PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of renal dysfunction on the management and outcome of acute heart failure: results from the French prospective, multicenter, DeFSSICA survey
AUTHORS	dos Reis, Dominique; Fraticelli, Laurie; Bassand, Adrien; Manzo-Silberman, Stéphane; Peschanski, Nicolas; Charpentier, Sandrine; Elbaz, Meyer; Savary, Dominique; Bonnefoy-Cudraz, Eric; Laribi, Said; Henry, Patrick; Guerraoui, Abdallah; Tazarourte, Karim; Chouihed, Tahar; El Khoury, Carlos

VERSION 1 – REVIEW

REVIEWER	Tobias Breidthardt Division of Internal Medicine and Cardiovascular Research Institute Basel both at the University Hospital Basel, Switzerland
REVIEW RETURNED	17-Apr-2018

GENERAL COMMENTS	In the current manuscript dos Reis and co-workers attempt to study whether impaired renal function decreased shot-term outcome in patients presenting to the emergency department with suspected acute heart failure. This question is of great clinical importance and the authors should be applauded for their efforts. However, I am afraid this manuscript does not further improve our understanding of the CRS (cardiorenal syndrome). 1: In the Method section, page 8, 1st line the authors describe how patients were assigned into the two study groups. The authors describe that only a single measurements of serum creatinine was assessed. This detail has major implications for the interpretation of the data. Using a spot measurement of serum creatinine does not allow the separation of patients with the acute cardiorenal syndrome (acute deteriorations over their own steady state baseline creatinine values) from patients with the chronic cardiorenal syndrome (i.e chronically impaired renal function in the setting of chronic stable heart failure). This is further highlighted by 1/3 of all patients assigned to the CRS group are known to suffer from chronic renal impairment. These patients will be assigned to the CRS group in this study, despite potentially not suffering from any acute changes in renal function. In contrast, patients with acute changes of serum creatinine compared to their own baseline (acute kidney injury), but not fulfilling the <eGFR 60 cutoff will be falsely described as not suffering from CRS. Follwing the classification by Ronco et al. (JACC 2008) the authors appear to mix CRS 1; CRS2 and possibly even CRS5. However the pathophysiologies of these groups and their implications for therapy and patient care are different (See transgloerular pressure

	gradient: Prowle JR DOI: 10.1038/nrneph.2009.213). . This needs to be pointed out by the authors and described as a limitation. 2: In the results section and Tables 1 to 3 the authors describe a vast amount of patient characteristics and significancy levels. Some of these data are only present and/or assessed in very limited patient subgroups and should be excluded from the analysis as the dataset is too small to reliably comment on these parameters (i.e. diabetes mellitus typ 1, n=14; pacemaker n=17; ICD n=16; Echocardiography only performed in 81patients etc). Also please provide significancy levels only to the second decimal. 3: Results: Hospitalization and clinical status The authors suggest that both patient groups were largely similar. I do not agree with this interpretation as there is a consistent trend to more congestion in CRS patients compared to No CRS patients (higher levels of dyspnea, more pulmonary infiltrates on X-Ray, higher NP levels, VC diameter twice the size in CRS compared to no CRS patients). (note: Check data given for CV diameter- should probably be IQR rather than percentage, or unit is not mm). The higher level of congestion might a: lead to the higher spot creatinine levels at admission in the CRS group (acute CRS); b be the reason for the longer in-hospital stay. Additionally, CRS patients were more dependent even before the index hospitalization. Hence CRS patients are worse off before the hospitalization and present with stronger signs of volume overload. The missing significancy are most likely due to the small sample size. 4: Typo in Table 2: GCS>15…..should probably be <15. Discussion: Page 15, line 260ff and oage 17, line 313ff: The authors advocate the use of novel renal biomarkers (such as NGAL and cystatin C) at various points throughout their discussion section. However, the evidence supporting the use of novel biomarkers in AHF is scares. In fact, NGAL was shown to not improve the early detection of AKI over serum creatinine in AHF (Maisel, Akinesis study JACC 2016; Breidthardt critical care 2012 (NGAL). Similar data is available for cystatin C(Breidthardt Clin Biochem. 2017 (Cystatin C). In contrast, the novel biomarker[TIMP-2]·[IGFBP7] which has recently been shown to contribute to a decreased AKI incidence after cardiac surgery by Melanie Meersch (Intensive Care medicine, 2017) is neither mentioned or cited. Please provide a more reflected discussion on the use of novel biomarkers in clinical practice. Page 16/17 The discussion on adequante decongestion is very important as it directly links to the discussion on adequate diuretic dosage, speed of decongesting and therapy duration. While this discussion is important, the current dataset is not able to add to our current understanding as it is lacks longitiudinal observations. The authors might want to include a section on hemoconcentration and timing of hemoconcentration (Haemoconcentration as a treatment goal in heart failure: ready for prime time? Tariq Ahmad and Jeffrey M. Testani, EJHF 2017)

