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Tachycardia does not imply an increased risk of mortality in trauma-related hemorrhagic shock - A Systematic Review and Meta-regression

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TACHYCARDIA DOES NOT IMPLY AN INCREASED RISK OF MORTALITY IN TRAUMA-RELATED HEMORRHAGIC SHOCK - A SYSTEMATIC REVIEW AND META-REGRESSION

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ABSTRACT

Introduction: Heart rate (HR) is one of the physiologic variables in the early assessment of trauma-related hemorrhagic shock, according to Advanced Trauma Life Support (ATLS). Regarding its efficiency as a predictor of mortality, there is contradictory data in literature. Furthermore, the linear association between HR and the severity of shock and blood loss presented by ATLS is doubtful. This systematic review updates current knowledge on the role of HR in the initial hemodynamic assessment of trauma patients.

Methods: A systematic search of EMBASE, MEDLINE, CENTRAL and Web of Science databases was performed to identify papers providing early HR and mortality data on bleeding trauma patients from the past decade. The association between HR and mortality of trauma patients was assessed using meta-regression analysis. As a subgroup analysis, meta-regression was performed on patients who received blood products.

Results: From a total of 2017 papers, 19 studies met our eligibility criteria. Our primary meta-regression did not find a significant relation (p=0.847) between HR and mortality in trauma patients with hemorrhage. Our subgroup analysis included 10 studies, and it could not reveal a linear association between HR and mortality rate.

Conclusions: Tachycardia should raise suspicion for bleeding, but it might not be appropriate to guide therapeutic decisions such as transfusion of blood products. In addition to the literature demonstrating the multi-phasic response of HR to bleeding, our study presents the lack of linear association with mortality. Considering these, modifying the pattern of HR derangements in the ATLS shock classification may result in a more precise teaching tool for young clinicians.

Keywords: "tachycardia"; "heart rate"; "hemorrhagic shock"; "multiple trauma"; "ATLS"

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study summarizes and analyzes scientific data from the past 10 years to investigate trauma-related hemorrhage, an issue with high clinical importance.
- 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 meat-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.

INTRODUCTION

Hypovolemia caused by hemorrhage is the most common cause of shock in trauma. Delay in the recognition of shock has been linked to unfavorable outcomes such as organ dysfuntion and mortality.[1,2] The initial assessment of trauma-related hypovolemic shock is based on derangements of physiologic variables (including base deficit) according to the recommendations of Advanced Trauma Life Support (ATLS).[3] Among these variables, heart rate (HR) is one of the most controversial when it comes to blood loss.[4-7] As commonly criticized, HR is not only influenced by hemodynamic changes, but also by several other factors such as anxiety, pain, and medications resulting in a low specificity for hemorrhage.[4,8,9] Furthermore, ATLS suggests the continuously increasing tendency of HR in accordance with the severity of bleeding.[3] However, in clinical reality, the HR response to hemorrhage is rather biphasic or triphasic than linear.[8,10,11] Consequently, the utility of HR in the early management of bleeding trauma patients was called into doubt during the past decades.[4,5,8,9]

The reliability of HR was already questioned in the early 2000s by a retrospective analysis on 14325 trauma patients. According to the results of this study, HR displayed insufficient sensitivity and specificity in predicting hypotension after trauma.[9] A few years later, a registry analysis denoted further doubts in HR, as it had performed poorly in predicting the need for an emergent intervention and administration of packed red blood cells (pRBC) in the first 24 hours post-injury.[4] Additionally, as ATLS was progressively widespread, the role of HR in the classification of hypovolemic shock sparked controversy. In 2013, 16305 patients from the german trauma register (DGU®) were allocated into shock classes according to ATLS guidance.[12] Ultimately, no significant alterations in mean HR were found within the four classes. According to these data, expecting tachycardia in case of hypovolemia can be misleading in many instances. Moreover, a false sense of hemodynamic stability based on normal HR can lead to fatal consequences, since the lack of tachycardia in hypoperfusion is associated with poor prognosis.[13]

Despite criticism, increased HR has been known as a characteristic of hypovolemic shock for a very long time. The utility of HR as a predictor of mortality is supported by several papers.[14,15] An international, cross-sectional study using data from two large trauma cohorts was conducted to develop and validate a prognostic model to predict death due to bleeding. Although HR showed a significant relation to mortality, the curve was U-shaped as opposed to the linear model presented by ATLS.[15]

A notable limitation of previous studies is that trauma protocols have undergone several changes, which makes recent information incomparable with data from the past. In 2010, the CRASH-2 trial brought one of the most prominent findings of the past decades with the validation of the safeness and effectivity of tranexamic acid (TXA).[16-18]

The present systematic review investigates the role of HR in the initial assessment of trauma patients with hemorrhage. Regarding the efficiency of HR as a predictor of outcome in trauma, there is contradictory data in the literature.[4,5,15] Furthermore, the linear association between HR and blood

loss presented by ATLS is questionable.[8,15] Due to the developement of trauma care and a paradigm shift in the initial fluid resuscitation approach in the past decades,[16,19] we aimed to update current knowledge on the effectivity of HR as predictor of mortality post-injury. For this purpose, a comprehensive database search has been conducted, data has been extracted and analyzed through meta-regressions. As a primary outcome, the relationship between HR and mortality has been assessed. Since the severity of bleeding has a close relation to the risk for adverse outcomes including increased organ dysfunction and mortality, our study may be able to initiate further research reappraising the validity of HR in the ATLS classification of hypovolemic shock.

MATERIALS AND METHODS

Protocol and search strategy

The present review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20] The PRISMA checklist for our work is available in the supporting information (Table S1). The review protocol was registered in the Open Science Framework (OSF) system under registration DOI: 10.17605/OSF.IO/HJWYR.

A systematic search of EMBASE, MEDLINE (via PubMed), Cochrane Controlled Register of Trials (CENTRAL) and Web of Science databases was performed with the following search terms: "trauma" AND ("heart rate" OR "pulse rate" OR "tachycardia" OR "bradycardia" OR "vital sign" OR "vital signs" OR "vital parameter" OR "vital parameters") AND "mortality" AND ("bleeding" OR "haemorrhage" OR "hemorrhage" OR "haemodynamic" OR "hemodynamic").

