Author's response to reviews

Title: Comorbidity Profiles and Inpatient Outcomes during Hospitalization for Heart Failure: An Analysis of the U.S. Nationwide Inpatient Sample

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RE: BMC Cardiovascular Disorders - MS: 5630662161250385 - Comorbidity Profiles and Inpatient Outcomes during Hospitalization for Heart Failure: An Analysis of the U.S. Nationwide Inpatient Sample

Response to Reviewers:

Our sincere thanks for your thoughtful review! In particular, we appreciate the comments that our work is valuable, important to the field and innovative. In brief, we have made all changes and edits that were suggested by these fine reviewers.

Reviewer 1 (A. Pucciarelli):

1) These patterns should be considered as being rather dynamic entities which can vary considerably over time, so as to render an over- rigid categorization as being problematic in each of the proposed profiles. These concepts should be briefly addressed in the section ‘Limitations of the study’.

This is an excellent point. We have added the following statement to the limitations sections as suggested: “It is also likely that the comorbidity profiles we identified are dynamic rather than fixed; thus, these profiles are likely to evolve over time along with the progression of both HF and concomitant comorbidities.” – Line 340

2) Another limitation of this work is the lack of discrimination between patients with preserved and those with reduced left ventricular ejection fractions. In studies that included both HFPEF and HFREF, patients with HFPEF were consistently found to be older, were more often female, more predominantly hypertensive, with a higher prevalence of atrial fibrillation but a lower prevalence of coronary artery disease compared with those with HFREF. This could also be highlighted in the section ‘Limitations of the study’ in order to be in keeping with reviews that tend to emphasize the existence of two distinct nosographic entities, namely HFPEF and HFREF, without the mandatory evolution of the former toward to the latter.

We agree and have added the following statement to the limitation section as suggested: “There are important socio-demographic (e.g. older age and female gender), etiological (e.g. greater prevalence of hypertension and atrial fibrillation, and less frequent coronary artery disease),[45] and non-cardiovascular comorbidity differences (e.g. high prevalence of chronic lung, liver and gastric disorders) comparing HF patients with preserved versus reduced ejection.[46] Hence, it will be important to differentiate comorbidity profiles by groups of HF patients with preserved and reduced ejection fraction in future research.” We have cited Lam et al., Eur J Heart Fail. 2011; 13:18-28 as suggested. We have also cited the MAGGIC meta-analysis (Eur Heart J 2012, 33(14):1750-1757) on this same topic. – Line 347
3) According to some authors, considerably more interconnection has been evidenced between etiopathogenesis of HFPEF and diseases that could benefit from interventions in lifestyle, such as diabetes mellitus, obesity and hypertension. Thus, in order to prevent HFPEF in predisposed individuals (mostly hypertensive or diabetic patients) both the rationalization of food intake and regular practice of aerobic exercise is strongly recommended. Thus, in my opinion, the suggested addition would be useful in order to emphasize the complexity of the issues that underlie the etiopathogenesis of these two types of chronic heart failure, whose potential relevance has been substantially disregarded in the new proposed categorization based on comorbidity profiles. **Please express these considerations in the Discussion.**

**Thanks for this great suggestion. We have added the following statement to the discussion:** “Since hypertension and diabetes mellitus were prominent features of both the common and lifestyle comorbidity profiles, dietary modifications and aerobic exercise are two specific lifestyle recommendations that may be helpful in the reduction of cardiovascular risk in these two groups.[32] It is also known that hypertension and obesity are more prevalent among HF patients with preserved versus reduced ejection fraction;[33] thus, interventions to reduce the risk of poor clinical outcomes may be further tailored by HF type within the observed comorbidity profiles.” We cited the AHA lifestyle management guideline and Owan et al., N Engl J Med 2006;355:251–259 as suggested. – Line 282

Reviewer 2 (A. Ciccarelli):

1) … the so-called "common" profile of chronic heart failure has not been outlined in a comprehensive manner. In fact, it seems to me that a detailed description of symptoms and signs is lacking for this pattern. The definition of the so-called “common” profile should be better presented.

