PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	THE PREDICTIVE VALUE OF TACHYCARDIA FOR MORTALITY IN TRAUMA-RELATED HEMORRHAGIC SHOCK: A SYSTEMATIC REVIEW AND META-REGRESSION
AUTHORS	Jávor, Péter; Hanák, Lilla; Hegyi, Péter; Csonka, Endre; Butt, Edina; Horváth, Tamara; Góg, István; Lukacs, Anita; Soós, Alexandra; Rumbus, Zoltán; Pákai, Eszter; Toldi, János; Hartmann, Petra

VERSION 1 – REVIEW

REVIEWER	Philippe Le Conte Université de Nantes, Emergency Medicine
REVIEW RETURNED	30-Nov-2021

GENERAL COMMENTS	Thank you to give me the opportunity to review this interesting paper. The authors investigated relationship between tachycardia and mortality in patients with hemorrhagic shock. The paper is well written, methodology is adequate, results are interesting. There are only two minor points to be addressed before publication: ◦ l120: hemodynamical instead of hemodinamical ◦ l173-178: please use the past tense

REVIEWER	Sam Hutchings Royal Centre for Defence Medicine, Queen Elizabeth Hospital, Birmingham, B152TH, United Kingdom
REVIEW RETURNED	20-May-2022

GENERAL COMMENTS	This is a well written study with appropriate methodology exploring the lack of relation between heart rate and mortality in haemorrhage.

REVIEWER	Etienne Dantan INSERM UMR 1246 Methods in Patients-Centered Outcomes and Health Research
REVIEW RETURNED	30-Jun-2022

GENERAL COMMENTS	Overall comments to the Author: In this article, the author conducted a systematic review to study the role of the heart rate in the initial hemodynamic assessment of patients suffering a trauma-related hemorrhagic shock. The authors clearly justify in the introduction the debate surrounding the heart rate and its possible linear relation with the shock severity. While the heart rate may be influenced by hemodynamic changes, it is also sensitive to other variables as anxiety, pain, etc. This is why the heart rate is still under debate to evaluate trauma patients. For these reasons, it is therefore important to have a clear current state of the art on the role of heart rate on trauma patients' assessment. This article presents a systematic review aiming to

	objectively describe the relation between heart rate and mortality from bleeding trauma patients. The answer is of major importance from a clinical perspective. The systematic review has been conducted following appropriate methodology and recommendations. Risk of bias assessment have been assessed. Nevertheless, I found the statistical analysis unclear and insufficiently developed to understand what have been done and be convinced by the results. In my opinion, this part should be completed to improve the article. Additionally, some precisions concerning expected reporting of systematic reviews can be provided to consolidate the article and facilitate its understanding. Major comments 1. In the abstract, you wrote “Regarding its efficiency as a predictor of mortality, there is contradictory data in the literature”. I find this sentence slightly fuzzy since we would like to understand in which ways goes the contradictions. 2. In the abstract, it may be relevant to indicate that the systematic review was conducted following the PRISMA recommendations, and also to mention the date at which the systematic review was performed. 3. I am not sure to understand the abstract conclusion. You did not observe any significant association from your meta-regression, but you concluded that “tachycardia should raise suspicion for bleeding. Can you clarify? 4. In the abstract conclusion, if I correctly understood, when analyzing the subgroup of patients receiving blood products, you interpret the inappropriateness to guide therapeutic decision as transfusion of blood products. In my opinion, this is a conclusion that overinterpreted the results. Your work was not a systematic review of randomized trial or observational studies that compare patients receiving the transfusion and patients not receiving the transfusion. I think that you have to temperate your conclusion. 5. First bullet of strengths and limitations is too imprecise in my opinion. 6. In the introduction, I am not sure to understand to what “base deficit” refers? 7. In the introduction, do I have to understand that were four classes in the “shock classes according to ATLS guidance”? 8. Is this systematic study was declared under PROSPERO register? 9. In the search strategy subsection, could you indicate the date for the articles search and if necessary the date restriction? I find that the information come late (in the study selection subsection). 10. An important remark concerns the necessity to clarify the eligibility criteria. In my opinion, this is important to better understand which studies could be retained and why they were included it in the statistical analysis.