Eligibility criteria

Records on bleeding trauma patients were considered for eligibility only if they provided initial HR values (prehospital (PH) or upon admission (AD)) in addition to mortality data covering a time interval not exceeding 30 days from the time of injury. If the inclusion criteria of the individual studies included transfusion of blood products and/or positive focused assessment with sonography for trauma (FAST) examination and/or hemodinamical instability after trauma and/or abdominal gunshot injury, the patient cohort was considered hemorrhagic.

Non-English language reports, records on special populations such as pregnant, pediatric (<18 years of age) or geriatric (≥55 years) were not considered. Studies on patients suffering burns, traumatic spinal or- brain injuries were excluded.

Taking the development of trauma care in the past decade into consideration (e.g.: introduction of TXA,[16] and paradigm shift in fluid resuscitation [19]) all studies that included data on patients who received treatment before 2010 were also excluded.

Study selection

After having duplicates removed with the help of a reference manager software (EndNote X7), articles published before 2010 were also discarded. On the remaining studies, title and abstract screenings were performed by two review authors (PJ, IG). Thereafter, the full texts of the potentially eligible records were obtained and assessed based on the criteria described above. Disagreements were resolved by consensus.

Data extraction

The following information was extracted from the eligible studies: title, first author's name, year of publication, study design, data origin (country, hospital database/registry), data collection period, inclusion criteria, subgroups, patient number of the subgroups, total patient number, HR (mean ± standard deviation (SD) or median [interquartile range] (IQR)), phase of recording HR values (PH/AD), mortality within 30 days (n, %). In case of studies using overlapping data, the less comprehensive report with the smaller sample size was excluded.

Risk of bias assessment

Quality In Prognostic Studies (QUIPS) tool was used separately by two authors (TH and ZR) to assess the risk of bias for each study.[21] Disagreements were resolved by consensus. QUIPS consists of six main domains: 'Study attrition', 'Study participation', 'Prognostic factor', 'Outcome measurement', 'Study confounding' and 'Statistical analysis and reporting'. A rating for each domain was assigned as carrying 'low', 'moderate' or 'high' risk of bias. Based on the ratings of the individual domains, the overall risk of bias was evaluated by each study.

Statistical analysis

The association between HR and mortality of trauma patients was assessed using meta-regression analysis. A result of $p<0.05$ was considered as significant. As a subgroup analysis, meta-regression was performed on trauma patients who received blood products. Statistical analyses were performed with Stata 16 (Stata Corp, College Station, TX, USA). To convert median values to means, we used the method of Xiang Wan.[22]

RESULTS

Results of systematic search and selection

Two thousand and seventeen records were identified through our search strategy on 1 September 2020. One thousand three hundred seventy-three articles were screened on title. Five hundred fifty-seven abstracts were assessed, and 132 publications were enrolled into the final, comprehensive full text analysis. Ultimately, 19 records met our eligibility criteria. The flowchart of study enrollment is shown in Figure 1.

Fig. 1. Study flowchart

Study characteristics

All publications processed data of trauma patients with suspected hemorrhage from the past 10 years. From 19 studies yielding 3057 patients in total, 13 records collected data retrospectively and 6 prospectively. The number of participants in each dataset ranged from 15 to 428. Ten studies enrolled patients only if they received blood products as a part of the initial management. Seven publications used hemodynamic instability identified mainly by vital parameters as inclusion criteria. One study analyzed patients with a positive result on FAST examination after blunt abdominal trauma. One research enrolled patients with abdominal gunshot injuries. Each of the inclusion criteria listed above entails a strong suspicion for significant bleeding. The main characteristics of the 19 eligible studies are summarized in Table 1. The more comprehensive description of the papers is available in the supplementary material (Table S2).

First author, year	Country	Data collection	Patient characteristics	Patient number	HR mean ± SD (PH/AD)	Mortality n, (%)
Bohonek 2019 [27]	*Czech Republic*	*retrospective*	*received blood products*	*46*	*94.8 ± 59.0 (AD)*	*10 (21.7)*
Boudreau 2019 [28]	*USA*	*retrospective*	*received blood products*	*116*	*101.3 ± 43.0 (PH)*	*27 (23.3)*
Duchesne 2019 [29]	USA	retrospective	hemodynamic instability	279	120.6 ± 27.7 (AD)	89 (32.0)
Montazer 2019 [30]	Iran	prospective	hemodynamic instability	400	110.0 ± 14.0 (AD)	67 (16.7)
Priestley 2019 [31]	*USA*	*retrospective*	*received blood products*	*283*	*104.0 ± 24.0 (PH)*	*88 (31.1)*
Barmparas 2018 [32]	*USA*	*retrospective*	*received blood products*	*120*	*101.1 ± 39.7 (AD)*	*59 (49.2)*
Chaochankit 2018 [33]	*Thailand*	*retrospective*	*received blood products*	*15*	*113.0 ± 22.1 (AD)*	*12 (80.0)*
Moore 2018 [34]	USA	prospective	hemodynamic instability	125	110.0 ± 15.9 (PH)	16 (12.8)
Ng 2018 [35]	Canada	retrospective	hemodynamic instability	117	112.0 ± 35.0 (AD)	22 (19.0)
Guo 2017 [36]	China	prospective	hemodynamic instability	428	111.3 ± 17.9 (AD)	104 (23.4)
Heidari 2017 [37]	Iran	prospective	blunt abdominal trauma with positive FAST	168	105.3 ± 23.4 (AD)	57 (33.9)
Luehr 2017 [38]	*USA*	*retrospective*	*received blood products*	*115*	*133.3 ± 21.4 (PH)*	*20 (17.4)*
Naumann 2017 [39]	*UK*	*retrospective*	*received blood products*	*17*	*108.0 ± 16.2 (AD)*	*3 (17.6)*
Savage 2017 [40]	*USA*	*retrospective*	*received blood products*	*330*	*108.2 ± 55.3 (AD)*	*82 (24.8)*
Day 2016 [41]	*USA*	*retrospective*	*received blood products*	*116*	*98.0 ± 24.0 (PH)*	*13 (11.0)*
Ordoñez 2016 [42]	Colombia	retrospective	hemodynamic instability	171	112.6 ± 23.5 (AD)	26 (15.2)
Shah 2015 [43]	Pakistan	retrospective	isolated abdominal gunshot wound	70	99.8 ± 30.3 (AD)	11 (15.7)

