Peer Review File
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Reviewer A

This is an important data revealing the current trend of mortality in Group 1 and Group 2-5 PH. In this retrospective study using mortality data from the CDC WONDER database, PH-related mortality continues to increase due to increased mortality in WHO groups 2-5 PH.

Comment 1: WHO groups 2-5 is too heterogenous. Significant advancement has been made in the treatment of CTEPH (e.g., pharmacological [Riociguat] and interventional treatment [BPA]). Thus, elucidation of temporal trends in PH-associated mortality in WHO group 1, group 4, and others PH is more important. It is plausible that an increase in PH-related mortality in WHO group 2 and 3 could be more intense compared to that in group 2-5. This point should be discussed in the individual paragraph.

Reply 1: Many thanks for this very pertinent comment. In response to this comment, we performed a post hoc analysis using multiple cause of death data files and reported mortality trends related to pulmonary hypertension with comorbid conditions associated with WHO group 2 and WHO group 3 pulmonary hypertension to elucidate the predominant subtype responsible for worsening mortality burden in groups 2-5 pulmonary hypertension. We observed doubling of group 2 PH related mortality and 27% increase in group 3 PH mortality. Unfortunately, due to less granular data, we were not able to perform post hoc analysis for WHO group 4 PH.

Changes in the text: We made the modifications in the text. Changes in the methods section pages 6,7,10,11 (lines (162 to 165; 173 to 180;186 to 198;202 to 214;283 to 297;309 to 311; 334 to 339). Table 6 and figures 9 and 10 are added to supplement the text.

Reviewer B

It was a privilege to review the article on temporal trends in PH mortality. I think that this is interesting data, a good use of an existing and well-manicured dataset, and a welcome focus on pulmonary hypertension. I do not have any particularly noteworthy comments on the data or analysis, but do feel like there would be value in better contextualizing the data including limitations.

A couple of points worthy of further consideration:

Comment 1: The authors frame the choice to focus on PH as a primary cause of death as a positive of this study. I would consider a much more measured approach including the addition of limitations around this choice. Specifically, this attribution is fairly clear

in PAH where PAH is the underlying cause of death for the majority of patients with the disease (although might be the proximate cause in <50%). This attribution is MUCH muddier in Group 2-5 PH where PH is not a separate disease process, but in most cases can be considered a marker of other severe diseases (e.g., severe COPD, severe heart failure, etc). This impacts the manuscript in two ways:

Comment 2: (a) framing- the authors refer to an epidemic of Group 2-5 PH. This is like saying there is an epidemic of chest pain when you mean that there is an epidemic of coronary artery disease. Group 2 and 3 PH in particular is a manifestation (and marker of severity) in the underlying heart and lung disease. While there are some who believe that the PH in these conditions is separately targetable, there is not yet strong evidence to support this assertion and many believe that treatment of Group 2 and 3 PH is merely more effective treatment of the underlying disease. Against the reality that there is an epidemic of left heart failure it is worth noting that "epidemics" of the driving disease process may be more relevant than the PH (which may merely be a marker of severity in these other "epidemics").

Reply 2: Thank you so much for your insightful comments and we appreciate your recommendations. To address this concern, the term "epidemic of PH" in the introduction is replaced with "epidemic of diseases associated with PH" and we hope this has satisfied your concerns.

Changes in the text: Changes made in the text page 4, Line 113 in introduction section.

Comment 3: (b) misclassification- as noted above, Group 2 and 3 PH (the likely major drivers of the non-PAH PH category) are predicated on a severe underlying disease as such the attribution of PH as the underlying cause of death is likely to be quite variable (and many would argue -for instance- that the PH is never the underlying cause of death but rather the severe heart failure with reduced ejection fraction). This distinction regarding UCD is based on semantic and not biologic differences given the lack of uniform guidance or stereotyped belief about this. As such, the "primary" attribution of Group 2-5 PH as the UCD is likely to represent a somewhat stochastic fraction of the individuals with an appropriate underlying disease and PH who die. As such, it is possible that the "increase" in ASMR merely reflects changing attitudes such that more people believe that their patient with bad HFrEF and PH died from PH rather than dying from their underling HFrEF. At its extreme, this could show "worsening" ASMR for Group 2 PH even if the prevalence and mortality of the cohort with Group 2 PH was exactly equal over time (and people just shifted their primary attribution from heart failure to PH). This limitation is central in the inference and while I still love this analysis and think that the data is interesting and worth reporting… this limitation needs to be strongly, bluntly, and enthusiastically emphasized.