	In the abstract, the study selection is insufficiently clear. What are the “eligibility criteria”? Could you slightly reformulate the eligibility criteria subsection to clarify the criteria concerning studies inclusion and those for patients? I understood that studies including bleeding trauma patients were included. Are there more patients’ criteria for inclusion? I understood that only English studies were included, those without any information about initial heart rate values were not included, etc. Are there other studies inclusion criteria? Is there any restriction for study design (observational cohorts, randomized clinical trials, pilot studies, etc.)? How were considered previous published reviews, meta-analysis, conference abstracts? The PRISMA flow diagram could also be completed by specify reasons of non-inclusion based on title and abstract screening. 11. Why did you not consider studies with patients older than 55 years? 12. The data extraction form could be provided in supplementary materials. Does Table 1 correspond to the exhaustive information that were collected from included articles? This is also an important remark to clarify the collected outcomes that will be then analyzed. Without being sure, the heterogeneity in the mortality outcomes definition could be an important issue for your meta-regression. 13. The statistical analysis is insufficiently developed to understand what have been done. “Meta-regression” term is too imprecise in my opinion. Could you improve this subsection? For instance, which modeling regression have been exactly used? There may be a heterogeneity in the main outcome definition? Mortality can be a censored outcome. Some included studies may have some patients lost of follow-up inducing censoring. In trauma context, patients are well followed, censoring would be therefore not an issue. If there was no censoring, the horizon time would differ between studies. It would be therefore difficult to perform the statistical analysis without considering this temporal issue. More precision could be added to convince readers. As it stands, Figure 3 and 4 seems to represent linear regression between heart rate and mortality percentage of each study. How do you consider size of the included studies? How do you assess the modeling assumptions, goodness-of-fit, etc.? How can you consider the fact the heart rate could be measured at prehospital admission or upon admission? 14. In table 1, why some texts are italic and others not? In table 1, what does mean the label data collection? Does it refer to patient study collection from prospective observational cohort or retrospective study? Table 1 title is about baseline characteristics of the included study. I find that may be enriched with additional description about gender, age, variables to describe shock gravity, etc. Mortality is possibly not the primary outcome and all the retained studies. If not, what were the other outcomes of interest? 15. In the paper, it is only questioned to assess the univariate relationship between the heart rate and mortality. But, confounding factors are probably highly important to consider in such context. At

	any time in the article, this is considered in the analysis or at least discussed. Minor comments 1. I am not sure of the term “meta-regression”. Does it mean meta-analysis? 2. In the strengths and limitations, I would find it preferable to indicate the exact period of the study instead of the expression “from the past 10 years”? 3. In the strengths and limitations, there is a typo: “meat-regression” 4. References in brackets should be reported before punctuations. 5. Title of Figure 1 could indicate that is the PRISMA flow diagram. 6. There are abbreviations in the footnote of table 1. All the abbreviations used in the article could be reported in a specific list.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Philippe Le Conte, Université de Nantes, Centre Hospitalier Universitaire de Nantes

Comments to the Author:

Thank you to give me the opportunity to review this interesting paper. The authors investigated relationship between tachycardia and mortality in patients with hemorrhagic shock. The paper is well written, methodology is adequate, results are interesting. There are only two minor points to be addressed before publication:

- **l120: hemodynamical instead of hemodinamical**
- **l173-178: please use the past tense**

Thank you for the positive criticism of our paper. The highlighted mistakes have been corrected accordingly:

Page 5, line 131: *“…examination and/or hemodynamical instability after trauma and/or abdominal gunshot injury, the patient…”*