Thurston 2015 [44]	South Africa	prospective	hemodynamic instability	50	123.3 ± 13.1 (AD)	11 (22.0)
Sisak 2013 [45]	*Australia*	*prospective*	*received blood products*	*91*	*100.0 ± 30.1 (AD)*	*13 (14.0)*

Table 1. Baseline characteristics of the included studies. The majority of the papers enrolled trauma patients receiving blood products and/or showing 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 is a significant heterogeneity in mortality between datasets. The need for massive transfusion is accompanied by a prominently high mortality rate. A mean heart rate (HR) > 120 bpm does not entail an outstanding mortality rate.
*only cohort B consisted of trauma patients with active bleeding
PH=prehospital, AD=upon admission, pRBC=packed red blood cells, RCT=randomized controlled trial, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, ISS=injury severity score, HR=heart rate, bpm=beats per minute, BD=base deficit, FAST=focused assessment with sonography for trauma

Study quality

The methodological quality of the enrolled papers was investigated with QUIPS tool. The domain 'Study attrition' was not suitable for the retrospective studies. In 5 prospective studies, a moderate risk for study attrition bias was identified. All papers were judged to carry a low risk of bias in 'Study participation' and 'Prognostic factor measurement' domains. In contrast, almost half of the records were accompanied by a moderate risk of bias with regards to 'Study confounding', since the role of important confounders was not clarified in these reports. The results of the QUIPS assessment are shown in Figure 2.

Fig. 2 Risk of bias assessment

Primary meta-regression

Our primary meta-regression investigated the relation between HR and mortality in trauma patients with hemorrhage based on all 19 datasets. We found no significant relation between HR and the outcome (p=0.847); thus, a linear association could not be confirmed. The results with the regression line are demonstrated in Figure 3.

Fig. 3 Relation between HR and mortality of bleeding trauma patients

Subgroup analysis

Due to the relative heterogeneity of the patient enrollment criteria of the individual papers, a subgroup of 10 studies utilizing the use of blood products in the initial management as inclusion criteria was formed and analyzed separately. Again, our findings demonstrated no significant relation and linear association between HR and mortality rate (Fig. 4).

Fig. 4 Subgroup analysis of studies on trauma patients who received blood products

DISCUSSION

Interpretation of results

The present study was designed to investigate and update current knowledge on the relation between HR and mortality in bleeding trauma patients. We identified 19 studies providing early HR and mortality data on trauma patients with hemorrhage from the past 10 years through database search. Due to the relative heterogeneity of the patient enrollment criteria of the individual papers, a subgroup of 10 records was created. Each of these 10 studies provided data on trauma patients who received blood products. Meta regressions were conducted on the data of all records and the subgroup, respectively.

No significant relation was found between HR and mortality in our meta regressions. This result supports the evidence provided by studies doubting the value of HR in the initial assessment of potentially bleeding trauma patients. Additionally, our findings raise further concerns over the validiy of HR in the ATLS classification of hypovolemic shock.

HR is an easily accessible vital parameter that indubitably reacts to circulatory volume depletion [5,6]. However, the complexity of this reaction seems to contain too many possibilites for misinterpretation to be used in the simplified scheme presented by ATLS. The current classification of hypovolemic shock suggests that HR increases continuously parallel to the severity of bleeding. The increase can stagnate between class I-II and III-IV according to ATLS.[3] This scheme seems to be incongruent with the existing literature on the physiology of HR change during intravascular volume depletion. The HR response tends to follow a biphasic or triphasic pattern instead of continuous increase [8,10,11]. If it comes to a decrease or stagnation in HR value, it is likely to occur at two separate stages of hemorrhage. First, due to increased vagal activity caused by a Bezold-Jarisch-like reflex just around 30% blood loss,[5,10] between shock classes II and III, where ATLS suggests a clear increase in HR. Secondly, at the end stage of hemorrhage, bradycardia appears preceding cardiac arrest.[15,23,24] Based on these observations, the pattern of HR alterations during hemorrhage suggested by ATLS may reflect the clinical condition more accurately after minor modifications (Table 2).

Severity classes / *Estimated blood loss*		*Class I* *<15%*	*Class II* *15-30%*	*Class III* *31-40%*	*Class IV* *>40%*
Physiologic variables	HR	↔	↔/↑	↑	↑/↑↑
	HR*	**↔**	**↑**	**↔/↑**	**↓/↑**
	SBP	↔	↔	↔/↓	↓
	GCS	↔	↔	↓	↓
	Pulse pressure	↔	↓	↓	↓
	Respiratory rate	↔	↔	↑	↑
	Urine output	↔	↔	↓	↓↓
	BD	0-2 mEq	2-6 mEq	6-10 mEq	≥10 mEq
Transfusion		Monitor	Possible	Yes	Massive transfusion

Table 2. Advanced Trauma Life Support (ATLS) classification of hypovolemic shock including suggested modifications in the pattern of heart rate (HR) derangements. The table is based on the 10th edition of ATLS. Estimated blood loss is shown as percentage of total blood volume.
*The suggested modifications are highlighted in bold: possible stagnation in HR value is indicated around 30% blood loss due to increased vagal activity. The possibility of bradycardia in profound bleeding in Class IV is highlighted
HR=heart rate, SBP=systolic blood pressure, GCS=Glasgow Coma Scale, BD=base deficit

Despite criticism, HR is a promptly available vital sign that may lead physicians in the right direction in a relatively high percentage of cases when it comes to the initial management of potentially bleeding trauma patients. However, the question remains if it is effective enough to be taken into consideration when we can also rely on parameters with higher sensitivity and specificity for bleeding – such as base deficit. Multiple studies have presented the inferiority of HR as compared to other predictors included in the ATLS criteria such as systolic blood pressure (SBP), Glasgow Coma Scale (GCS) and base deficit (BD).[25,26] Based on these concerns, the role of HR in the classification of hypovolemic shock and the initial management of the severely injured should be re-evaluated.