Reply 3: Many thanks for your comments. To address the concerns (as well as those of reviewer A), we have reviewed our primary analysis and performed a post hoc analysis

using CDC multiple cause of death data files and reported mortality trends related to pulmonary hypertension with comorbid conditions associated with WHO group 2 and WHO group 3 pulmonary hypertension, in an attempt to elucidate the predominant factor responsible for worsening mortality related to groups 2-5 pulmonary hypertension. We observed almost 100% increase on ASMRs related to WHO group 2 comorbidities and 27% increase in ASMRs related to WHO group 3 comorbidities. In addition, we report median age of death as surrogate marker of survival. Corresponding changes in the methods, results, and discussion have also been made. Also, the limitation section of the discussion has been expanded to emphasize that any changes in prevalence over time is not accounted for, and that case fatality cannot be informed from the current iteration of CDC UCOD or MCOD data files.

Changes in the text: We made the modifications in the text. Changes in the methods section pages 6,7,10,11 (lines (162 to 165; 173 to 180;186 to 198;202 to 214;283 to 297;309 to 311; 334 to 339). Table 6,7 and figures 9 and 10 are added to supplement the text.

Comment 4: There is a discussion of sex-based differences in mortality rate. In many areas this is confusing. The discussion is focused most closely on the epidemiologic correlate of case fatality which is not presented in this manuscript. There are gender-based differences in absolute mortality, yet without accompanying prevalence the case fatality (and increased likelihood of survival by sex) is not informed by this work. The casual reader is very likely to misunderstand this point especially with the difference in absolute mortality-rate presented alongside a discussion of case fatality in the discussion. Although this topic is interesting, I would consider a more reductionist approach of reporting the mortality, noting the difference by gender, and being very clear that (without prevalence) the case fatality and likelihood of survival by gender among patients with PH or PAH cannot be informed by this study (where differences in absolute mortality could represent differences in case fatality, misclassification, or prevalence).

Reply 4: Many thanks for your thoughtful comments. CDC MCOD or UCOD datafiles unfortunately do not compile prevalence data. Consequently, in the situation where there is a difference in the prevalence of the disease or prevalence is unknown, direct comparison of ASMRs among variables such as gender and race need to be interpreted with caution. To address this particular concern, we performed post hoc analysis to report median age of death related to PH as a surrogate marker of survival and compared by dichotomizing in two-time frames (2003 to 2010) and (2011 to 2020) (table 7). We also made appropriate necessary changes in the limitation section to highlight this limitation.

Changes in the text: Page 7,10, and 15 and lines (197 to 198;294 to 297;370 to 371;446 to 450). Table 7 for median age of death added.

Reviewer C

• The authors seek to investigate the differences in mortality/outcomes based on PAH WHO-Group subtype in the context of a retrospective cohort study utilizing a CDC database (CDC WONDER).
• The CDC WONDER database derives its information from the national vital statistics system, which in turn obtains mortality data from death certificates in the US, including ICD-10 and demographic data. This was juxtaposed with the age-standardized mortality rates for the US population obtained data from 2003-2020.
• De-identified public data in aggregate did not require IRB approval.
• Comparison between PH mortality across ICD-10 group codes, and longitudinally using change in slope over time for mortality trends.
• 126,526 deaths from PH. Mortality (ASMR) as a whole increased over time, in females it increase and in males it initially decreased and then increased based on jointpoint analysis. PH subtype mortality higher than PAH itself and increased over time (driven by non-PAH mortality).
• PAH mortality declined over time, higher mortality in female versus male. non-PAH mortality increased over time, higher in female versus male.

Comments

Comment 1: Minor – would include years of acquisition of data in methods (2003-2020).

Reply 1: Thanks so much for highlighting this. Changes have been made accordingly. Page 7 and line 202.

Comment 2: Does the dataset (death certificates) contain race/ethnicity information? It would be nice to see if there was a difference in mortality rates for PH or PAH across racial groups, potentially examining if increase in secondary PH driving the increase in PH mortality is concentrated in the non-White population. The latter would be an important piece of information, to help identify the groups that might benefit most from additional research and more targeted screening/diagnostic programs. Historically, data for PH/PAH has come from people who identify as White race, and there has been increasing appreciation that health disparities (socioeconomic status, race, etc.) may play a considerable role in PH and PAH survival and treatment outcomes (Talwar et al. Am J Respir Crit Care Med 2017;196(8):e32-e47.).