Page 7, lines 183-189: *“Table 1. Baseline characteristics of the included studies. The majority of the papers enrolled trauma patients who received blood products and/or showed signs of hemodynamic instability. Hemodynamic instability was defined by vital parameters in most cases. Most of the data was collected retrospectively. The number of participants in each dataset ranged from 15 to 428. There was a significant heterogeneity in mortality between datasets. The need for massive transfusion was accompanied by a prominently high mortality rate. A mean heart rate (HR) > 120 bpm did not entail an outstanding mortality rate.”*

Reviewer: 2

Dr. Sam Hutchings, Royal Centre for Defence Medicine, Queen Elizabeth Hospital, Birmingham, B152TH, United Kingdom, Kings College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom

Comments to the Author:

This is a well written study with appropriate methodology exploring the lack of relation between heart rate and mortality in haemorrhage.

Thank you for reviewing our paper.

Reviewer: 3

Dr. Etienne Dantan, INSERM UMR 1246 Methods in Patients-Centered Outcomes and Health Research

Comments to the Author:

Overall comments to the Author:

In this article, the author conducted a systematic review to study the role of the heart rate in the initial hemodynamic assessment of patients suffering a trauma-related hemorrhagic shock. The authors clearly justify in the introduction the debate surrounding the heart rate and its possible linear relation with the shock severity. While the heart rate may be influenced by hemodynamic changes, it is also sensitive to other variables as anxiety, pain, etc. This is why the heart rate is still under debate to evaluate trauma patients.

For these reasons, it is therefore important to have a clear current state of the art on the role of heart rate on trauma patients' assessment. This article presents a systematic review aiming to objectively describe the relation between heart rate and mortality from bleeding trauma patients. The answer is of major importance from a clinical perspective.

The systematic review has been conducted following appropriate methodology and recommendations. Risk of bias assessment have been assessed. Nevertheless, I found the statistical analysis unclear and insufficiently developed to understand what have been done and be convinced by the results. In my opinion, this part should be completed to improve the article. Additionally, some precisions concerning expected reporting of systematic reviews can be provided to consolidate the article and facilitate its understanding.

Major comments

1.) In the abstract, you wrote "Regarding its efficiency as a predictor of mortality, there is contradictory data in the literature". I find this sentence slightly fuzzy since we would like to understand in which ways goes the contradictions.

Thank you for this remark. We have rephrased this sentence to express its intended message more clearly (page 2, lines 28-29): *"However, its efficiency as a predictor of mortality is contradicted by several studies."*

2.) In the abstract, it may be relevant to indicate that the systematic review was conducted following the PRISMA recommendations, and also to mention the date at which the systematic review was performed.

Thank you for this advice. The abstract has been extended accordingly:

Page 2, lines 41-42: *"The study follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations."*

Page 2, lines 33-35: *"Systematic search of EMBASE, MEDLINE, CENTRAL and Web of Science databases was performed on 1-September-2020 to identify papers providing early HR and mortality data on bleeding trauma patients from the past decade."*

3.) I am not sure to understand the abstract conclusion. You did not observe any significant association from your meta-regression, but you concluded that "tachycardia should raise suspicion for bleeding. Can you clarify?

Thank you for drawing attention to this. We intended to moderate our conclusion stating that heart rate is an inadequate guide for clinical decision-making in the initial management of trauma patients with hemorrhage. However, we agree that this resulted in a somewhat obscure message; thus, we reformulated the Conclusions part of our abstract (page 2, lines 47-50):

"In accordance with the literature demonstrating the multi-phasic response of HR to bleeding, our study presents the lack of linear association between post-injury HR and mortality. Modifying the pattern of HR-derangements in the ATLS shock classification may result in a more precise teaching tool for young clinicians."

4.) In the abstract conclusion, if I correctly understood, when analyzing the subgroup of patients receiving blood products, you interpret the inappropriateness to guide therapeutic decision as transfusion of blood products. In my opinion, this is a conclusion that overinterpreted the results. Your work was not a systematic review of randomized trial or observational studies that compare patients receiving the transfusion and patients not receiving the transfusion. I think that you have to temperate your conclusion.