REVIEWER	Luca Di Lullo Department of Nephrology and Dilaysis, L. PArodi - Delfino Hospital, Colleferro (Rome) . Italy
REVIEW RETURNED	01-May-2018

GENERAL COMMENTS	Dear Authors,

	I have read with interest your paper. I think it's very interesting but it presents some criticisms: 1) First of all, it doses provide a whole picture of CKD patients with HF. I think it could be intersting to take a look at more recent paper on cardiorenal syndromes, especially Type - 1 CRS 2) Assessment of renal function has to be performed by single formula and I hope that CKD - EPI is the best one 3) Among medications, it could be interesting to write something more on sacubitril/valsartan therapy and clarify how many patients take this new drug in both groups 4) I suggest to provide more complete selection between CKD stage groups (CKD 1 - 2; CKD 3, CKD 4 and CKD 5) 5) Finally, I suggest improvements in english grammar; some sentences are too long and do not provide clear concepts

VERSION 1 – AUTHOR RESPONSE

Comment	Response
Formatting amendments	
Please provide another copy of your figures with better qualities and please ensure that Figures are of better quality or not pixelated when zoom in. NOTE: They can be in TIFF or JPG format and make sure that they have a resolution of at least 300 dpi. Figures in PDF, DOCUMENT, EXCEL and POWER POINT format are not acceptable. *figure uploaded only 96dpi, should be at least 300dpi	The figure formatting has been updated by a graphics expert and is provided with the resubmitted article as a tif file.
Reviewer #1 (Tobias Breidthardt)	
<u>General comment:</u> This question is of great clinical importance and the authors should be applauded for their efforts. However, I am afraid this manuscript does not further improve our understanding of the CRS (cardiorenal syndrome).	
1. In the Method section, page 8, 1st line the authors describe how patients were assigned into the two study groups. The authors describe that only a single measurements of serum creatinine was assessed. This detail has major implications for the	We thank the reviewer for this interesting comment. We admit that the definition of acute renal failure in our study based on a single estimation of glomerular filtration rate (eGFR) is a limitation for the comparison of the two groups.

	interpretation of the data. Using a spot measurement of serum creatinine does not allow the separation of patients with the acute cardiorenal syndrome (acute deteriorations over their own steady state baseline creatinine values) from patients with the chronic cardiorenal syndrome (i.e chronically impaired renal function in the setting of chronic stable heart failure). This is further highlighted by 1/3 of all patients assigned to the CRS group are known to suffer from chronic renal impairment. These patients will be assigned to the CRS group in this study, despite potentially not suffering from any acute changes in renal function. In contrast, patients with acute changes of serum creatinine compared to their own baseline (acute kidney injury), but not fulfilling the <eGFR 60 cutoff will be falsely described as not suffering from CRS. Follwing the classification by Ronco et al. (JACC 2008) the authors appear to mix CRS 1; CRS2 and possibly even CRS5. However the pathophysiologies of these groups and their implications for therapy and patient care are different (See transgloerular pressure gradient: Prowle JR DOI: 10.1038/nrneph.2009.213). . This needs to be pointed out by the authors and described as a limitation.	The pathophysiology of worsening renal function (WRF) in acute heart failure is complex because of an interaction between multiple mechanisms (e.g. hemodynamic, neurohormonal, intrinsic renal, and therapeutic) as described by Aronson et al 2013 EHJ. We have added this to the Discussion section. Despite the lack of effective therapies or evidence to guide current treatments, cardiorenal syndrome was formerly sub-classified into five subtypes on the basis of the expert opinion of Ronco et al. JACC 2008 (we have added this citation to the sentence in the Discussion in which we refer to the 5 stages of CRS). Therefore, assessment of renal function changes relative to 'baseline' as well as serial creatinine evaluations is critical for the proper assessment of transient WRF (e.g. associated with the introduction of beneficial treatments such as renin– angiotensin– aldosterone blockers and/or congestion relief) and not necessarily associated with adverse events as described by Scheerin et al IJC 2014. The presence of renal failure on admission remains strongly associated with a poor prognosis whatever the anterior renal status and despite the lack of WRF within the first 5 days (Shirakabe et al ESC Heart Failure 2018; 5: 322–331). The use of the 60 mL/min threshold is already included in the limitations paragraph of the Discussion but we have extended this section to include the important points raised by the reviewer as limitations of the study.
2.	In the results section and Tables 1 to 3 the authors describe a vast amount of patient characteristics and significancy levels. Some of these data are only present and/or assessed in very limited patient subgroups and should be excluded from the analysis as the dataset is too small to reliably comment on these parameters (i.e. diabetes mellitus typ 1, n=14; pacemaker n=17; ICD n=16; Echocardiography only performed in 81patients etc).	We have deleted the pacemaker (N=17-36) and defibrillator (N=16) echography data from Table 3 (N= 82). We agree with the reviewer that these data are not particularly robust due to their small sample size. We have added statements to this effect in the Results section, and have removed description of these data from the text. Although we agree that the sample size is also low for Diabetes type I, we have left these data in Table

