PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of COPD and asthma on in-hospital mortality and management of patients with heart failure in England and Wales: an observational analysis
AUTHORS	Gulea, Claudia; Zakeri, Rosita; Kallis, Constantinos; Quint, Jennifer

VERSION 1 – REVIEW

REVIEWER	Mandeep Rahi Bridgeport Hospital
REVIEW RETURNED	02-Jan-2022

GENERAL COMMENTS	I would like to congratulate authors on completion of this manuscript. with great date comes great responsibility, in current era of large data analysis this phrase has an important value. Authors recognize this very well in their limitations and are able to draw certain important conclusions from their analysis impacting real-life management of patients with chronic lung disease and cardiovascular disease. Only comment I have is that in introduction section lines 13-23 needs a reference. Under statistical analysis line 30-31 should include 'continuous variables'.

REVIEWER	Andrea S. Melani Univ Siena, Scienze mediche
REVIEW RETURNED	13-Jan-2022

GENERAL COMMENTS	The paper evaluates the effect of some common respiratory diseases, such as asthma and COPD, on in-hospital mortality and management outcomes in subjects hospitalized with heart failure. The paper is well written and interesting. I would like some explanations: to page 6, you write “COPD was defined as having a history of COPD confirmed by spirometry or beta-agonist/ICS inhaler use. However, LABA/ICS are also commonly used in asthma. How many COPD subjects did use LABA/ICS? And which was the percentage of COPD diagnosis based on spirometry? I think that the number of COPD subjects enrolled for LABA/ICS use was very small as more than 90% of included subjects had missing data for bronchodilators. Please add these details Please specify how many asthmatics had a history of childhood asthma, atopy or an asthma diagnosis confirmed by a respiratory physician or both ones, if data are available. Alternatively explain that this information is lacking It is known that some subjects have both asthma and COPD, sometimes named ACOS. Did you succeed in understanding how many subjects might have ACOS in your study? Do you attribute

	ACOS patients to asthma? Please discuss this point briefly Authors write that HF diagnosis was based either on diagnostic tests of clinical investigations which limited misclassifion: However, this is not true for HfpEF, as you recognize. Please underline this point. I see that a a low referral to post-discharge follow-up was a main finding in COPD subjects. It might be that was this remark related to admission in internal wards? Please control and expand this point Authors properly recignize that the large proportion of missing data regarding bronchodilators and inhaled corticosteroids prescriptions prevented evaluation of whether the impact of COPD and asthma on outcomes in patients with HF is mediated by the treatment for their respiratory disease. Perhaps you should emphasize this point into the discussion section. Despite this limit it might be interesting to add a phrase into the discussion section about authors'point-of-view on link between bronchodilators and ICS use and cardiovascular diseases. May you expand this point and eventually comment if ICS/LABA use was harmful or useful for cardiovascular problems in our opinion? I see the lack of several data (missing smoking status in almost 90% of cases) on smoking status. To page 13, you write that smoking status do not modify your conclusions. Are you sure that this comment is proper? To page 8, you write Death occurred in 12% of patients. Did you mean in-hospital death? Please to page 2, into the abstract section, modify Wale into Wales To page 8, you write IHD. Please clear the means of IHD. I suppose Ischaemic Heart Disease. Please also give detail of other similar terms, such as ACE, ARB, MRA. Please adjust the authors'name to page 45, supplemental references, No 4 Figure inserted to page 30. May the addition of level of significance be useful?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Mandeep Rahi, Bridgeport Hospital
Comments to the Author:

I would like to congratulate authors on completion of this manuscript. with great date comes great responsibility, in current era of large data analysis this phrase has an important value. Authors recognize this very well in their limitations and are able to draw certain important conclusions from their analysis impacting real-life management of patients with chronic lung disease and cardiovascular disease. Only comment I have is that in introduction section lines 13-23 needs a reference.

Under statistical analysis line 30-31 should include 'continuous variables'.

Response

We thank the reviewer for the overall appreciation of our study and evaluation of our paper. We have added two references to the Introduction, as suggested.

We have added the suggested wording on page 7:

"…and interquartile ranges [IQR] for continuous variables."