Thank you for this advice. The conclusion section has been rephrased (page 2, lines 47-50).

5.) First bullet of strengths and limitations is too imprecise in my opinion.

Thank you for notifying this. The Strengths and Limitations section has been revised, and we agree that the first bullet point is neither precise nor informative in the presence of the second bullet point which summarizes the main methodological steps of the study. The first bullet point statement has been removed and replaced with an important limitation which we believe is worth to be emphasized (4. bullet point). The revised list of statements is the following:

- *The paper provides a systematic search of EMBASE, MEDLINE (via PubMed), Cochrane Controlled Register of Trials (CENTRAL) and Web of Science databases, utilizes rigorous study selection criteria, assesses each enrolled paper for bias, and performs meta-regression analyses.*

- *Studies focusing on special populations including pregnant, pediatric (<18 years of age), geriatric (≥55 years), burned and traumatic spinal- or brain injured patients were excluded from the study.*

- *The heterogeneity and the difference in patient number among the included studies prevented us from performing an adequate meta-analysis.*
- *Although mortality is a highly objective outcome, the fact that in some cases hemorrhage might not been the direct cause of death even if bleeding was present is an important limitation of the study.*

6.) In the introduction, I am not sure to understand to what "base deficit" refers?

Thank you for this comment. We agree that highlighting base deficit in that particular sentence in the introduction is neither necessary nor helpful to understand the context better. Thus, it has been removed from the sentence (page 3, lines 68-70): *"The initial assessment of trauma-related*

hypovolemic shock is based on derangements of physiologic variables according to the recommendations of Advanced Trauma Life Support (ATLS)."

7.) In the introduction, do I have to understand that were four classes in the "shock classes according to ATLS guidance"?

Thank you for drawing attention to the imprecise formulation of these sentences, they have been rephrased to be clear and more concise (page 3, lines 83-85): *"In 2013, 16305 patients from the German trauma register (DGU®) were allocated into shock severity classes (I-IV) according to ATLS guidance. [12] Ultimately, no group displayed relevant tachycardia at all."*

8.) Is this systematic study was declared under PROSPERO register?

Thank you for this question. No, the review protocol was registered in the Open Science Framework (OSF) system (page 4, lines 113-114).

9.) In the search strategy subsection, could you indicate the date for the articles search and if necessary the date restriction? I find that the information come late (in the study selection subsection).

Thank you for this suggestion. The search strategy subsection has been extended accordingly (page 4, lines 115-117).

10.) An important remark concerns the necessity to clarify the eligibility criteria. In my opinion, this is important to better understand which studies could be retained and why they were included it in the statistical analysis. In the abstract, the study selection is insufficiently clear. What are the "eligibility criteria"?

Could you slightly reformulate the eligibility criteria subsection to clarify the criteria concerning studies inclusion and those for patients? I understood that studies including bleeding trauma patients were included. Are there more patients' criteria for inclusion? I understood that only English studies were included, those without any information about initial heart rate values were not included, etc. Are there other studies inclusion criteria? Is there any restriction for study design (observational cohorts, randomized clinical trials, pilot studies, etc.)? How were considered previous published reviews, meta-analysis, conference abstracts?

The PRISMA flow diagram could also be completed by specify reasons of non-inclusion based on title and abstract screening.

Thank you for your advice. The Methods part of the Abstract has been extended (respecting the word count limit of 300 words for the abstract) to give more detailed information on the eligibility criteria (page 2, lines 33-42):

"Systematic search of EMBASE, MEDLINE, CENTRAL and Web of Science databases was performed on 1-September-2020 to identify papers providing early HR and mortality data on bleeding trauma patients from the past decade. If the inclusion criteria of the studies included transfusion and/or positive focused assessment with sonography for trauma (FAST) and/or post-injury hemodynamical instability and/or abdominal gunshot injury, the patient cohort was considered hemorrhagic. Non-English language reports and records on special populations such as pregnant were not considered. Studies on burns, traumatic spinal or- brain injuries were excluded. The association between HR and mortality was assessed using meta-regression analysis. As subgroup analysis, meta-regression was performed on patients who received blood products. The study follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations."

