

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Gender disparities among hospitalized patients with acute myocardial infarction, acute decompensated heart failure, or pneumonia: a retrospective cohort study
AUTHORS	alsawas, mouaz; Wang, Zhen; Murad, M. Hassan; Yousufuddin, Mohammed

VERSION 1 – REVIEW

REVIEWER	Cathleen Muche-Borowski Institute and Polyclinic for Primary Care and Family Medicine, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany
REVIEW RETURNED	30-May-2018

GENERAL COMMENTS	<p>Page 7: Measure of multi-comorbidities: What are the criteria for choosing the twenty chronic conditions. Supplementary table 4 unclear, comorbidities unsorted or sorted by prevalence in row or column?</p> <p>Page 9:results: ..., men were younger! not older in all three conditions. summary of outcomes: 71,94% of men had multi-comorbidities compared to 69,99 of woman. Where do these rates come from? the same question by AMI and pneumonia. I can't find these rates in table 1.</p> <p>Page 10 first row: it should be table 1 not table 2.</p> <p>Page 11: discussion: Why is chest pain or discomfort in AMI now discussed, because ist not mentioned at introduction or at results.</p> <p>Page 12: Pneumonia: Men with pneumonia had significant lower! not higher???(OR:1.19) 30 day mortality...</p> <p>Figure 1 is missed as description and it is men not med</p> <p>Supplementary table 1-3: I can't find code number 428.21, 428.22, 428.23 and so with two numbers behind the point.</p> <p>What does it mean with frequency and %? In relation to what?</p>
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REVIEWER	Raffaele Palladino Imperial College, London, the UK
REVIEW RETURNED	07-Jun-2018

<p>GENERAL COMMENTS</p>	<p>In the present research paper Alsawas and Colleagues aim to investigate gender inequalities in individuals admitted to a tertiary hospital in the US between 1995 and 2015. While the topic might be of interest, there are methodological and conceptual flaws that need to be addressed. Please see comments below:</p> <ol style="list-style-type: none"> 1. By reading the tile it seems like authors are looking at the combined effect of gender and co-morbidities (i.e. whether the gender inequalities differ considering the number of co-morbidities). However, co-morbidities is only a confounder in the main analyses and no interaction term has been fitted to look at this association properly. Therefore, I would suggest to either re-think about the methodological approach or to change the title. Furthermore, authors refer sometimes to "multimorbidity" while the paper clearly looks at specific conditions and adjust for number of co-morbidities, therefore, in this context the term would be misleading. 2. The rationale for specifically choosing these three conditions should be strengthened in the introduction. Why is it important to look at these three and what really this study might add? 3. In the methods section the authors state that in case of multiple hospital admissions they only included the first admission for each patient. While this might be correct when presenting baseline data, I don't see the point of doing so for the main analyses (e.g. 30-day mortality and re-admission) as they are excluding precious data. Instead the authors might decide to fit a two-level mixed-effect logistic model to account for the repeated measures within individuals when computing the standard error. 4. Again, if authors are interested in exploring whether the gender inequalities change by number of co-morbidities they might want to consider to fit an interaction term between gender and co-morbidities groups 5. A quite large proportion of patients have at least two of the three conditions the paper is focusing on (it becomes clear when looking at Table 1). I might have overlooked it but authors do not seem to consider additional sub-groups having more than one of the three conditions when conducting the analyses. Why?
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Cathleen Muche-Borowski

Institution and Country: Institute and Polyclinic for Primary Care and Family Medicine, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany Competing Interests: none declared

Page 7: Measure of multi-comorbidities:

What are the criteria for choosing the twenty chronic conditions. Supplementary table 4 unclear, comorbidities unsorted or sorted by prevalence in row or column?

Thank you for your comment. The comorbidities were chosen based on the Office of the Assistant Secretary for Health. These comorbidities are commonly used in research in the US because of this designation by this office. The methods section cites the rationale for this choice.

Page 9:results: ..., men were younger! not older in all three conditions.

Thank you, corrected

Summary of outcomes: 71,94% of men had multi-comorbidities compared to 69,99 of woman. Where do these rates come from? the same question by AMI and pneumonia. I can't find these rates in table 1.