**Since this is an administrative database (an in concert with your next comment below), we have neither signs nor symptoms to describe or compare among groups. We agree fully with this reviewer that a better description of the “common” profile is require to provide an effective reference to which we can compare the other comorbidity profiles and have added the following description under the “Identifying Profiles of Comorbidity” subsection under the Results: “There were 2 fewer comorbidities on average in the common profile than the other profiles. The common profile also had the lowest prevalence of cerebrovascular disease (0.8%), myocardial infarction (13.9%), peripheral vascular disorders (5.2%), depression (7.5%), renal disease (0.5%), fluid and electrolyte disorders (20.8%), hypertension (55.8%), and obesity (9.3%) compared with the other profiles. The prevalence of uncomplicated diabetes in the common profile was 27.4% and there were no cases of diabetes with chronic complications. The common profile, named in part because of the size of the profile and the relatively limited comorbid burden, served as a reference to which the other profiles could be compared.” – Line 183

2) This classification was constructed on the basis of administrative data, that is, by evaluating and by numbering the principal diagnosis and secondary ones, as reported in an electronic database prepared by the hospital directorates; as such, it is adversely affected by the inaccuracy that is typical of large studies that do not include clinical data. Thus, my impression is that this classification may be useful for putting forward predictions about hospital costs and the financial management of disease; however, in my opinion, it does not bring much important information to the clinician who wants to schedule the therapeutic management of a
patient with chronic congestive heart failure. In case the authors are in agreement on this point, a few comments about the lack of clinical data (e.g., left ventricular ejection fraction, estimated glomerular filtration rate, mean values of systolic blood pressure, the 6-min walking test, etc.) should be included in the "Strengths and Limitations". In other words, the authors should emphasize that, since clinical data are unavailable, the chance to extract useful information from summary administrative data is rather limited.

We have edited our existing comments about this limitation to now read: “Because of the administrative nature of this data source, we were unable to incorporate granular clinical data (e.g. ejection fraction, which ventricles are involved, blood pressure, glomerular filtration rate, and functional performance measures).” – Line 352

3) The choice of codifying several profiles characterized by different clinical severity and developed on the basis of a simple list of concurrent diseases really offers a rather crude nosographic arrangement. In fact, with such a superficial classification of the comorbidities, the target of defining whether or not there is a causal relationship between chronic cardiac failure and the concomitant pathology is not reached. In other words, the renal dysfunction that occurs in the context of heart failure syndrome after prolonged vigorous diuretic therapy or ultrafiltration for the removal of interstitial fluid generally has a less severe significance compared to the impairment of renal function resulting from diabetic glomerulopathy or nephroangiosclerosis, namely from diseases that are originally independent of chronic heart failure. Ascertaining whether the concomitant disease is a complication of heart failure, a predisposing condition or a simple pathological overlap without any causal relationship is sometimes very difficult or impossible in the presence of only administrative data. This issue should be addressed in the Discussion.

Indeed, our definition of comorbidities was “coexisting conditions to HF” precisely because of our inability to distinguish casual relationships among comorbidities, those having risk factors in common, and those unrelated to HF or one another in this single evaluation of administrative data. Moreover, it was definitely not our intent, explicit or otherwise, to make a causal link between the heart failure and the concomitant pathology and cite other work (not our own) when making assumptions about the pathologies. To address this important comment, we have edited our existing language in the Discussion to now read: “Given the nature of these data, it is not possible to understand the temporal and/or causal nature of relationships among the key differentiating comorbidities in the renal or other profiles.” – Line 295 We have also added the following statement to the Limitations: “We are also unable to distinguish casual relationships among comorbidities, those simple having risk factors in common and the potential pathological links to HF (e.g. complication of, predisposing factor for, or unrelated) in this single evaluation of administrative data; hence, that was not our goal.” – Line 342

4) Since the distinction between left and right or bilateral ventricular failure is often omitted from the electronic archives for administrative use, this important information is lost. In this regard, it should be considered that the renal dysfunction that occurs in left-sided chronic cardiac insufficiency is less frequent and far less serious than that which is realized in right ventricular or biventricular chronic heart failure. Also this issue could be addressed in the Discussion.