The Eligibility Criteria subsection in the text has been extended and divided into two paragraphs. The first paragraph discusses the eligibility criteria concerning study design, methodology and the study period (page lines). The second paragraph focuses on the study population and the inclusion criteria of the individual papers (page lines).

Thank you for drawing attention to the missing information regarding the reasons of non-inclusion based on title and abstract screening, the authors agree that this should be available for the readers. The rationale behind leaving this out from the PRISMA Flow Diagram was the avoidance of squeezing a multitude of information into one diagram, which may reduce the clarity and conciseness of the Figure.

We have detailed the reasons of non-inclusion based on title and abstract screening in the Figure Legend of the PRISMA Flow Diagram (page 16, lines 464-478):

"…After excluding articles published before 2010 and duplicates, 1373 papers were screened based on title and abstract. In 79 cases the title clearly indicated non-eligible study design such as review or systematic review. Twenty-four title pointed out that the paper is a case report of a sole case. In 124 cases, the title clearly indicated non-eligible study population such as pregnant or pediatric. Five hundred sixteen titles revealed that the study is not closely related to our research topic. In 73 cases the title clearly indicated an animal experiment. Twenty-one records were excluded based on abstract due to a non-eligible study design such as review or systematic review. The abstract indicated a non-eligible study population such as pregnant or pediatric in 94 cases. In 110 cases, the abstract indicated that the study is not closely related to our research topic. Thirty-nine animal experiments were filtered out based on abstract. Eight studies did not have an English language abstract. In 112 cases, the abstract revealed that the study includes data that is more than 10 years old. Forty-one case reports with a patient number <10 were excluded based on abstract.

After excluding a total of 816 papers based on title and 425 based on abstract, 132 full-texts were assessed for eligibility. Reasons for non-inclusion of full-text articles are detailed above in the Figure. Ultimately, 19 studies were enrolled to our meta-regression"

11.) Why did you not consider studies with patients older than 55 years?

Thank you for this question. With excluding pediatric and older age groups we aimed to reduce the influence of conditions that are not related to the injury. Older trauma patients frequently take medication affecting the heart rate and they tend to display increased rates of comorbidities and mortality. Nevertheless, there is no clear consensus regarding the appropriate age cutoff in this issue. Other studies of "elderly" or "geriatric" patients with trauma have used age cutoffs ranging from 55 to 80 years [1-3]. Although the age of 65 is a commonly used cutoff, health changes commonly concentrate already in the decade prior to age 65 [4]. In accordance with this, an age above 55 is considered as cardiovascular risk, and the incidence rate of stroke doubles itself and the risk for venous thromboembolism increases dramatically after 55 years of age [5-7]. Choosing a cutoff constituted a matter of long discussion among the authors. Ultimately, to diminish the effects of age-related confounding factors, we decided to exclude age groups ≥55. This issue is now mentioned in the Eligibility Criteria section (page 5, lines 134-137).

References:

1. McGwin Jr G, MacLennan PA, Fife JB, et al. Preexisting conditions and mortality in older trauma patients. J Trauma 2004;56(6):1291-6.

2. Meldon SW, Reilly M, Drew BL, et al. Trauma in the very elderly: a community-based study of outcomes at trauma and nontrauma centers. J Trauma 2002;52(1):79-84.

3. Caterino JM, Valasek T, Werman HA. Identification of an age cutoff for increased mortality in patients with elderly trauma. Am J Emerg Med. 2010 Feb;28(2):151-8. doi: 10.1016/j.ajem.2008.10.027. PMID: 20159383.

