

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Predictors of hospitalizations for heart failure and mortality in patients with pulmonary hypertension associated with left heart disease: A systematic review
AUTHORS	Dzudie, Anastase; Kengne, Andre; Thienemann, Friedrich; Sliwa, Karen

VERSION 1 - REVIEW

REVIEWER	Yoshihiro Fukumoto Kurume University, Japan
REVIEW RETURNED	19-Mar-2014

GENERAL COMMENTS	<p>This is a systematic review regarding the evidences on predictors of hospitalization for heart failure and mortality in patients with pulmonary hypertension due to left heart diseases. This is clinically important and interesting. This reviewer has some comments as described below.</p> <p>Comments:</p> <ol style="list-style-type: none">1. This manuscript has online Table 1 and online Figure 2. Where is online Figure 1?2. Also, this manuscript has Tables 1-3; however, there is no description regarding these tables in the text. The authors should put them in the fitted part in the text.3. Further, the authors should visualize the results as in figures, at least regarding mortality and the presence of pulmonary hypertension.4. Through the whole manuscript, the authors should discuss separately estimated pulmonary hypertension by echocardiography from evaluated pulmonary hypertension by right heart catheter.
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REVIEWER	Ennezat, Pierre CHU de Grenoble France
REVIEW RETURNED	18-May-2014

GENERAL COMMENTS	<p>Congratulations for this very comprehensive review on pulmonary hypertension (PH) due to left heart disease. I would see a discussion on the reliability of Doppler echocardiography in the assessment of PH as right cardiac catheterism (RHC) is the gold standard to evaluate PH. Is there any difference between studies that used echo versus RHC (prevalence of patients with PH might be underestimated in echo studied</p>
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	<p>population)?</p> <p>Is there a relationship between the event rate of the population studied and the hazard ratio of PH?</p> <p>Using a cut off for PH the annual event risk of patients with PH and without PH could be shown in each study</p> <p>The discussion should include 3 paragraphs: HF due to reduced EF, HFpEF and valvular disease.</p> <p>The issue of heart transplant and/or LVAD in HFrEF patients with PH should be discussed.</p> <p>The outcome of patients with mitral valve disease and PH could be compared to patients with aortic valve disease and PH</p> <p>Various multivariable prognostic models have been used in these studies; the common variables between studies could be detailed</p> <p>Minor comments: P12 line 27: RVSP increase P12 line 34-35: the sentence regarding RHD is not appropriate in the paragraph on heart failure.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer Name Yoshihiro Fukumoto

Institution and Country Kurume University, Japan

Please state any competing interests or state 'None declared': None declared

This is a systematic review regarding the evidences on predictors of hospitalization for heart failure and mortality in patients with pulmonary hypertension due to left heart diseases. This is clinically important and interesting. This reviewer has some comments as described below.

Comments:

1. This manuscript has online Table 1 and online Figure 2. Where is online Figure 1?

Our response: We thank the reviewer for his comments and for raising this point. The online section now has one box, one table and three figures. Numbers have been removed when necessary.

2. Also, this manuscript has Tables 1-3; however, there is no description regarding these tables in the text. The authors should put them in the fitted part in the text.

Our response: We thank the reviewer for raising this point. We have inserted table 1-3 in the fitted part in the text.

3. Further, the authors should visualize the results as in figures, at least regarding mortality and the presence of pulmonary hypertension.

Our response: We thank the reviewer for raising this important point. 02 figures have been added to better visualize prevalence of PH across studies (when reported) as well as the 12 months mortality when reported.

4. Through the whole manuscript, the authors should discuss separately estimated pulmonary hypertension by echocardiography from evaluated pulmonary hypertension by right heart catheter.

Our response: We thank the reviewer for raising this point which we have addressed by now presenting the result throughout for all studies, and separately for those with a diagnosis of PH based on cardiac echo, and those with diagnosis based on cardiac catheterization. The reviewer will realize that studies relating PH to outcomes during following are overwhelmingly dominated by studies of PH based on cardiac echo. This limitation precluded any meaningful discussion of the relationship of PH with the outcome according to the method for diagnosing PH. Nevertheless we have discussed the limitations of Doppler echo diagnosing PH on page 16.

Reviewer Name Ennezat

Institution and Country CHU de Grenoble

France

Please state any competing interests or state 'None declared': None declared

Congratulations for this very comprehensive review on pulmonary hypertension (PH) due to left heart disease.

I would see a discussion on the reliability of Doppler echocardiography in the assessment of PH as right cardiac catheterism (RHC) is the gold standard to evaluate PH. Is there any difference between studies that used echo versus RHC (prevalence of patients with PH might be underestimated in echo studied population)?

Our response: We thank the reviewer for his appreciation and for raising this point. There was a multiplicity of PH definitions based both on RHC and echocardiography parameters, limiting any possibility of pooling and not all studies reported the prevalence of PH. Furthermore, only 2 of 13 studies using RHC reported on the prevalence of PH, surely because performing RHC on all patients to determine a prevalence of PH would bear excessive risks and be impractical in any cost-constrained environment. We have reflected this on the online figure 2 and we have inserted a paragraph on reliability of Doppler echocardiography in the assessment of PH as compared with RHC.

Is there a relationship between the event rate of the population studied and the hazard ratio of PH? Using a cut off for PH the annual event risk of patients with PH and without PH could be shown in each study

Our response: We thank the reviewer for raising this point. Assuming that the proportional hazard assumption is fulfilled one would expect the hazard ratio to be almost of the same magnitude regardless of the event rate in a given population. What the event rate adds however is the precision (confidence interval) around the estimate of the hazard ratio. The higher the event rate, the narrower the confidence interval; the lower the event rate, the wider the confidence interval.

In Table 2, we have provided the cut-off used in each study to define PH, but in the absence of primary data from each study, we are unable to provide the annual event rate at this cut-off for each study.

The discussion should include 3 paragraphs: HF due to reduced EF, HFpEF and valvular disease.

Our response: We thank the reviewer for raising this point. Discussion has been structured in 3 paragraphs as per request.

The issue of heart transplant and/or LVAD in HFrEF patients with PH should be discussed.

Our response: We thank the reviewer for raising this point. Only studies in patients awaiting heart transplant were included and this is PH due to HFrEF. Studies on persistent PH following heart transplantation were not included because of the complexity of classification of PH in this population. This has now been reflected in the method section.

The outcome of patients with mitral valve disease and PH could be compared to patients with aortic valve disease and PH.

Our response: We thank the reviewer for raising this point. Unfortunately, once again, the multiplicity of PH definitions based both on RHC and echocardiography parameters, the heterogeneity of the population (Isolated mitral and aortic valve disease but also combined mitral and aortic valve disease) and duration of follow up precluded any pooling.

Various multivariable prognostic models have been used in these studies; the common variables between studies could be detailed

Our response: We thank the reviewer for raising this important point. In table 3 we have highlighted a

variety of other prognostic factors that were invariably used in the models and commented on the most relevant.

Minor comments:

P12 line 27: RVSP increase

Our response: We have corrected.

P12 line 34-35: the sentence regarding RHD is not appropriate in the paragraph on heart failure.

Our response: The sentence has been removed.

VERSION 2 – REVIEW

REVIEWER	Fukumoto, Yoshihiro Kurume University Japan
REVIEW RETURNED	17-Jun-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	Ennezat, Pierre CHU de Grenoble, France
REVIEW RETURNED	15-Jun-2014

- The reviewer completed the checklist but made no further comments.