Also please provide significancy levels only to the second decimal.	1 in order to complement the data for Diabetes type II (rather than removing the data for Diabetes type I but leaving those for Diabetes type II). We have amended all p-values to two decimal places in the tables and text as suggested by the reviewer. Note that some p-values that were below 0.05 become 0.05 after rounding to two decimal places (e.g. 0.049 for chronic heart failute in Table 1): for these the p-value is now set to '<0.05'.
3. Results: Hospitalization and clinical status The authors suggest that both patient groups were largely similar. I do not agree with this interpretation as there is a consistent trend to more congestion in CRS patients compared to No CRS patients (higher levels of dyspnea, more pulmonary infiltrates on X-Ray, higher NP levels, VC diameter twice the size in CRS compared to no CRS patients). (note: Check data given for CV diameter- should probably be IQR rather than percentage, or unit is not mm). The higher level of congestion might a: lead to the higher spot creatinine levels at admission in the CRS group (acute CRS); b be the reason for the longer in-hospital stay. Additionally, CRS patients were more dependent even before the index hospitalization. Hence CRS patients are worse off before the hospitalization and present with stronger signs of volume overload. The missing significancy are most likely due to the small sample size.	This section of the Results has been re-written per the reviewer's comments. We have not included the speculation on the sequelae of the potential trend to more congestion in Group 1 in the results section but have added some text to the second paragraph of the Discussion where the differences between the two groups are discussed (eg, higher BNP and proBNP in CRS patients). We are reluctant to speculate further. The comment regarding VC diameter is now moot since these data have now been removed due to the low sample size (see previous comment and response, and the associated removal of the echography data from the analysis).
4. Typo in Table 2: GCS>15…..should probably be <15.	We have corrected >15 to <15 for GCS.
<u>Discussion:</u> Page 15, line 260ff and oage 17, line 313ff: The authors advocate the use of novel renal biomarkers (such as NGAL and cystatin C) at various points throughout their discussion section. However, the evidence supporting the use of novel biomarkers in AHF is scares. In fact, NGAL was shown to not improve the early detection of AKI over serum creatinine in AHF (Maisel, Akinesis study JACC 2016; Breidthardt critical care 2012 (NGAL). Similar data is available for cystatin C(Breidthardt Clin Biochem. 2017 (Cystatin C). In contrast, the novel biomarker[TIMP-2]·[IGFBP7] which has recently been shown	We have added text to the cited parts of the Discussion to moderate the language used supporting the use of biomarlers ('*While it* is therefore important *to consider the use of* biomarkers…*it is also important to note that the evidence supporting the preferential use of novel biomarkers rather than serum creatinine to detect acute kidney injury can be inconsistent and remains an area for further research*'. Additionally we have added reference to Maisel et al 2016, Briedthardt et al 2012 and 2017, and Meersch 2018).

to contribute to a decreased AKI incidence after cardiac surgery by Melanie Meersch (Intensive Care medicine, 2017) is neither mentioned or cited. Please provide a more reflected discussion on the use of novel biomarkers in clinical practice.	For the sentence starting 'Novel biomarkers such as urinary angiotensin…', we have added '*…with the caveat that the use of such biomarkers can be inconsistent as described earlier.*'
The discussion on adequante decongestion is very important as it directly links to the discussion on adequate diuretic dosage, speed of decongesting and therapy duration. While this discussion is important, the current dataset is not able to add to our current understanding as it is lacks longitiudinal observations. The authors might want to include a section on hemoconcentration and timing of hemoconcentration (Haemoconcentration as a treatment goal in heart failure: ready for prime time? Tariq Ahmad and Jeffrey M. Testani, EJHF 2017)	We agree with the reviewer that hemoconcentration monitoring can be useful to monitor the level of congestion or decongestion, and have added the following text to the Discussion. '*Hemoconcentration monitoring can be useful for monitoring the level of (de)congestion (Ahmad & Testani, 2017) and several routinely assessed biological parameters, e.g. serum protein, albumin, hemoglobin, and hematocrit, have been proposed as surrogate markers (Girerd et al, 2018). Furthermore, formulae have been developed to indirectly estimate plasma volume using hemoglobin and/or hematocrit data (Mentz et al, 2014; Duarte et al, 2015).*' We have not elaborated further since the Discussion is already long and, as the reviewer points out, the current dataset is not able to add to the current understanding, but agree that this is worth mentioning.
Reviewer #2 (Luca Di Lullo)	
General comment: I have read with interest your paper. I think it's very interesting but it presents some criticisms:	
1. First of all, it doses provide a whole picture of CKD patients with HF. I think it could be intersting to take a look at more recent paper on cardiorenal syndromes, especially Type - 1 CRS	We have added to the Introduction that the classification of Ronco et al of CRS into 5 stages is mechanistic, and that the clinical management must consider the full clinical presentation. In the second paragraph of the Introduction we describe that treatments for HF can worsen renal insufficiency (including reference to Testani et al 2016 and Chouihed et al 2016) and have added that the physician should make an appropriate risk risk:benefit assessment for each patient.