Reviewer: 2
Dr. Andrea S. Melani, Univ Siena
Comments to the Author:
The paper evaluates the effect of some common respiratory diseases, such as asthma and COPD, on in-hospital mortality and management outcomes in subjects hospitalized with heart failure.
The paper is well written and interesting.

Response

We thank the reviewed for the positive assessment of our paper.

I would like some explanations: to page 6, you write "COPD was defined as having a history of COPD confirmed by spirometry or beta-agonist/ICS inhaler use. However, LABA/ICS are also commonly used in asthma. How many COPD subjects did use LABA/ICS? And which was the percentage of COPD diagnosis based on spirometry? I think that the number of COPD subjects enrolled for LABA/ICS use was very small as more than 90% of included subjects had missing data for bronchodilators. Please add these details
Please specify how many asthmatics had a history of childhood asthma, atopy or an asthma diagnosis confirmed by a respiratory physician or both ones, if data are available. Alternatively explain that this information is lacking

Response

According to the data dictionary provided by the National Heart Failure audit[1] (version 4, applicable to the data cut used in this study), the diagnosis of COPD was taken from patient history and was based on spirometry and medication use while asthma was based on a confirmation by a respiratory physician. However, neither quantitative results from the spirometry test, nor data on chronic use of COPD/asthma medication is provided in the dataset and this is a limitation of our study. The exact algorithm and data based on which these diagnoses are entered into the audit are not provided, preventing assessment of diagnoses accuracy. This is mentioned in the Discussion on page 15:

"We did not have however have information on duration and severity of asthma or COPD, nor lung function test results and thus we could not verify accuracy of these diagnoses, which are often subject to misclassification, especially in the elderly. Data on bronchodilator use was largely missing for our cohort (Supplemental Table 2), limiting assessment of both diagnostic accuracy of the respiratory diseases, and association with outcomes evaluated in this study. We also could not differentiate between childhood asthma or late-onset asthma which may have different implications."

It is known that some subjects have both asthma and COPD, sometimes named ACOS. Did you succeed in understanding how many subjects might have ACOS in your study? Do you attribute ACOS patients to asthma? Please discuss this point briefly

Response

[1] https://www.nicor.org.uk/national-cardiac-audit-programme/datasets/

The patient flow is presented on page 14 of the Supplementary Appendix. There were 4,762 patients with ACOS, defined as the presence of both asthma and COPD. However, due to limitations in diagnosis ascertainment discussed in the previous response to reviewers, we cannot ensure validity of this diagnosis. Nonetheless, we evaluated the potential effect of ACOS (as defined in our study notwithstanding the potential large misclassification bias that could be introduced in the analysis) on the main outcome of our study by including an interaction effect (asthma x COPD) in the random-effects logistic regression of in-hospital death. We did not detect a significant association. This is explained on page 1 of the Supplementary Appendix.

The analysis for the main outcome was implemented in a stepwise manner. First, an unconditional model including, COPD was considered. In a second step we added asthma. Third, we added an interaction term between COPD and asthma, to assess whether both diagnoses had a significant contribution to the model. In lack of statistical significance these patients were not considered in further analyses.

For these reasons, we have decided to exclude the ACOS population from the analysis.

Authors write that HF diagnosis was based either on diagnostic tests of clinical investigations which limited misclassifion: However, this is not true for HfpEF, as you recognize. Please underline this point.

Response

The main factor based on which patients entered our cohort was hospitalisation due to HF. HF was based on echocardiography, MRI, nuclear scan, or angiogram – investigations which ensure validity of this diagnosis. We agree that the differentiation between HFrEF and HFpEF has not been based on detailed clinical investigation. HFpEF was an "exclusion diagnosis" (i.e., those not labelled as HFrEF were labelled HFpEF). This is stated on page 6 *("Due to a lack of information regarding specific diagnostic tests required to make a HFpEF diagnosis, we determined HFpEF as patients not categorised as HFrEF[8].")* and page 15 *("HFpEF was determined as a HF diagnosis without systolic dysfunction, which has been used in previous NHFA reports. Nevertheless, there is no consensus gold standard HFpEF diagnosis8 and it remains difficult to validate. Further work in this area is needed, particularly in accurately distinguishing between HFpEF and COPD, which have similar clinical presentation.").*

We have added a sentence on page 4 to underline this point:

"• HF with preserved ejection fraction was an exclusion diagnosis (i.e., defined as HF patients that did not have reduced ejection fraction) due to lack of information regarding specific diagnostic tests to confirm preserved ejection fraction status."