Strenghts and limitations

Our study focuses on injury-related severe hemorrhage, a condition carrying high clinical importance. In the previous decades, trauma care has gone through remarkable development. On that note, we decided to use scientific data only from the past 10 years. The included papers were judged to carry a relatively low risk of bias.

Naturally, our study also has its limitations. Although mortality is a highly objective outcome and we included patients only with significant hemorrhage, the direct cause of death may be difficult to determine in some cases. Prehospital measures may have affected the HR values registered upon admission. There is a notable difference in patient number among some of the included studies. The characteristics of the patient population by the individual records show a significant heterogeneity. To minimize this, a subgroup analysis was performed on patients who received blood products during initial in-hospital trauma care. These limitations prevented us from performing an adequate meta-analysis; however, we believe that we managed to raise attention on a clinically important issue.

Conclusions

The legitimity of HR in the initial assessment of hypovolemic shock seems to be obvious, but in fact, its usefulness is questionable due to unsatisfactory sensitivity and specificity. The complexity of HR response during hemorrhage leads to the possibility of misinterpretation, false sense of hemodynamic stability and consequent delay in adequate therapy.

Further research is required to reappraise HR as a physiologic variable in the ATLS classification of hypovolemic shock. As a reaction frequently associated with bleeding, tachycardia should raise suspicion for hemorrhage, but it might not be appropriate as one of the determining factors of therapeutic decisions, such as administration of blood products. In addition to the literature demonstrating the multi-

phasic response of HR to bleeding, our study presents the lack of linear association with mortality. Considering these, modifying the pattern of HR derangements in the ATLS shock classification may make this pragmatic guide even more precise.

STATEMENTS

Conflict of Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

PJ: preparation of the draft of the manuscript, contribution in study design, selection of studies, data extraction; LH: statistical analysis, interpretation of data; PH: expert in the field of internal medicine, provided revisions to the scientific content of the manuscript; EC: expert in the field of traumatology, substantial contribution in study design and interpretation of data, provided revisions to the scientific content of the manuscript; EB: data extraction, preparation of the standardized data collection sheet; TH: risk of bias assessment, stylistic and grammatical revision of the manuscript; IG: substantial contribution in study design, selection of studies, data extraction; AL: formatting the manuscript, stylistic revision of the manuscript; AS: statistical analysis, interpretation of data; ZR: risk of bias assessment, preparation of the manuscript; EP: participation in the design of the study and its coordination; JT: provided revisions to the scientific content of the manuscript, validation of data extraction; PH: study design, preparation of the manuscript, provided revisions to the scientific content of the manuscript

Hereby, all authors certify that they have participated sufficiently in the work to take public responsibility for the content.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Our study uses published data only. The original contributions presented in the study are included in the article and supplementary material, further inquiries can be directed to the corresponding author.

Patient and public involvement

Patients and public were not specifically involved in designing the study.

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FIGURE LEGENDS

Fig. 1. Study flowchart. Our search strategy resulted 2017 papers. After excluding articles published before 2010 and duplicates, a systematic screening was performed. Ultimately, 19 studies were enrolled to our meta-regression

*heart rate (HR) was not provided in mean or median, only the number of patients in ranges of HR (e.g., 100-120 bpm) was given

Fig. 2. Risk of bias assessment.

a: The figure shows the risk of bias in the 6 main domains of the Quality In Prognostic Studies (QUIPS) assessment, in each paper. 'Study attrition' was not suitable for the retrospective studies. In 5 prospective studies, there was a moderate risk for study attrition bias. All studies were judged to carry a low risk of bias in 'Study participation' and 'Prognostic factor measurement' domains. 'Study confounding' was the worst rated domain: a moderate risk appeared in almost half of the records, in which the role of important confounders was not reported thoroughly. Based on the assessment of the 6 main domains, the overall risk of bias was determined for each study

b: The summarized risk of bias is illustrated in percentages in the main domains

Fig. 3. Relation between heart rate (HR) and mortality of bleeding trauma patients. Linear association between HR and mortality could not be identified.

HR=heart rate

Fig. 4. Subgroup analysis of studies on trauma patients who received blood products. Linear association between early heart rate (HR) and mortality rate of patients could not be identified.

HR=heart rate

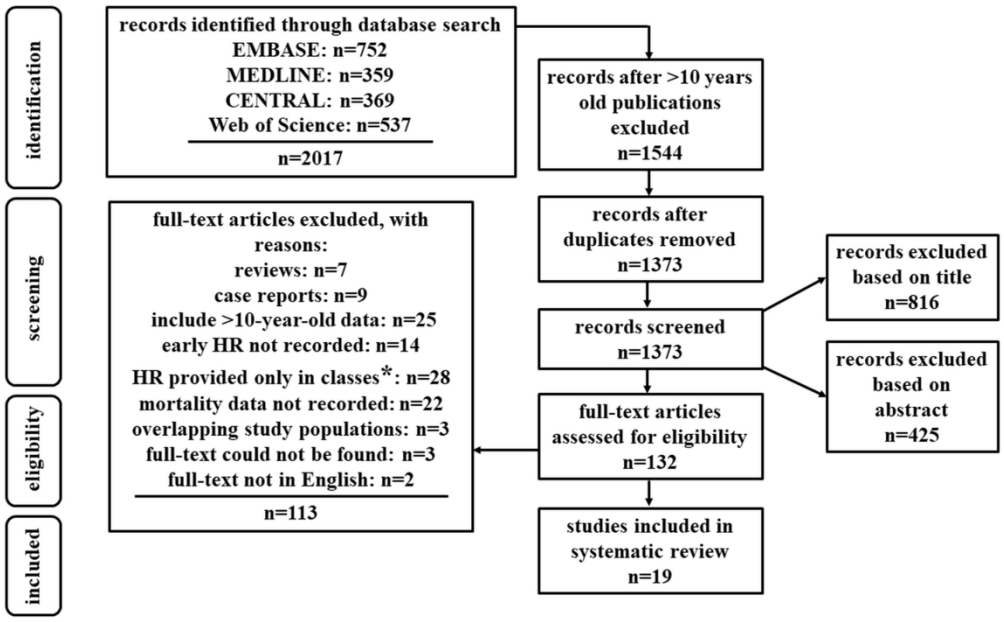

Fig. 1. PRISMA flow diagram. Our search strategy resulted 2017 papers. After excluding articles published before 2010 and duplicates, 1373 papers were screened based on title and abstract. In 79 cases the title clearly indicated non-eligible study design such as review or systematic review. Twenty-four 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
*heart rate (HR) was not provided in mean or median, only the number of patients in ranges of HR (e.g., 100-120 bpm) was given