Based on this and a comment above, we have also edited our existing language in the Limitations to now read: “Because of the administrative nature of this data source, we were unable to incorporate granular clinical data..."
Moreover, the nosographic discrimination between heart failure with reduced (HFrEF) and that with preserved left ventricular ejection fraction (HFpEF) is only very succintly mentioned. The omission of the well-known distinction between HFpEF and HFrEF is recognized by the Authors, but they underrate the differences in clinical phenotype, judging by their statement that the comorbidities usually do not show any significant differences in comparison between HFrEF and HFpEF (please see the section "Strengths and Limitations": “We also did not differentiate between HF with preserved or unpreserved ejection fraction, although coupling of comorbidities do not seem to differ considerably between these subgroups of HF”). This is incorrect because the burden of co-morbidities is certainly greater in patients with HFpEF, if only for the fact that their mean age is higher. It is important to note that in HFpEF category, female sex, older age, poorly controlled hypertension, diabetes mellitus type II, atrial fibrillation and obesity are much more represented compared to HFrEF. The text should be changed accordingly in the section "Strengths and Limitations", and this issue should be adequately addressed in the Discussion.

Thank you for your attention to this matter. We have removed the citation that caused the concern (was not our original notion). We have also altered our existing text in the Limitations section base on this and the similar comment from Reviewer 1 so now this issue is adequately addressed: “There are important socio-demographic (e.g. older age and female gender), etiological (e.g. greater prevalence of hypertension and atrial fibrillation, and less frequent coronary artery disease),[45] and non-cardiovascular comorbidity differences (e.g. high prevalence of chronic lung, liver and gastric disorders) comparing HF patients with preserved versus reduced ejection.[46] Hence, it will be important to differentiate comorbidity profiles by groups of HF patients with preserved and reduced ejection fraction in future research.” – Line 347

Therefore the subdivision by comorbidity profiles presented by the Authors does not take into account some established distinctive profiles of chronic heart failure, such as the distinction between left-sided, right and biventricular heart failure and that between HFpEF and HFrEF. In truth, each innovative classification should take into account those already existing, to demonstrate that the new proposed schema brings some advantages or additional information with respect to the existing categorizations. Thus, I would advise the Authors to elaborate in the Discussion a brief list of the clinical classifications adopted so far. Thereafter, it would be desirable to highlight the possible points of intersection and divergence with respect to their novel classification based on lists of comorbidities.

Of course this is a good idea. We have added the following paragraph to the Discussion: “There are several existing schemes for classifying the risk of poor inpatient outcomes in HF. For example, Fonarow and colleagues determined that blood urea nitrogen, admission systolic blood pressure, and serum creatinine were predictive of inpatient mortality among adults admitted for decompensated HF.[42] Coronary artery disease, renal
insufficiency and diabetes were more prevalent in the high-versus the low-risk groups in that study. As an additional example, Peterson and group determined that age, systolic blood pressure, blood urea nitrogen, heart rate, serum sodium, coexisting chronic obstructive pulmonary disease, and race were predictive of inpatient mortality among adults admitted for decompensated HF.[43] Thus, the incorporation of coexisting comorbidities into inpatient prognostic models is not new. But, what our findings add to extant knowledge about the influence of comorbidities on inpatient outcomes is a new approach the naturally-occurring clusters of prevalent and coexisting that complicate HF admissions and are associated with significant differences in inpatient outcomes.” We have cited two commonly cited prognostic modes in this paragraph (i.e. Fonarow et al., JAMA 2005, 293(5):572-580, and Peterson et al., Circ Cardiovasc Qual Outcomes 2010, 3(1):25-32.” – Line 316

Our sincere thanks for such a great review!!

Warmest Regards,

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