Reviewer's report

Title: Early postoperative serum cystatin C predicts severe acute kidney injury following cardiac surgery

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Reviewer: zaccaria ricci

Reviewer's report:

The study is interesting even if not completely original, since as you correctly discuss, other authors have examined the value of CysC in cardiac surgery patients. However, the message they carry might be of some value: CysC is fairly useful to shortly predict RRT need.

I have several MAJOR concerns I would like the authors to address:

1) The NCT reference number you present apparently does not match with the present study. It is likely referred to the manuscript referenced as [10] in the text: however no mention is made in the published protocol about AKI, renal function, CRRT and cystatin C serial measurements. I would not state that “The study protocol was reviewed and approved by the local university ethics committee (340/10) and registered at ClinicalTrials.gov (NCT01247051)” because this crucial information is inaccurate and misleading.

2) In this light the study seems to be biased by the rational at the base of the original study. In particular, I found that if age>70 is an enrollment criteria, I think that it should be remarked in the methods and in the title that this observation is in older patients.

3) Also it is not completely clear why, once you are validating the use of CysC in cardiac surgery (older) patients, should “ejection fraction >45%, anaemia (Hb <12mg/dL), re-intervention, myocardial infarction (STEMI or NSTEMI) within the past 7 days and off-pump method” be considered exclusion criteria: please specify.

4) Also please state in the title “post hoc analysis”

5) Methods:

   - if as secondary endpoint you analyzed AKIN criteria, it is not clear what you mean at “The RIFLE (risk of renal dysfunction) score for the GFR was nevertheless recorded at all measurement time points”

   - The statement “An additional AKI criterion of the Acute Kidney Injury Network is oliguria (urine excretion <0.5mL/kg/h for 6 hours). We decided not to use this criterion since urine excretion is maintained by intravenous fluid administration and diuretic therapy as part of postoperative ICU monitoring” is misleading: AKIN criteria should be applied using both urine and creatinine criteria. If urine flow is
maintained by diuretics and the urine output is not below the AKIN score threshold, hence masking an AKI event, then the hypothetic renal damage might be evidenced by creatinine. On the other side the authors might have missed patients with normal creatinine (due to hemodilution) with pathologically decreased urine output. To design studies on AKI using only creatinine criteria is (unfortunately) common: nevertheless the authors have to acknowledge that this is a limit of the study or to justify the rationale of their choice.

- please explain what you mean at “Expanding the time window to postoperative day 3-4 is possible due to CPB-related haemodilution and this has already happened in some studies”: was YOUR time window 48 or 96 hours?

- please provide some information on CysC reference values for patients with normal renal function and patients with AKI

-I would indicate as “RRT patients” or “AKIN3” those achieving the primary end-point, and “AKI patients” or “AKIN1” those with milder AKI forms in order to improve clarity

6) Results:

-from a conceptual point of view, it results that CysC soon after surgery (T4) is able to fairly detect patient who will undergo RRT. The major issue here is that we need to exactly know when were the 8 RRTs started since, if all RRTs started soon after surgery, then the prediction time would be so short to result useless. In other words from your article the reader would like to learn how much time could potentially be gained before RRT by knowing that CysC is increased after CPB. The same is for T5: even if I agree that the AUC ROC value is fair to good, it should be important to know what is the actual clinical meaning of knowing that AKI will occur in the next few hours. Then, were some of those RRT patients started BEFORE the T5? This is not unlikely: in such a case AUC ROC analysis should be performed in patients not having AKI at T5. Finally, the same is for AKIN1 patients: when were they “tagged” as AKIN1?

-Again, the authors should attempt (if they have such values) the same analysis they performed with CysC even with creatinine: we currently do not know if, for example, creatinine slight increases at T4 might anticipate a subsequent indication to RRT exactly as CysC did.

Discussion:

-In the discussion, it emerges that it is not clear which classification you used. As stated in the methods this seems AKIN (“AKI was defined as an increase of 50% or 0.3mg/dL over the baseline creatinine value”) whereas in the discussion you cite RIFLE: “the development of AKI (defined as a serum creatinine increase of 25% as compared to the baseline value)”. Please correct and clarify.

-I would shorten the analysis on the multiple studies showing similar and different result from yours. On the other side, an important concept you missed to discuss in the text is: what is the value of predicting AKI occurrence? Is there something that could be done in cardiac surgery patients in order to avoid the predicted event? How much time on the basis of your results could be gained by CysC? Is that enough in your opinion? This kind of reasoning might add some originality to
The multiple limits of your study should be explicitly stated before the conclusion.

MINOR:

- English language revision is needed
- Tabs: AKIN and RIFLE classes are not exactly the same, please specify which classification you used
- Figure legends are in German

-discussion: Rifle “Fail” should be intended as RIFLE “Failure”, if you will leave the RIFLE criteria. Please note that, as already remarked above, RIFLE and AKIN do have some significant differences. In particular, while all RRT patients are automatically defined as AKIN3 this is not necessarily (and not automatically) the same for RIFLE
- discussion: please correct this typo “[Error! Reference source not found.]” that occurs twice in the text

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I do not have to disclose any conflict of interest