4. National Research Council (US) Panel on Statistics for an Aging Population; Gilford DM, editor. The Aging Population in the Twenty-First Century: Statistics for Health Policy. Washington (DC): National Academies Press (US); 1988. 3, Health Status and Quality of Life. Available from: https://www.ncbi.nlm.nih.gov/books/NBK217732/

5. Nguyen QT, Anderson SR, Sanders L, Nguyen LD. Managing hypertension in the elderly: a common chronic disease with increasing age. Am Health Drug Benefits. 2012 May;5(3):146-53. PMID: 24991317; PMCID: PMC4046467.

6. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. Clin Geriatr Med. 2009 Nov;25(4):563-77, vii. doi: 10.1016/j.cger.2009.07.007. PMID: 19944261; PMCID: PMC2797320.

7. Singh S, Bajorek B. Defining 'elderly' in clinical practice guidelines for pharmacotherapy. Pharm Pract (Granada). 2014 Oct;12(4):489. doi: 10.4321/s1886-36552014000400007. Epub 2014 Mar 15. PMID: 25580172; PMCID: PMC4282767.

12.) The data extraction form could be provided in supplementary materials. Does Table 1 correspond to the exhaustive information that were collected from included articles?

This is also an important remark to clarify the collected outcomes that will be then analyzed. Without being sure, the heterogeneity in the mortality outcomes definition could be an important issue for your meta-regression.

Thank you for this remark. Originally, we intended Table 1 to be more detailed, corresponding to the information that were collected from the included articles. However, the Writing and Formatting guidelines of the Journal states that *"Any tables submitted that are longer/larger than 2 pages will be published as online only supplementary material."* (https://authors.bmj.com/writing-and-formatting/formatting-your-paper/)

Therefore, we redesigned Table 1 to be more concise, and provided the original, detailed version of the Table as Supplementary Material (Table S2).

13.) The statistical analysis is insufficiently developed to understand what have been done. "Meta-regression" term is too imprecise in my opinion. Could you improve this subsection?

For instance, which modeling regression have been exactly used? There may be a heterogeneity in the main outcome definition? Mortality can be a censored outcome. Some included studies may have some patients lost of follow-up inducing censoring. In trauma context, patients are well followed, censoring would be therefore not an issue. If there was no censoring, the horizon time would differ between studies. It would be therefore difficult to perform the statistical analysis without considering this temporal issue. More precision could be added to convince readers.

As it stands, Figure 3 and 4 seems to represent linear regression between heart rate and mortality percentage of each study. How do you consider size of the included studies? How do you assess the modeling assumptions, goodness-of-fit, etc.?

How can you consider the fact the heart rate could be measured at prehospital admission or upon admission?

Thank you for drawing attention to this issue. The term „Meta-regression" is a standard expression for the generalization of the linear regression (which is conducted on an individual level) to study level, where the dependent variable as well as the predictors are aggregated for each study involved.

In our study we investigated the possible linear relationship between HR and mortality, the former being the linear predictor and the latter being the dependent variable. We used a random effect model, which refers to the fact that we have two independent error terms in our model. The first one is the sampling error through which the effect size of a study deviates from its true effect. The second error indicates that even the true effect size of the study is only sampled from a distribution of effect

sizes. This means that between-study heterogeneity exists in our data, which is captured by the heterogeneity variance tau2. In meta-regression, contrary to the simple linear regression, a modified method called weighted least squares is used, which means that studies with a smaller standard error are given a higher weight. The standard error, and therefore their weights in the analysis are determined by the size of the studies. (Harrer, M., Cuijpers, P., Furukawa, T.A., & Ebert, D.D. (2021). Doing Meta-Analysis with R: A Hands-On Guide. Boca Raton, FL and London: Chapmann & Hall/CRC Press. ISBN 978-0-367-61007-4.)

The goodness fit of the meta-regression model can be assessed by checking how much of the heterogeneity variance it explains. In our model it is 0% which supports our conclusion that HR is not a good predictor of mortality.