I see that a a low referral to post-discharge follow-up was a main finding in COPD subjects. It might be that was this remark related to admission in internal wards? Please control and expand this point

Response

One reason why patients with HF and COPD were less likely to be referred to cardiology follow-up post discharge may be explained by the fact that more than 60% of these patients had been admitted to a general ward rather than a cardiology ward, for their index HF event. This point has been added to the Discussion, on page 14:

"Further, more than 60% of patients with COPD and HF were admitted to a general ward rather than a specialised cardiology ward, which may also explain the low likelihood of cardiology referrals in this group."

Authors properly recignize that the large proportion of missing data regarding bronchodilators and inhaled corticosteroids prescriptions prevented evaluation of whether the impact of COPD and asthma on outcomes in patients with HF is mediated by the treatment for their respiratory disease. Perhaps you should emphasize this point into the discussion section. Despite this limit it might be interesting to add a phrase into the discussion section about authors' point-of-view on link between bronchodilators and ICS use and cardiovascular diseases.

Response

Since we do not have any reliable data on bronchodilator use in our cohort, it is difficult to speculate on the effect of these treatments on the outcomes considered. We have added a paragraph on this important limitation on page 13:

"However, due to large amounts of missing data on respiratory disease medication prescription in our cohort, we could not verify these assumptions in our dataset. Future studies incorporating accurate information on bronchodilator use in patients with concomitant HF and respiratory disease should be conducted."

We have also discussed data from previous studies and attempted to contextualise previous literature, on page 13:

"RCTs have not demonstrated mortality benefits with ICS in individuals with COPD, although some observational studies suggest the opposite. The largest trial examining all-cause mortality in 16,000 patients with COPD and risk of cardiovascular disease showed the treatments evaluated (long-acting beta-agonists and/or inhaled corticosteroids) were well tolerated by patients, however the effect on patients with existing HF remains under debate."

Previously, we commented on the potential effect of respiratory indications therapies in the context of cardiovascular disease, on page 12 (*"One hypothesis which may underlie the diverging findings on the effect of the two lung diseases on outcomes in patients with HF thus relates to differences in management and their subsequent differential cardiovascular risk. Bronchodilator medications, which are central to the symptomatic treatment of COPD, have been associated with increased cardiovascular risk. While combination treatments such as ICS/LABA may have a good cardiovascular safety profile in asthma, this differs in COPD. RCTs have not demonstrated mortality benefits with ICS in individuals with COPD, although some observational studies suggest the opposite. Since both lung diseases were diagnosed prior to HF admission, it would be plausible to assume that any effects of long-term pulmonary medication could influence the chance of death in our cohort. Thus, the heightened risk of in-hospital mortality observed in the COPD-HF group, but not in asthma-HF could be related to more frequent use of bronchodilators and a poorer safety profile of ICS in COPD compared to asthma.")*

May you expand this point and eventually comment if ICS/LABA use was harmful or useful for cardiovascular problems in our opinion?

Response

Given the large amount of missing data on ICS/LABA use in our data set – 91.4% (please see Supplementary Appendix, page 4), it would be difficult to answer this question with our current data. Possible interpretations have been discussed - please see response to point above.

I see the lack of several data (missing smoking status in almost 90% of cases) on smoking status. To page 13, you write that smoking status do not modify your conclusions. Are you sure that this comment is proper?

Response

We have clarified that results from the analysis including smoking status were based on an imputed dataset (i.e., smoking status was imputed). This has been added on page 16:

"Smoking status was also characterised by a large percentage of missing data, however an analysis using multiple imputation indicated that even after adjusting for this confounder in the imputed dataset, the association between both COPD and asthma on in-hospital mortality remained unchanged."