Reply 2: Thank you very much for the comment. To address the reviewers' concerns, we performed additional analysis and reported racial data segregated by WHO Group 1 and WHO Groups 2-5 categories.

Changes in the text: Changes reported on page 5,6,7,8,9,13, lines (156;177 to 180;203 to 208;226 to 228; 237 to 238; 264 to 267; 275 to 277; 402 to 426). Corresponding

changes reported in the tables 2, 4, 5, and 7 are made. Figures 4 and 7 are added as well.

Comment 3: Regarding the role of targeted therapy in non-PAH disease (groups 2-5), the authors did not note the significant benefit of inhaled prostacyclin therapy in WHO-Group III PH (due to lung disease) demonstrated by the INCREASE study (Waxman et al. NEJM 2021;384:325-334) and the benefits of targeted therapy in CTEPH (Group IV PH) noted by RCT data in the MERIT-1 study (Ghofrani et al. Lancet Respir Med 2017;5(10):785-794). I would not phrase the current state of targeted therapy as small studies with questionable benefit and clear recommendations against targeted therapy (lines 238-242, page 8). Certainly, the risk is present and the lack of benefit well studied in Group II.

Reply 3: Thank you very much for the suggestions. Changes have been made in the introduction section adding Waxman trial as per reviewers' recommendations. In addition, the "small studies" section has been removed and text changed accordingly.

Changes in the text: page 1,11 lines (106 to 110; 353 to 355).

Reviewer D

Review Summary:
In the submitted manuscript, the authors used CDC's WONDER database to evaluate temporal trends in mortality from PH between 2003 and 2020. PH mortality, defined as having any of the ICD10 codes within I27 as "primary underlying cause of death", increased from 2003-2020 for both males and females. To evaluate subtypes, they separated the I27 codes into I27.0 (designated PAH) and the remainder (designated as Groups 2-5 PH). The overall increasing PH mortality is driven by Groups 2-5 PH, while PAH mortality is declining. Furthermore, they show that mortality from Group 2-5 PH is far more common than mortality from PAH.
I agree with the authors that for uncommon diseases like PH/PAH, centralized data repositories that capture a broader population (in this case, deaths in the US), are important to understanding epidemiology of the disease. The manuscript is well-written. I have some suggestions for improving clarity of the methods.

A major critique, though, is that very similar work was recently published elsewhere. See Kang, et al. Ann Epidemiol 2002 (DOI: 10.1016/j.annepidem.2022.09.001). In that study, Kang used the same data (CDC WONDER) over a slightly different period (1999-2019 rather than 2003-2020) and used the "multiple cause of death" rather than "underlying cause of death" as reported here. Kang reported similar trends to this paper and included breakdown by Group 2 and 3 PH as well as by race and age groups.

Major Concerns:

Comment 1: The report is quite similar in scope and findings to a recent paper by Kang et al referenced above. Would recommend addressing how this work expands on this recently published manuscript (if at all) and compare/contrast your results.

Reply 1: Thank you very much for the comment. We feel that the major difference between our study and the paper by Kang et al is that our study is based on underlying cause of death attributed to pulmonary hypertension, as compared to multiple cause of death used by Kang et al. We believe that reporting the principal cause of death for disease such as PAH adds to the existing body of literature. Furthermore, we dichotomized PH into two cohorts Group 1 and Groups 2-5 to better understand individual mortality burden and temporal trends. In addition, we also amended the manuscript to report median age of death as surrogate marker of survival.

Comment 2: Abbreviations are not consistently defined upon first use.

Reply 2: Many thanks for this comment and changes have been made accordingly.

Comment 3: Introduction (line 82-83) notes "there are no approved pharmacotherapies for PH secondary to … chronic hypoxic lung disease." This is not entirely true given FDA approval for inhaled treprostinil for Group 2 PH due to ILD.

Reply 3: This has been updated in the manuscript to reflect this important point. Text reported on page 1, line (106 to 110).

