

Peer Review File

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Reviewer A

The paper by Lee et al. is a meta-analysis investigating the utility of the effectiveness of pulmonary artery catheter monitoring in cardiogenic shock. The current literature on the effectiveness of PAC monitoring in cardiogenic shock is inconclusive. Most studies are retrospective observational and have many possible confounders. The metanalysis aims to review the current literature and understand PAC's utility in different forms of cardiogenic shock by etiology.

The study screened 79 papers and included 12 in the final analysis. The study was overall well performed and well written. Though it has several limitations that I believe should be addressed

1. Despite starting with 12 papers, the meta-analysis divided the causes of cardiogenic shock into three categories, two distinct (ACS and ADHF) and one all-inclusive for "non-specific etiologies." This poses two main issues:

a. There is a high probability that many patients in the latter group fall into the first two groups.

Reply: We appreciate the reviewer's valuable comments. As you have recommended, we reviewed the six studies categorized as "non-specific etiology". Except for two articles that did not document the causes of cardiogenic shock, the proportions of patients with ACS in the overall cardiogenic shock groups ranged from approximately 40% to 74%. We have summarized this in Table 2. In response to the reviewer's comment, we have mentioned this in

the Result and Discussion section of the manuscript

Table 2 Summary of proportions of patients with ACS among those with cardiogenic shock in the studies of non-specific causes

Study ID	PAC	No PAC
Doshi 2018	ACS: 45.5%	ACS: 53.2%
Hernandez 2019	STEMI 24.3% Non-STEMI 12.9% Acute HF 11.4%	
Ranka 2020	Unknown	Unknown
Sionis 2020	ACS 74%	ACS 85%
Osman 2021	STEMI 19.9% Non-STEMI 21.9%	STEMI 20.3% Non-STEMI 22.2%
Sidhu 2017	Unknown	Unknown

Abbreviations: ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; PAC, pulmonary artery catheterization.

Result, Page 9, Line 160-163

In the studies that the cause of CS was not accurately described, the proportions of patients with ACS in the overall cardiogenic shock groups ranged from approximately 40% to 75%. These data were summarized in Table 2.

Discussion, Page 12, Line 224-233

In the present study, we hypothesized that outcomes associated with invasive hemodynamic monitoring would vary depending on the cause of CS. We found that a specific subgroup of patients with CS caused by ADHF potentially derived a survival benefit from PAC use, while patients with CS caused by ACS did not. Also, the use of PAC did not have a significant benefit in the subgroup of patients with CS cause by non-specific etiology, but the proportion of ACS in these studies was about 40% to 70%. These factors would affect entire analysis. This analysis provides the first evidence of varying PAC-related outcomes according to the underlying cause of shock. Additionally, this is the first meta-analysis to reveal a beneficial effect of PAC for CS caused by ADHF, a result that conflicts with the conventional belief that PAC is not useful in the management of ADHF.

b. The conclusions drawn on the two sub-groups are based on very few papers.

Reply: We appreciate the reviewer's valuable comment, and we totally agree. We searched several studies in various ways, but it was difficult to find studies that clearly documented the cause of cardiogenic shock and in-hospital mortality based on each cause. However, the subgroup data were from prospective research. Although randomized clinical trials are not included, the evidence level is stronger than if only retrospective data were used. It might be good to implement IPD meta-analysis, but it would be challenging to collect data in this case. We sincerely hope that the reviewer understands this situation.

2. The group of ADHF patients consisted of only two studies. Both are already known as positive studies. Although this is helpful information to any clinician, performing a meta-

analysis did not provide new insight into this group.

Reply: We appreciate the reviewer's valuable comment. Through this meta-analysis, we tried to figure out the efficacy of using PAC for specific causes of cardiogenic shock. In particular, subgroup data collection was challenging because PAC was not routinely used. However, this review is meaningful in that it can be used to verify continuity between previous studies investigating PAC use in patients with ADHF and can be beneficial for comparisons with other causes of cardiogenic shock.

3. The level of heterogeneity is evident by the i2 score is very high in 2 groups (ACS, non-specific). This can be due to differences in participants, interventions, or outcomes and is not sufficiently addressed.

Reply: We appreciate the reviewer's valuable comment. As reviewer mentioned, the level of heterogeneity is high, and most of the data are retrospective. These are limitations of our review. Therefore, future prospective studies investigating the use of PAC for patients with cardiogenic shock are required to overcome this limitation. In response to the reviewer's comment, we have mentioned this in the Discussion section of the manuscript.

Discussion, Page 10-11, Line 187-192

In this systematic review and meta-analysis comprising twelve observational studies, the use of PAC did not significantly impact in-hospital mortality among CS patients overall; however, a nonsignificant trend favoring PAC use was found. The results of this review were inconsistent with the results of earlier studies that found PAC to be useful in the management of CS. However, the results of this analysis highlight the need for more evidence based on prospective, randomized clinical trials investigating PAC use in the management of CS.

Minor Comments

- **Line 92 – "of" should be "in"**

Reply: This has been changed.

Introduction, Page 5, Line 92

From.

A recent large cohort study showed a decline of PAC use for CS, despite improved outcomes

To.

A recent large cohort study showed a decline in PAC use for CS, despite improved outcomes

- **Line 194 – "meta-analysis" should be "meta-analyses" (referring to plural)**

Reply: This has been changed.

Discussion, Page 10, Line 194

From.

Recently, several meta-analysis have been reported for CS.

