stability of FLCs in the urine and added that this ‘appears’ true for the serum as well, quoting Katzmann’s 2002 manuscript in which he used a historical population and a prospective population to define the reference ranges.
5. This reference has been corrected
6. Corrected
7. The area under the curve increases from 0.96 to 0.99, from the standard to the renal ranges
8. We have deleted the sentence that was unclear and expanded figure 3’s legend to follow your suggestions.
9. We have changed this to read: ‘monoclonal FLCs were not detected by urinary immunofixation’

Discretionary revisions:
1. We have followed your advice and changed references of Katzmann’s range to ‘reference’ rather than ‘normal’.
2. We have removed the comments about ‘more abnormal ratios’ as advised.
3. This information has been added to the results section pages 9 and 10.
4. We will report these results in future publication addressing factors influencing renal outcomes in patients with multiple myeloma.
5. This has been changed.

Reviewer: Gerassimos A. Pangalis

Thank you for your review of our manuscript, your insightful comments have helped us provide for useful information to the reader.

Minor comments:
1. We have added to the introduction that an abnormal FLC ratio indicative of monoclonal FLC production can occur with both intact immunoglobulin myeloma and FLC only myeloma.
2. Yes this patients was a very unusual presentation of cast nephropathy in a patient with an IgM plasma cell dyscrasia, following you advice we have added a short summary to the table’s legend.

3. We have added this useful reference to the discussion (page 13).