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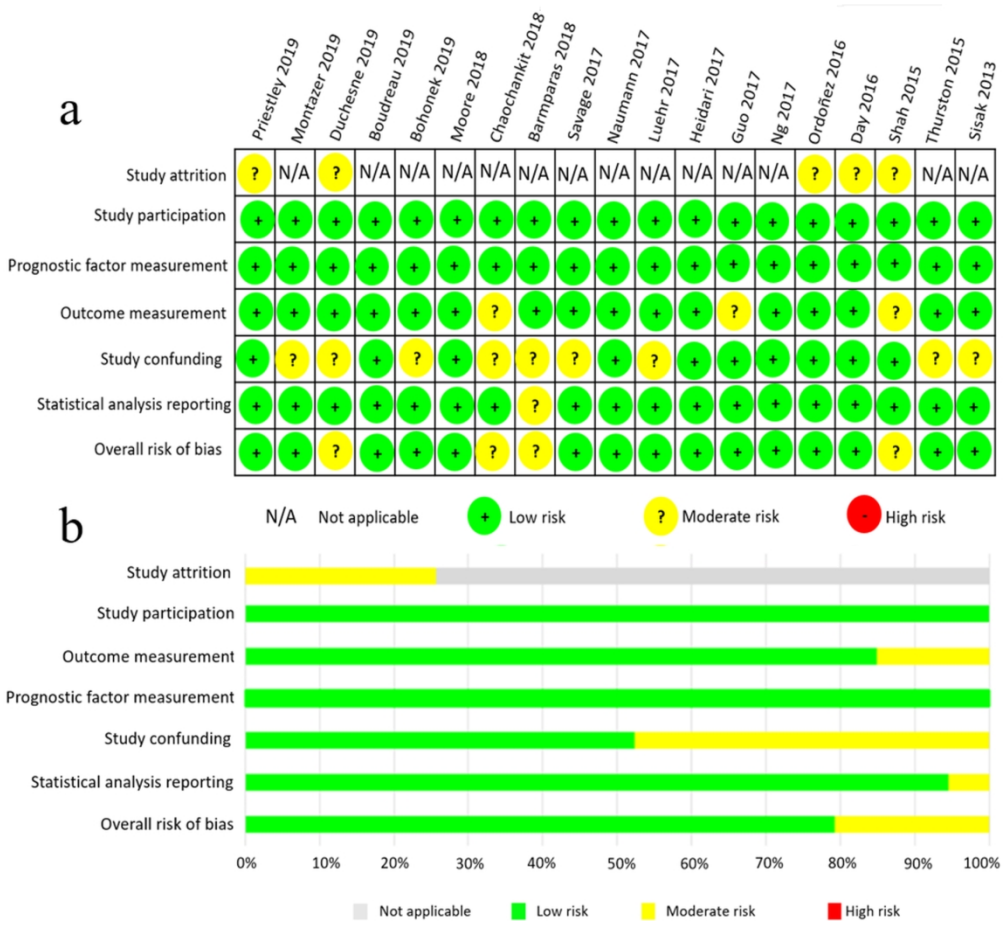

Fig. 2. Risk of bias assessment.
a: The figure shows the risk of bias in the 6 main domains of the Quality In Prognostic Studies (QUIPS) assessment, in each paper. 'Study attrition' was not suitable for the retrospective studies. In 5 prospective studies, there was a moderate risk for study attrition bias. All studies were judged to carry a low risk of bias in 'Study participation' and 'Prognostic factor measurement' domains. 'Study confounding' was the worst rated domain: a moderate risk appeared in almost half of the records, in which the role of important confounders was not reported thoroughly. Based on the assessment of the 6 main domains, the overall risk of bias was determined for each study
b: The summarized risk of bias is illustrated in percentages in the main domains

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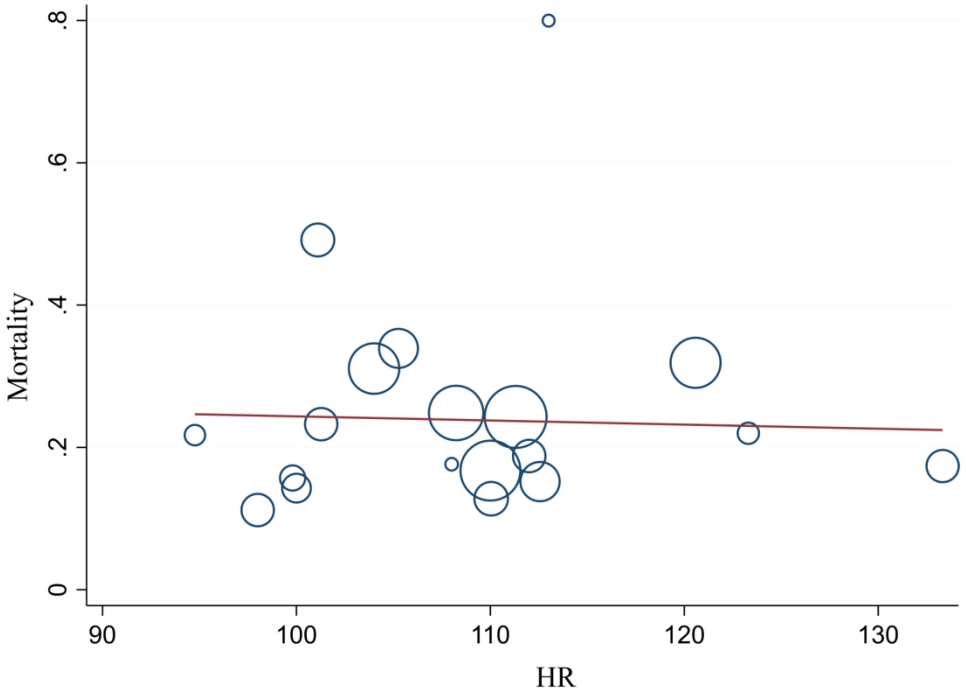