To.

Recently, several meta-analyses have been reported for CS.

- **Line 228 – "administered to" should be changed to "used in"**

Reply: This has been changed.

Discussion, Page 12, Line 228

From.

In addition, among patients treated with CS with ACS, PAC would have administered to patients who had a greater disease severity that required MCS, compared with patients of the non-PAC group

To.

In addition, among patients treated with CS with ACS, PAC would have use in patients who had a greater disease severity that required MCS, compared with patients of the non-PAC group

Finally – I believe that the scarcity of papers in each sub-group, especially the ADHF, and the high level of heterogeneity make this study a very interesting analysis but one that will not alter or affirm current clinical practice. I would suggest trying to obtain the etiologies of cardiogenic shock in the papers in the third group and thus enhance the patient population of each sub-group. Alternatively, avoid making the division into sub-groups the paper's focus, and provide more emphasis on the pooled effect mentioning the sub-groups in specific paragraphs in the results and discussion sections.

Reply

This is an excellent point that was well taken by the authors. As per the reviewer's comment, we have modified the expression emphasizing the division into subgroups in the introduction, discussion, conclusions, and even the title. We have added new paragraphs explaining the meaning of the pooled effect of PAC monitoring of patients with CS. In other words, we have changed the paper's focus into the pooled effect of PAC as per the reviewer's advice.

Additionally, the PAC outcomes according to the cause of shock are discussed in a paragraph in the Discussion section. We have also reorganized the Discussion section according to your

advice. We hope that our revisions meet the reviewers' approval.

Abstract, Conclusion, Page 4, Line 58-63

Overall, our meta-analysis demonstrated no significant association between PAC monitoring and in-hospital mortality among patients managed for cardiogenic shock. The use of PAC in the management of cardiogenic shock caused by acute decompensated heart failure was associated with lower in-hospital mortality, but there was no association between PAC monitoring and in-hospital mortality among patients with cardiogenic shock caused by acute coronary syndrome.

Discussion, Page 12, Line 211-233

The use of PAC monitoring for patients with CS has decreased even though its use has shown clinical benefits (21). One reason has been the difficulty in interpreting data obtained from PAC studies and the consequent difficulty with clinical decision-making. Another reason has been the poor quality of evidence regarding the use of PAC. Many CS studies have been retrospective, observational studies. Moreover, many of the relevant randomized controlled studies have not proven improvements in outcomes associated with PAC monitoring in the management of various conditions (27, 28). It could be argued that sicker patients may receive PAC and have a high a risk of mortality that is not specifically related to the PAC use itself. However, PAC has been reported to cause complications, such as bleeding or infection (8). In this review and meta-analysis, PAC use was not significantly associated with in-hospital mortality among CS patients, even though a nonsignificant trend favoring PAC use was found. This result does not imply that PAC should not be used in the management of CS; rather, the findings may point to an emphasis on better selection of patients who may benefit from PAC.

In the present study, we hypothesized that outcomes associated with invasive hemodynamic monitoring would vary depending on the cause of CS. We found that a specific subgroup of patients with CS caused by ADHF potentially derived a survival benefit from PAC use, while patients with CS caused by ACS did not. Also, the use of PAC did not have a significant benefit in the subgroup of patients with CS cause by non-specific etiology, but the proportion of ACS in these studies was about 40% to 70%. These factors would affect entire analysis. This analysis provides the first evidence of varying PAC-related outcomes according to the underlying cause of shock. Additionally, this is the first meta-analysis to reveal a beneficial effect of PAC for CS caused by ADHF, a result that conflicts with the conventional belief that PAC is not useful in the management of ADHF.

Reference

27. Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006;354:2213-24.
28. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003;348:5-14.

Reviewer B

Authors combine too many observational studies which vary significantly in terms of underlying patient population in this meta analysis. Furthermore, multiple NIS studies have been used which do not lend themselves to meta analysis due to overlapping patient population.

Reply: We appreciate the reviewer's valuable comment. In our review, many observational studies with various populations were included. However, all studies included patients with cardiogenic shock. Also, there were some observational studies based on NIS data. However, the studies varied in terms of sampling periods and the presence or absence of adjustments for confounding variables. We admit that collecting subgroup data (according to the causes of cardiogenic shock) was challenging. This is a limitation of our study. However, as far as we know, this is the first meta-analysis attempting to figure out the efficacy of using PAC for specific causes of cardiogenic shock through several observational studies. Also, it may bring attention to the necessity of further prospective studies or randomized controlled trials to provide stronger evidence to support (or refute) these findings.

Discussion, Page 14, Line 259-263

Although this is a large database of patients managed in the United States, even though the studies varied in terms of sampling periods and the presence or absence of adjustments for confounding variables, many studies have overlapping time frames, and there is potential for unmeasured confounding. Caution should, therefore, be taken when interpreting the results.

Authors have not used Garab et al study showing clear benefit in CS when all swan

numbers are available.

Reply; We appreciate the reviewer's valuable comment. As you have mentioned, it would be more helpful if the meta-analysis included the data from the article by Garan *et al.* However, that article does not include the exact numbers of in-hospital deaths according to causes of cardiogenic shock. Thus, we twice tried to contact Garan and Kapur, the first and corresponding authors of the paper, by e-mail. Unfortunately, we did not receive replies. We totally agree with the reviewer's opinion that the meta-analysis should include these data from Garan's study, but we sincerely hope the reviewer can understand our challenges.