To page 8, you write Death occurred in 12% of patients. Did you mean in-hospital death?

Response

This has been corrected to*: "In-hospital death occurred in 12% of patients."*

Please to page 2, into the abstract section, modify Wale into Wales

Response

We have corrected the spelling for Wales in the abstract.

To page 8, you write IHD. Please clear the means of IHD. I suppose Ischaemic Heart Disease.

Response

The abbreviation for ischemic heart disease (IHD) is provided on page 7:

"… ischemic heart disease [IHD] …"

Please also give detail of other similar terms, such as ACE, ARB, MRA.

Response

Abbreviations for these terms have been added on page 7:

"… angiotensin-converting-enzyme inhibitors [ACEis], angiotensin receptor blockers [ARBs] and mineralocorticoid receptor antagonists [MRAs]) …"

Please adjust the authors'name to page 45, supplemental references, No 4
Figure inserted to page 30. May the addition of level of significance be useful?

Response

Authors' names have been adjusted in the Supplemental references – reference 4. Figure 3 illustrates percentage of medications prescribed at discharge, across the four groups considered in this analysis. We have chosen not to present statistical comparisons across these groups due to the possibility of detecting small significant statistical differences which don't translate to meaningful clinical interpretation – a frequent caveat of utilizing big data for clinical research.

VERSION 2 – REVIEW

REVIEWER	Andrea S. Melani Univ Siena, Scienze mediche
REVIEW RETURNED	03-Apr-2022

GENERAL COMMENTS	The paper is interesting and well written. the abstract section is accurate and complete. Outcomes are clearly defined. The results sections address the research question or objective The study design is appropriate to answer the research question. Methods are properly described, but I suggest some changes (see following paragraph) I think that some references are partially up-to-date and appropriate. Authors have inserted the old Salpeter's review, but this study seems be overcome. If authors think that bronchodilators can be dangerous, they can write it, but they should update their reference or simply write that it is their opinion, as it is inserted into the discussion. Authors conclude that COPD subjects had worst prognosis and less follow-up visits. As about 40% of subjects are hospitalized into cardiology wards and the others in general wards, they could perhaps adjust their data for this variable. This might confirm if difference in prognosis and follow-up are related to the association COPD-HF itself or to management by different specialists Authors explain that subjects with an EF <40% were categorized as HFrEF. Then they write "Due to a lack of information regarding specific diagnostic tests required to make a HFpEF diagnosis, we determined HFpEF as patients not categorised as HFrEF" I suggest that authors introduce a phrase into the introduction or discussion section to explain their definition of HFpEF or, overall, of HF. At present they write into the main text that there is no agreement on this diagnosis (see page 17) Authors write that COPD was defined as having a history of COPD - chronic bronchitis and/or emphysema, confirmed by spirometry or beta agonist/steroid inhaler use. Please add into the results section the percentage of included COPD subjects based on the first or the second criterium. In addition, ICA/LABA are commonly used even in asthmatic subjects. You should explain your definition in a larger way By contrast , you define Asthma as having a history of childhood asthma and atopy or having an asthma diagnosis confirmed by a respiratory physician. You should enlarge the discussion to explain your definition. Why did you not include COPD diagnosis as confirmed by a respiratory physician?

	You can explain the significance of some abbreviations, such as IHD or AF

VERSION 2 – AUTHOR RESPONSE

Comments to the Author:
The paper is interesting and well written.
the abstract section is accurate and complete.
Outcomes are clearly defined. The results sections address the research question or objective
The study design is appropriate to answer the research question.
Methods are properly described, but I suggest some changes (see following paragraph)

Response: Many thanks for the positive feedback on our paper.

I think that some references are partially up-to-date and appropriate. Authors have inserted the old Salpeter's review, but this study seems be overcome. If authors think that bronchodilators can be dangerous, they can write it, but they should update their reference or simply write that it is their opinion, as it is inserted into the discussion.