Fig. 3. Relation between heart rate (HR) and mortality of bleeding trauma patients. Linear association between HR and mortality could not be identified.
HR=heart rate

170x123mm (300 x 300 DPI)

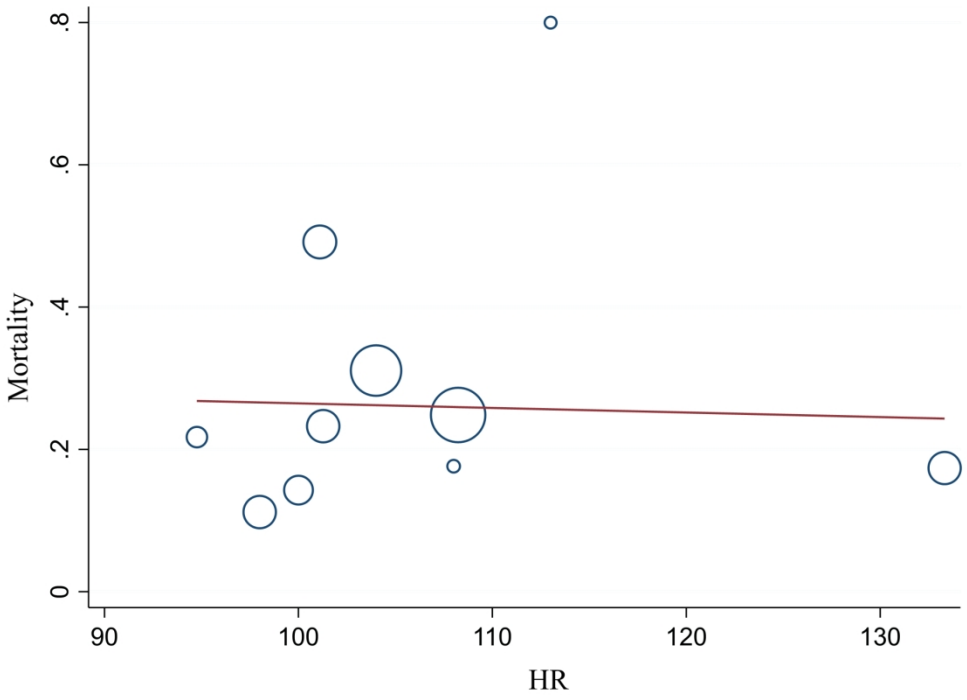

Fig. 4. Subgroup analysis of studies on trauma patients who received blood products. Linear association between early heart rate (HR) and mortality rate of patients could not be identified.
HR=heart rate

170x123mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported (Page nr.)
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4, 10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported (Page nr.)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	-
Study characteristics	17	Cite each included study and present its characteristics.	6 (Table 1)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6-7 (Fig. 2)
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7 (Fig 3-4)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6-7, (Fig. 2)
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7-8
	23b	Discuss any limitations of the evidence included in the review.	9
	23c	Discuss any limitations of the review processes used.	9
	23d	Discuss implications of the results for practice, policy, and future research.	9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	9
Competing interests	26	Declare any competing interests of review authors.	9
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	10

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Study: first author, year of publication	Data origin: institute, country	Data collection: type, date	Patient characteristics	Patient number	HR mean ± SD (PH/AD)	Mortality n, (%)
Bohonek 2019	*Military University Hospital Prague, Czech Republic*	*retrospective, single-center, 2014-2018*	*received blood products (fresh apheresis platelets or cryopreserved platelets)*	*46*	*94.8 ± 59.0 (AD)*	*10 (21.7)*
Boudreau 2019	*University of Cincinnati Medical Center, Cincinnati, Ohio, USA*	*retrospective, single-center, April 2014 – October 2015*	*received blood products and tranexamic acid*	*116*	*101.3 ± 43.0 (PH)*	*27 (23.3)*
Duchesne 2019	11 level I trauma centers, 1 level II trauma center from the USA	retrospective, multi-center, *January 2011 – December 2016*	pelvic fracture with SBP ≤ 90 mmHg and/or HR ≥ 120 bpm and/or BD ≥ 5 mEq	279	120.6 ± 27.7 (AD)	89 (32.0)
Montazer 2019	Imam Khomeini Hospital, Sari, Iran	prospective, single-center, March 2014 – February 2015	multiple trauma with hemodynamic instability (not defined)	400	110.0 ± 14.0 (AD)	67 (16.7)
Priestley 2019	*LAC+USC Medical Center, LAC+USC blood bank database, University of Southern California, Los Angeles, CA, USA*	*retrospective, single-center, January 2010 – October 2014*	*received 3 units of pRBC in any 60-minute period within 24 hours of admission and received interventional radiology or surgery for definitive hemorrhage control*	*283*	*104.0 ± 24.0 (PH)*	*88 (31.1)*
Barmparas 2018	*Cedars-Sinai Medical Center Los Angeles, CA, USA*	*retrospective, single-center January 2011 – October 2016*	*received massive transfusion (defined as 3 units of pRBC within the first hour from admission)*	*120*	*101.1 ± 39.7 (AD)*	*59 (49.2)*
Chaochankit 2018	*Songklanagarind Hospital, Hat Yai, Thailand*	*retrospective, single-center, January 2014 – December 2014*	*received massive transfusion, met trauma team activation criteria*	*15*	*113.0 ± 22.1 (AD)*	*12 (80.0)*
Moore 2018	Denver Health Medical Center, Denver, CO, USA	prospective, single-center, April 2014 – March 2017	SBP ≤ 70 mmHg or 71-90 mmHg with HR ≥ 108 bpm	125	110.0 ± 15.9 (PH)	16 (12.8)
Ng 2018	British Columbia Trauma Registry, Canada	retrospective, single-center, April 2012 – June 2015	SBP ≤ 90 mmHg and/or HR ≥ 110 bpm	117	112.0 ± 35.0 (AD)	22 (19.0)
Guo 2017	33 academic hospitals in 16 Chinese	prospective, multi-center, December 2013 – April 2014	new-onset hypotension unexplained by any other cause than	428	111.3 ± 17.9 (AD)	104 (23.4)