These rates are for patients with two or more comorbidities.

Page 10 first row: it should be table 1 not table 2.

Thank you, corrected

Page 11: discussion: Why is chest pain or discomfort in AMI now discussed, because ist not mentioned at introduction or at results.

Chest pain is a classic example in which gender disparities are present. Women have atypical presentation, receive delayed treatment and have worse outcomes. This is not from our data. We used it in the discussion section to postulate a possible reason for AMI gender disparities.

Page 12: Pneumonia: Men with pneumonia had significant lower! not higher???(OR:1.19) 30 day mortality...

Thank you, corrected

Figure 1 is missed as description and it is men not med

Thank you, corrected

Supplementary table 1-3: I can't find code number 428.21, 428.22, 428.23 and so with two numbers behind the point.

428.21: Acute systolic heart failure

428.22: Chronic systolic heart failure

428.23: Acute on chronic systolic heart failure

What does it mean with frequency and %? In relation to what?

The frequency means the number of patients that were diagnosed based on that code, and the % is the percentage of the code out of total number of patients. In the revised manuscript, we added this clarification as a footnote to the table.

Reviewer: 2

Reviewer Name: Raffaele Palladino

Institution and Country: Imperial College, London, the UK Competing Interests: No competing interest

In the present research paper Alsawas and Colleagues aim to investigate gender inequalities in individuals admitted to a tertiary hospital in the US between 1995 and 2015. While the topic might be of interest, there are methodological and conceptual flaws that need to be addressed. Please see comments below:

1. By reading the tile it seems like authors are looking at the combined effect of gender and co-morbidities (i.e. whether the gender inequalities differ considering the number of co-morbidities). However, co-morbidities is only a confounder in the main analyses and no interaction term has been fitted to look at this association properly. Therefore, I would suggest to either re-think about the methodological approach or to change the title. Furthermore, authors refer sometimes to "multimorbidity" while the paper clearly looks at specific conditions and adjust for number of co-morbidities, therefore, in this context the term would be misleading.

Thank you for your comment. We agree, the title implies an interaction, which was not our goal. We modified the title to focus on gender disparities.

2. The rationale for specifically choosing these three conditions should be strengthened in the introduction. Why is it important to look at these three and what really this study might add?

Thank you, we added some text to strengthen the rationale for choosing these three conditions in particular. The following paragraph emphasizes the importance of these 3 conditions and why we chose them:

“Acute decompensated heart failure (ADHF), acute myocardial infarction (AMI), and pneumonia are among the most common causes of hospitalization in the United States, with more than 2.5 million hospitalizations per year, and estimated annual hospital cost of \$31.3 billion.^{1,2} Hospitalized patients with ADHF, AMI, or pneumonia are at high risk of death and readmission at 30 days after index hospitalization.^{1,2} In the United States, 15.1% of patients with acute myocardial infarction (AMI), 11.4% of patients with ADHF, and 11.3% patients with pneumonia die within 30 days after hospitalization for respective disorders.^{3,4} Likewise, 24.8%, 19.9% and 18.3% of patients hospitalized for ADHF, AMI, and pneumonia respectively are readmitted within 30 days of the first hospitalization.⁵ Annually, the Centers for Medicare & Medicaid Services (CMS) publically reports a comprehensive overview of national performance as part of the Hospital Inpatient Quality Reporting (IQR) Program, using these three conditions. ^{1,2}”

3. In the methods section the authors state that in case of multiple hospital admissions they only included the first admission for each patient. While this might be correct when presenting baseline data, I don't see the point of doing so for the main analyses (e.g. 30-day mortality and re-admission) as they are excluding precious data. Instead the authors might decide to fit a two-level mixed-effect logistic model to account for the repeated measures within individuals when computing the standard error.

Thank you for your suggestion. We only had data from the first admission for each condition. We mentioned in the limitation section.

Thank you for your suggestion. The data we have were only for patients with first admission for each condition. We added the rationale in the methods part. And we mentioned it in the limitations section.

4. Again, if authors are interested in exploring whether the gender inequalities change by number of co-morbidities they might want to consider to fit an interaction term between gender and co-morbidities groups

As answered above, title was changed for better clarity.