Response: We have added references containing more recent data in our Introduction, on page 5 and acknowledge that evidence to support the association between cardiovascular events and beta-agonists comes from meta-analyses and observational studies. We modified the sentence on page 5:

"Meta-analyses and observational studies have suggested the use of beta-agonists or inhaled corticosteroids in both COPD and asthma has been associated with HF-onset, HF-related hospitalisation and increase in cardiovascular events9-11, which depend on disease severity and study setting, but nevertheless worsen prognosis1 7. "

Authors conclude that COPD subjects had worst prognosis and less follow-up visits. As about 40% of subjects are hospitalized into cardiology wards and the others in general wards, they could perhaps adjust their data for this variable. This might confirm if difference in prognosis and follow-up are related to the association COPD-HF itself or to management by different specialists

Response: Thank you for brining attention to this aspect of our study. Our main analysis (to evaluate in-hospital mortality) as well as analyses of post-discharge referrals have been adjusted for place of care (whether patient was admitted to cardiology versus not cardiology ward), please see the footnotes in Table 2 on page 22, as well as Tables 3 and 4 in the Supplementary materials. These data support the interpretation that patients with COPD were more likely to experience in-hospital death, while taking into account the effect of their place of care. Note we made a correction to Table 4 in the Supplementary materials to indicate the Odds Ratio (OR) associated with 'Place of care' refers to the comparison between admission to cardiology ward versus not cardiology ward (OR=0.69, 95%CI [0.67-1.71]).

Authors explain that subjects with an EF <40% were categorized as HFrEF. Then they write "Due to a lack of information regarding specific diagnostic tests required to make a HFpEF diagnosis, we determined HFpEF as patients not categorised as HFrEF" I suggest that authors introduce a phrase into the introduction or discussion section to explain their definition of HFpEF or, overall, of HF. At present they write into the main text that there is no agreement on this diagnosis (see page 17).

Response: The discussion on the gold-standard definition for HFpEF is ongoing in the research community, while the definition for HFrEF is more straightforward and is provided on page 6:

"EF status was defined as HFrEF and HF with preserved EF (HFpEF), determined through echocardiography, MRI, nuclear scan, or angiogram. Those with an EF <40% were categorised HFrEF."

This is to say that the HF diagnosis in our cohort was made after extensive clinical investigations, and that of HFrEF was determined used an accepted definition of less than 40% ejection fraction. The lack of in-depth clinical investigation results for HFpEF are lacking in the data source and thus, this remains a limitation of our study. However, the definition of HFpEF used in this study is mentioned on page 16:

"HFpEF was determined as a HF diagnosis without systolic dysfunction, which has been used in previous NHFA reports."

Authors write that COPD was defined as having a history of COPD - chronic bronchitis and/or emphysema, confirmed by spirometry or beta agonist/steroid inhaler use.
Please add into the results section the percentage of included COPD subjects based on the first or the second criterium. In addition, ICA/LABA are commonly used even in asthmatic subjects. You should explain your definition in a larger way

Response: These data are not available in the National Heart Failure Audit where COPD presence is denoted by a yes/no variable, with no diagnostic tests available. However, according to the National Heart Failure audit data dictionary, COPD is defined as:

"History of COPD - chronic bronchitis, emphysema or their cooccurrence. Must be indicated by pulmonary function testing evidence .ie FEV1<75% predicted value or use of beta agonist/steroid inhalers." – see Table 2 in Supplementary Materials. However, these investigation results are not made available to researchers.

By contrast , you define Asthma as having a history of childhood asthma and atopy or having an asthma diagnosis confirmed by a respiratory physician. You should enlarge the discussion to explain your definition. Why did you not include COPD diagnosis as confirmed by a respiratory physician?

Response: Please note the response above, which also applies to asthma. Asthma is defined in the data dictionary as:

"History of childhood asthma and atopy, or asthma confirmed by respiratory physician for adult onset." – see Table 2 in the Supplementary Appendix – however these data are not made available to researchers.

You can explain the significance of some abbreviations, such as IHD or AF

Response: These abbreviations are explained on page 7:

"…comorbidities (atrial fibrillation [AF], ischemic heart disease [IHD]…". They are also explained in Table 1 (page 20).