	provinces, China		hemorrhage (SBP < 90 mmHg, DBP < 60 mmHg, or MAP < 65 mmHg or decreased SBP with more than 40 mmHg from baseline in a hypertensive patient), and signs of tissue hypoperfusion (tachycardia, oliguria, mottled skin, altered mental state)			
Heidari 2017	4 level I trauma centers from Iran	prospective, multi-center, April 2015 – September 2015	blunt abdominal trauma with positive FAST	168	105.3 ± 23.4 (AD)	57 (33.9)
Luehr 2017	*Mercy Hospital-Springfield, Springfield, MO, USA*	*retrospective, single-center, 2013 - 2016*	*received blood products and tranexamic acid*	*115*	*133.3 ± 21.4 (PH)*	*20 (17.4)*
Naumann 2017	*University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK*	*retrospective, single-center, July 2015 – January 2017*	*received blood products, required intensive care and had a lactate value >2 mmol/l (cohort B*)*	*17*	*108.0 ± 16.2 (AD)*	*3 (17.6)*
Savage 2017	*Indiana University School of Medicine, Indianapolis IN, USA; The University of Tennessee Health Science Center, Memphis, TN, USA*	*retrospective, multi-center, September 2013 – May 2015*	*received at least one unit of pRBC within the first 24 hours of admission*	*330*	*108.2 ± 55.3 (AD)*	*82 (24.8)*
Day 2016	*The Queen's Medical Center, Honolulu, Hawaii, USA*	*retrospective, single-center, September 2011 – March 2013*	*received at least one unit of pRBC in the first 6 hours, met trauma team activation criteria*	*116*	*98.0 ± 24.0 (PH)*	*13 (11.0)*
Ordoñez 2016	Fundación Valle del Lili, University Hospital, Cali, Colombia	retrospective, single-center, January 2012 – December 2013	ISS > 15 with hemodynamic instability (SBP < 100 mmHg and/or HR > 100 bpm and/or the need for at least 4 units of packed red blood	171	112.6 ± 23.5 (AD)	26 (15.2)

			cells in the trauma bay)			
Shah 2015	Aga Khan University Hospital, Karachi, Pakistan	retrospective, single-center, January 2011 – December 2012	isolated abdominal gunshot wound	70	99.8 ± 30.3 (AD)	11 (15.7)
Thurston 2015	Trauma Center, Groote Schuur Hospital and Faculty of Health Sciences, University of Cape Town, South Africa	prospective, single-center, September 2013 – November 2013	SBP < 90 mmHg and/or HR >110 bpm at any time from admission to 3 hours after injury	50	123.3 ± 13.1 (AD)	11 (22.0)
Sisak 2013	*John Hunter Hospital and University of Newcastle, Newcastle, NSW, Australia*	*prospective, single-center, January 2010 – January 2011*	*received blood products within the first 24 hours from admission*	*91*	*100.0 ± 30.1 (AD)*	*13 (14.0)*

Table S2. Detailed description of the characteristics of the included studies. Most papers enrolled trauma patients receiving blood products and/or showing 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 is a significant heterogeneity in mortality between datasets. The need for massive transfusion is accompanied by a prominently high mortality rate. A mean heart rate (HR) > 120 bpm does not entail an outstanding mortality rate.
*only cohort B consisted of trauma patients with active bleeding
PH=prehospital, AD=upon admission, pRBC=packed red blood cells, RCT=randomized controlled trial, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, ISS=injury severity score, HR=heart rate, bpm=beats per minute, BD=base deficit, FAST=focused assessment with sonography for trauma

BMJ Open

THE PREDICTIVE VALUE OF TACHYCARDIA FOR MORTALITY IN TRAUMA-RELATED HEMORRHAGIC SHOCK: A SYSTEMATIC REVIEW AND META-REGRESSION

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Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Medical education and training
Keywords:	Trauma management < ORTHOPAEDIC & TRAUMA SURGERY, Bleeding disorders & coagulopathies < HAEMATOLOGY, ORTHOPAEDIC & TRAUMA SURGERY, ACCIDENT & EMERGENCY MEDICINE

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THE PREDICTIVE VALUE OF TACHYCARDIA FOR MORTALITY IN TRAUMA-RELATED HEMORRHAGIC SHOCK: A SYSTEMATIC REVIEW AND META-REGRESSION

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ABSTRACT

Objectives: Heart rate (HR) is one of the physiologic variables in the early assessment of trauma-related hemorrhagic shock, according to Advanced Trauma Life Support (ATLS). However, its efficiency as predictor of mortality is contradicted by several studies. Furthermore, the linear association between HR and the severity of shock and blood loss presented by ATLS is doubtful. This systematic review aims to update current knowledge on the role of HR in the initial hemodynamic assessment of trauma patients.

Design: The present study is a systematic review and meta-regression that follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

Data sources: EMBASE, MEDLINE, CENTRAL and Web of Science databases were systematically searched through on 1-September-2020.

Eligibility criteria: Papers providing early HR and mortality data on bleeding trauma patients were included. Patient cohorts were considered hemorrhagic if the inclusion criteria of the studies contained transfusion and/or positive focused assessment with sonography for trauma (FAST) and/or post-injury hemodynamical instability and/or abdominal gunshot injury. Studies on burns, traumatic spinal or- brain injuries were excluded. Papers published before January 2010 were not considered.

Data extraction and synthesis: Data extraction and risk of bias were assessed by 2 independent investigators. The association between HR and mortality of trauma patients was assessed using meta-regression analysis. As subgroup analysis, meta-regression was performed on patients who received blood products.