Comment 4: In methods, PAH is defined as I27.0 only. However, some "associated" forms of PAH, such as PAH complicating connective tissue disease would fall under I27.21. Is this relevant to the CDC WONDER data? While there is always potential for misclassification in ICD-based analyses, does the way the authors queried WONDER potentially systematically misclassify this large group of PAH (CTD-associated)?

Reply 4: Thank you very much for the comment. Misclassification remains one of the limitations of the CDC mortality datafiles and is discussed throughout the manuscript including a dedicated paragraph page 14,15 Lines (428 to 434). However, to highlight the misclassification of secondary PAH, we amended the limitation of the manuscript.

Changes in the text: Page 15 line 442 to 444.
Text changes are: In current study, PAH is defined an ICD code I27.0 only, however some forms of PAH such as PAH secondary to connective tissue diseases might be reported under ICD code I27.2.

Comment 5: Authors should clarify analysis methods and what "statistical testing" was performed. For example, Results, line 157-158 states: "Joinpoint analysis showed one distinct trend indicating a significant increase in PH associated mortality from 2003 to 2020 (EAPC: 2.3% [confidence interval {CI}: 2% – 2.6%]; p = 0.001)". The wording

of “distinct trend”, and “significant” are not clear in this context. Additionally, I suspect the P value is for whether the slope of the line is zero or not, but this is not stated in methods. Please clarify method.

Reply 5: Thank for pointing this out. Changes have been made in the methods section line clarifying the statistical methodology.

Changes in the text: Page 6 lines 173 to 180.

Comment 6: Figures numbered 1-4 are not referenced in the text in that order.

Reply 6: Many thanks for this observation and apologies for this oversight. The figures have been re-labelled based on the order that they are referenced.

Comment 7: Data shows that PAH mortality was 0.67/million in 2020. Thinking about the estimated prevalence of PAH (e.g., estimated at 15-25 cases per million US adults), does this death rate seem correct? If both of these are accurate, only 1:30 cases would die per year, which seems unlikely.

Reply 7: Our study reports PH related mortality using underlying cause of death as case definition. UCOD tend to underestimate and MCOD tend to overestimate the mortality burden from a given condition. The possibility of underestimation has been highlighted in the limitation section of the manuscript.

Comment 8: In Discussion, lines 216-217, authors reference Hyduk and note that PH mortality 1980-2002 was stable. This is likely an oversimplification of the work of Hyduk since there were differences between sex and this is important to note in the current work which also focuses on the effect of sex.

Reply 8: Thanks for noting this. We have reviewed the original manuscript and trends of gender disparity reported by Hyduk et al are mentioned in a different section of discussion to maintain the organization and flow of discussion. The text documented in the original manuscript is now reported on page 12 lines 366 to 368.

Comment 9: Table 2 column for “Relative Change” should be labeled as a percent. Furthermore, the number of decimals could likely be reduced as the hundredth of a percent level of precision is unimportant.

Reply 9: Many thanks for these observations, and we have changed the manuscript accordingly.

Reviewer E

Comment 1: The authors aimed to analyze mortality associated with pulmonary

hypertension using data from the Centers for Disease Control and Prevention Wide-ranging Online for Epidemiologic Research (CDC WONDER) database using ICD-10. The manuscript is well written, however the main issue is the simplicity of ICD-10 for a complex hemodynamic condition like pulmonary hypertension. While I27.0 refers to primary pulmonary hypertension, it is unknown if other PAH subgroups have been coded using I27.0. For e.g. a systemic sclerosis associated PAH may be coded as I27.2 (Other secondary pulmonary hypertension) where in fact we have to deal with a PH Group I. There is also a huge bias in interpreting I27.8 - Other specified pulmonary heart diseases or I27.9 - Pulmonary heart disease, unspecified, where both codes my be referred to either PH Group 2 or 3.

Reply 1: We appreciate the reviewer's comment. To address the reviewers' concerns, we have performed a post hoc analysis using multiple cause of death data files and reported mortality trends related to pulmonary hypertension with comorbid conditions associated with WHO group 2 and WHO group 3 pulmonary hypertension, to elucidate the predominant factor responsible for worsening mortality burden related to groups 2-5 pulmonary hypertension.

Changes in the text: We made the modifications in the text. Changes in the methods section pages 6,7,10,11 (lines (162 to 165; 173 to 180;186 to 198;202 to 214;283 to 297;309 to 311; 334 to 339). Table 6,7 and figures 9 and 10 are added to supplement the text.