		In the Discussion we have reiterated that this is a mechanistic classification and now refer to the earlier (new) text.
2.	Assessment of renal function has to be performed by single formula and I hope that CKD - EPI is the best one	As described in the Methods section, GFR was calculated in our study using the Cockroft-Gault, MDRD, or CKD-EPI equations. We have added further detail to indicate that 8 centres used two methods and 18 centers used one method (the CKD-EPI equation was calculated by 14 centers, MDRD by 12 centers and Cockroft-Gault by 9 centers).
3.	Among medications, it could be interesting to write something more on sacubitril/valsartan therapy and clarify how many patients take this new drug in both groups	No patient were taking sacubitril/valsartan in this study, and so we have not added any text for this.
4.	I suggest to provide more complete selection between CKD stage groups (CKD 1 - 2; CKD 3, CKD 4 and CKD 5)	Unfortunately, the data from the study do not allow us to make this distinction. This is discussed in the paragraph on limitations to the study in the Discussion section.
5.	Finally, I suggest improvements in english grammar; some sentences are too long and do not provide clear concepts	We have made some amendments to the text to reduce the length of some sentences and to try to clarify the concepts presented. Additionally, some items in the Discussion have been removed for clarity and if considered unnecessary, to help focus on the salient points and improve their clarity. The manuscript has been produced and reviewed for English with the support of Lane Medical Writing (cited in the Acknowledgements).

VERSION 2 – REVIEW

REVIEWER	Tobias Breidthardt University Hospital Basel
REVIEW RETURNED	13-Jul-2018

GENERAL COMMENTS	Since the Initial Submission of the publication by dos Reis et al, the manuscript has been improved considerably. The authors should be congratulated for their efforts. However, some minor issues should still be revised before publication of this manuscript. 1. Page 17; lines 303-323: please remove this paragraph. 2. Page 18; Lines 333ff: Hemoconcentration does not only allow to monitor adequalte decongestion, but significantly improves the

	short-term outcome of AHF patients. This should be mentioned. In contrast, the references to novel biomarkers need to be toned down. "further Research is needed to establish the ability of novel biomarkers such as....., to improve clinical decision making and therapy."

REVIEWER	Luca Di Lullo Department of Nephrology and Dilaysis, L. Parodi, Delfino Hospital, Colleferro (Rome), Italy
REVIEW RETURNED	08-Aug-2018

GENERAL COMMENTS	I think that your paper can be now suitable for publication on BMJ Open

VERSION 2 – AUTHOR RESPONSE

Reviewer #1 comment: 1. Page 17; lines 303-323: please remove this paragraph.

Response: We have removed this paragraph as suggested by the reviewer.

Reviewer #1 comment: 2. Lines 333ff: Hemoconcentration does not only allow to monitor adequalte decongestion, but significantly improves the short-term outcome of AHF patients. This should be mentioned. In contrast, the references to novel biomarkers need to be toned down. "further Research is needed to establish the ability of novel biomarkers such as....., to improve clinical decision making and therapy."

Response: We have the text amended to read as below, and have replaced reference 44 (Ahmad & Testani Eur J Heart Fail 2017;19(2):237-240) with Breidthardt et al Eur J Heart Fail 2017;19(2)226-236:

'Additionally, hemoconcentration monitoring can be useful for monitoring congestion and significantly improves the short-term outcome of AHF patients [44] and several routinely assessed biological parameters, e.g. serum protein, albumin, hemoglobin, and hematocrit, have been proposed as surrogate markers [45]. Furthermore, formulae have been developed to indirectly estimate plasma volume using hemoglobin and/or hematocrit data [46-47]. Further research is needed to establish the ability of novel biomarkers such as urinary angiotensinogen [48], neutrophil gelatinase-associated lipocalin [49 50], kidney injury molecule-1 [51], interleukin-18 [52 53], N-acetyl-β-d-glucosaminidase [54], cystatine C [55 56] or a combination of some or all of these could also be used to improve clinical decision making and therapy.'