5. A quite large proportion of patients have at least two of the three conditions the paper is focusing on (it becomes clear when looking at Table 1). I might have overlooked it but authors do not seem to consider additional sub-groups having more than one of the three conditions when conducting the analyses. Why?

Thank you for this suggestion. We evaluated the effect of gender disparities in three different cohorts. In the revised manuscript, a subgroup analysis for patients who had any 2 of these conditions was done and added to the manuscript.

VERSION 2 – REVIEW

REVIEWER	Cathleen Muche-Borowski Institute and Polyclinic for Primary Care and Family Medicine University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany
REVIEW RETURNED	08-Aug-2018
GENERAL COMMENTS	references: the youngest reference is from 2014, a lot of references are older

	Results: Information in the text and in the tables should be consistent, especially the data documentation (with or without . or , or to and with or without p-value in the text) In the STROBE Checklist the information e.g. for statistical analysis you will find on page 9 and not on page 8. Please check this.
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REVIEWER	Raffaele Palladino Imperial College London, the UK
REVIEW RETURNED	09-Aug-2018

GENERAL COMMENTS	I found way too vague the authors' reply to the point where I asked reasons why they only considered the first admission for each patients . They stated that they only considered first admission for each patients because those patients are at higher risk of re-admission and mortality. I still think that there is value in considering the entire dataset as a true representation of real-world data, at least as secondary analysis. And proper statistical approaches can take this into consideration. Please strengthen the rational for this choice.
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VERSION 2 – AUTHOR RESPONSE

Reviewer #2 comment

I found way too vague the authors' reply to the point where I asked reasons why they only considered the first admission for each patient. They stated that they only considered first admission for each patient because those patients are at higher risk of re-admission and mortality. I still think that there is value in considering the entire dataset as a true representation of real-world data, at least as secondary analysis. And proper statistical approaches can take this into consideration. Please strengthen the rational for this choice.

Response

We are most grateful and greatly appreciate the time and efforts by the reviewer for critical analysis of this manuscript. We understand reviewer's concern and our response is as follows.

We conceive that the first-ever hospitalization for acute myocardial infarction, acute decompensated heart failure, or pneumonia provide a unique opportunity to study the subsequent mortality or hospital readmission and also to examine the natural history following acute care hospitalization. A prior hospitalization for acute myocardial infarction, heart failure or pneumonia impacts the risk of future events for several reasons.

Patients who experience a hospitalization for acute care condition is at high risk for subsequent hospitalization and mortality. This was elegantly described by Dr. Krumholz from Yale University in a perspective titled "post-hospital syndrome – an acquired, transient condition of generalized risk" in New England Journal of Medicine (N Engl J Med 2013;368:100-102). In a post hoc analysis of data from the Candesartan in Heart failure: Reduction in Mortality and morbidity (CHARM) program (one of the largest heart failure trials), the authors concluded that hospitalization for heart failure prior to enrolment was a powerful predictor of subsequent hospitalization and mortality (Bello et al. Circ Heart Fail 2014;7(4):590-595). Similarly, Solomon and colleagues from Harvard University reported that among heart failure patients, the risk of death is directly related the frequency of prior heart failure

hospitalization (Circulation 2007;116(13):1482-7). We have recently reported that in patients hospitalized for first-ever transient ischemic attack, subsequent mortality is strongly associated with burden of succeeding hospitalizations, measured as number of readmissions (transient ischemic attack-related or unrelated) and days and percentage of follow-up time spent hospitalized (Yousufuddin et al. J Stroke Cerebrovasc Dis 2018 [Epub ahead of print]). These findings suggest that prior hospitalizations for disease-specific condition likely to confound the results of readmission and mortality if 2nd or subsequent hospitalization rather than first-ever hospitalization is used as index hospitalization. Therefore, we considered first-ever hospitalization for index condition for the each study patient.

VERSION 3 – REVIEW

REVIEWER	Raffaele Palladino Imperial College London, the UK
REVIEW RETURNED	27-Nov-2018
GENERAL COMMENTS	Authors clearly explained the rationale supporting their work. I recommend the paper for publication