Meta-regression Number of obs = 19

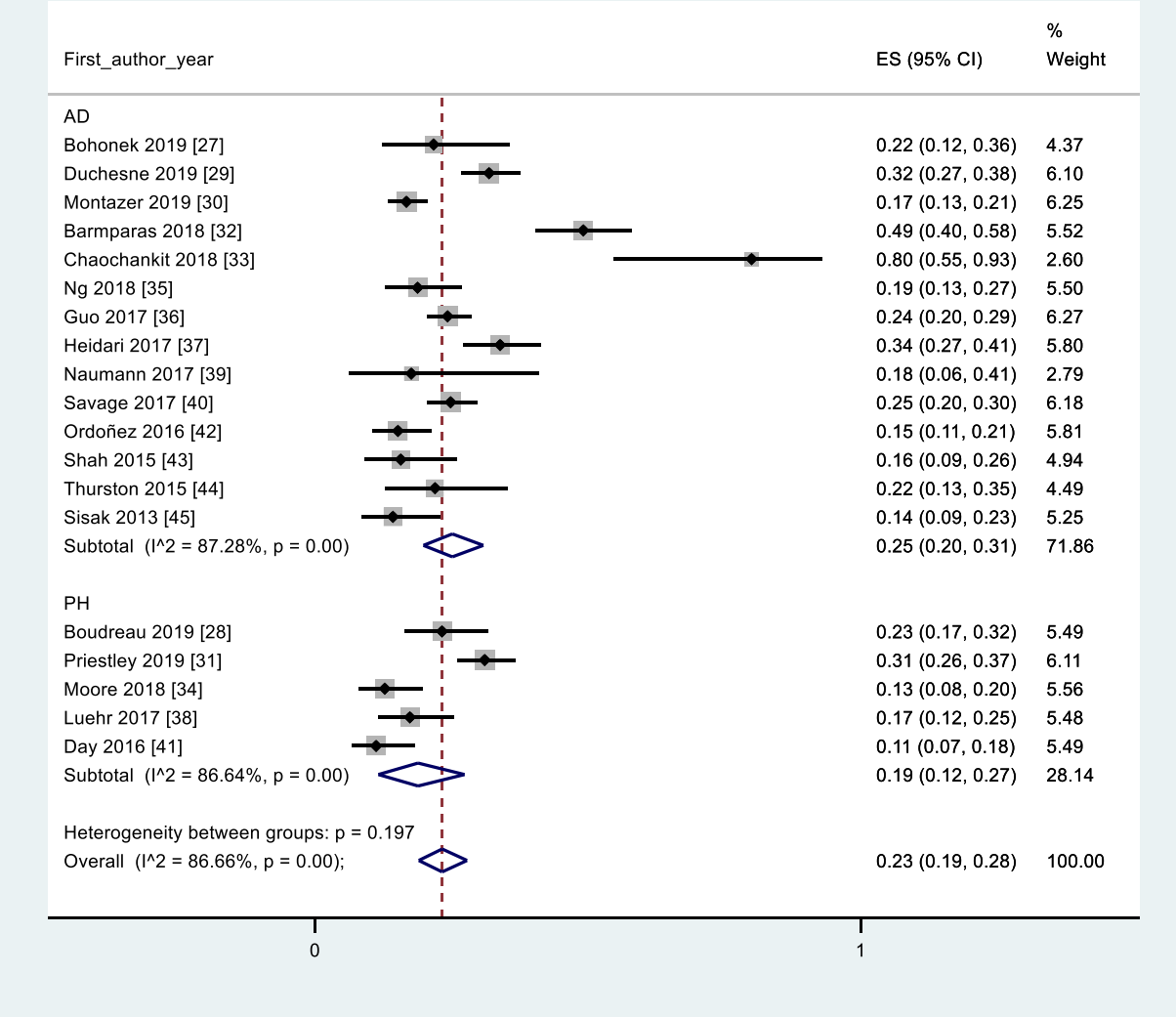
REML estimate of between-study variance tau2 = .002701

% residual variation due to heterogeneity I-squared_res = 35.83%

Proportion of between-study variance explained Adj R-squared = 0%

With Knapp-Hartung modification

ES	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
HR mean	-.0005727	.0029537	-0.19	0.85	-.0068045	.0056592
constant	.3008338	.3237643	0.93	0.37	-.3822492	.9839168



We conducted a subgroup analysis to investigate if there is a difference in mortality depending on heart rate was measured during prehospital admission or upon admission. The p value for the heterogeneity between groups shows no significant difference (p = 0.197).

14.) In table 1, why some texts are italic and others not? In table 1, what does mean the label data collection? Does it refer to patient study collection from prospective observational cohort or retrospective study?

Table 1 title is about baseline characteristics of the included study. I find that may be enriched with additional description about gender, age, variables to describe shock gravity, etc.

Mortality is possibly not the primary outcome and all the retained studies. If not, what were the other outcomes of interest?

Thank you for these questions. We indicated the studies of our subgroup analysis (patient cohorts that received blood products) with italics. We have extended the description of Table 1 with mentioning the aim of using italics (page 7, line 184).

With “data collection” we intended to indicate the study design regarding data collection (retrospective or prospective).

Table S2 has been extended with demographic data and main study outcomes. Beyond mortality, (which was the most frequent primary outcome), transfusion and massive transfusion need, ICU-admission, length of hospital- and ICU-stay were commonly utilized outcomes.

15.) In the paper, it is only questioned to assess the univariate relationship between the heart rate and mortality. But, confounding factors are probably highly important to consider in such context. At any time in the article, this is considered in the analysis or at least discussed.

Thank you for highlighting this. We agree with the importance of drawing attention on the presence of potential confounding factors. We have further emphasized this in the "Strengths and Limitations section" (page 9, lines 259-261): *"Although studies on special populations have been excluded from our analysis, it is important to emphasize that the presence of potential confounding factors affecting HR values could not be ruled out completely."* Since heart rate may react sensitively on several impacts such as pain, anxiety, medication, alcohol consumption, etc., it is difficult to eliminate confounding factors in clinical studies on heart rate in emergency trauma. The medical history and the general health condition of the injured is often unknown, and trauma surgeons have to evaluate the risk of bleeding without such information, based on a complex assessment, striving to rely on more objective indicators of hemorrhage and shock, such as bedside imaging. For this reason, we have a critical approach to simplified teaching tools such as the ATLS classification of hemorrhagic shock, especially the role of heart rate in it.

Minor comments

1.) I am not sure of the term "meta-regression". Does it mean meta-analysis?

Meta-regression is a special form of meta-analysis which explains the heterogeneity of effect sizes found during pooling the effect sizes. As in case of simple linear regression, we have a dependent variable, and the aim is to determine how it depends on the predeictor variable(s). This is a study level linear regression, where studies are weighted depending on their standard error. A larger study will have a larger weight and therefore will have a larger impact on the final results.

2.) In the strengths and limitations, I would find it preferable to indicate the exact period of the study instead of the expression "from the past 10 years"?

Thank you for the advice. We have corrected the strengths and limitations section accordingly (page 9, lines 254-255).

3.) In the strengths and limitations, there is a typo: "meat-regression"

Thank you for notifying this. The spelling mistake has been corrected.

4.) References in brackets should be reported before punctuations.

Thank you for this remark. According to the formatting guidelines of the journal "Reference numbers in the text should be inserted immediately after punctuation (with no word spacing) - for example,[6] not [6]." (https://authors.bmj.com/writing-and-formatting/formatting-your-paper/)

5.) Title of Figure 1 could indicate that is the PRISMA flow diagram.

Thank you for the advice. The title of Figure 1 has been changed accordingly to PRISMA flow diagram.

6.) There are abbreviations in the footnote of table 1. All the abbreviations used in the article could be reported in a specific list

Thank you for suggesting this. A "List of Abbreviations" has been added to the manuscript (page, lines).

Finally, we would like to thank the Reviewers for their conscientious work and overall positive criticism of our manuscript. We hope that the revised paper is now acceptable for publication in the Journal.