Results*:* From a total of 2017 papers, 19 studies met our eligibility criteria. Our primary meta-regression did not find a significant relation (p=0.847) between HR and mortality in trauma patients with hemorrhage. Our subgroup analysis included 10 studies, and it could not reveal a linear association between HR and mortality rate.

Conclusions*:* 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.

Keywords: "tachycardia"; "heart rate"; "hemorrhagic shock"; "multiple trauma"; "ATLS"

STRENGTHS AND LIMITATIONS OF THIS STUDY

- 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.

INTRODUCTION

Hypovolemia caused by hemorrhage is the most common cause of shock in trauma. Delay in the recognition of shock has been linked to unfavorable outcomes such as organ dysfuntion and mortality.[1,2] 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).[3] Among these variables, heart rate (HR) is one of the most controversial when it comes to blood loss.[4-7] As commonly criticized, HR is not only influenced by hemodynamic changes, but also by several other factors such as anxiety, pain, and medications resulting in a low specificity for hemorrhage.[4,8,9] Furthermore, ATLS suggests the continuously increasing tendency of HR in accordance with the severity of bleeding.[3] However, in clinical reality, the HR response to hemorrhage is rather biphasic or triphasic than linear.[8,10,11] Consequently, the utility of HR in the early management of bleeding trauma patients was called into doubt during the past decades.[4,5,8,9]

The reliability of HR was already questioned in the early 2000s by a retrospective analysis on 14325 trauma patients. According to the results of this study, HR displayed insufficient sensitivity and specificity in predicting hypotension after trauma.[9] A few years later, a registry analysis denoted further doubts in HR, as it had performed poorly in predicting the need for an emergent intervention and administration of packed red blood cells (pRBC) in the first 24 hours post-injury.[4] Additionally, as ATLS was progressively widespread, the role of HR in the classification of hypovolemic shock sparked controversy. 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. According to these data, expecting tachycardia in case of hypovolemia can be misleading in many instances. Moreover, a false sense of hemodynamic stability based on normal HR can lead to fatal consequences, since the lack of tachycardia in hypoperfusion is associated with poor prognosis.[13]

Despite criticism, increased HR has been known as a characteristic of hypovolemic shock for a very long time. The utility of HR as a predictor of mortality is supported by several papers.[14,15] An international, cross-sectional study using data from two large trauma cohorts was conducted to develop

and validate a prognostic model to predict death due to bleeding. Although HR showed a significant relation to mortality, the curve was U-shaped as opposed to the linear model presented by ATLS.[15]

A notable limitation of previous studies is that trauma protocols have undergone several changes, which makes recent information incomparable with data from the past. In 2010, the CRASH-2 trial brought one of the most prominent findings of the past decades with the validation of the safeness and effectivity of tranexamic acid (TXA).[16-18]

The present systematic review investigates the role of HR in the initial assessment of trauma patients with hemorrhage. Regarding the efficiency of HR as a predictor of outcome in trauma, there is contradictory data in the literature.[4,5,15] Furthermore, the linear association between HR and blood loss presented by ATLS is questionable.[8,15] Due to the developement of trauma care and a paradigm shift in the initial fluid resuscitation approach in the past decades,[16,19] we aimed to update current knowledge on the effectivity of HR as predictor of mortality post-injury. For this purpose, a comprehensive database search has been conducted, data has been extracted and analyzed through meta-regressions. As a primary outcome, the relationship between HR and mortality has been assessed. Since the severity of bleeding has a close relation to the risk for adverse outcomes including increased organ dysfunction and mortality, our study may be able to initiate further research reappraising the validity of HR in the ATLS classification of hypovolemic shock.

MATERIALS AND METHODS

Protocol and search strategy

The present review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20] The PRISMA checklist for our work is available in the supporting information (Table S1). The review protocol was registered in the Open Science Framework (OSF) system under registration DOI: 10.17605/OSF.IO/HJWYR.

A systematic search of EMBASE, MEDLINE (via PubMed), Cochrane Controlled Register of Trials (CENTRAL) and Web of Science databases was performed on 1 September 2020 with the following search terms: "trauma" AND ("heart rate" OR "pulse rate" OR "tachycardia" OR "bradycardia" OR "vital sign" OR "vital signs" OR "vital parameter" OR "vital parameters") AND "mortality" AND ("bleeding" OR "haemorrhage" OR "hemorrhage" OR "haemodynamic" OR "hemodynamic"). Articles published before 2010 were excluded from our study.

Eligibility criteria

Records on bleeding trauma patients were considered for eligibility only if they provided initial HR values (prehospital (PH) or upon admission (AD)) in addition to mortality data covering a time interval not exceeding 30 days from the time of injury. Only full-text articles were considered. Non-English language reports, reviews, conference abstracts and case reports with low patient number (<10) were excluded. Taking the development of trauma care in the past decade into consideration (e.g.: introduction

of TXA,[16] and paradigm shift in fluid resuscitation [19]) all studies that included data on patients treated before 2010 were also excluded.

To consider a patient cohort hemorrhagic, the inclusion criteria of the individual studies had to include transfusion of blood products and/or positive focused assessment with sonography for trauma (FAST) examination and/or hemodynamical instability after trauma and/or abdominal gunshot injury. Records on special populations such as pregnant, pediatric (<18 years of age) or geriatric (≥55 years) were not considered. Studies on patients suffering burns, traumatic spinal or- brain injuries were excluded.
With excluding special populations and pediatric and older age groups we aimed to reduce the influence of confounding factors. Since studies of geriatric trauma patients have used age cutoffs ranging from 55 to 80 years and there is no clear consensus in the literature,[21,22] we decided to exclude study populations of 55 years of age or older to diminish the effects of age-related confounding factors.

Study selection

After having duplicates removed with the help of a reference manager software (EndNote X7), articles published before 2010 were also discarded. On the remaining studies, title and abstract screenings were performed by two review authors (PJ, IG). Thereafter, the full texts of the potentially eligible records were obtained and assessed based on the criteria described above. Disagreements were resolved by consensus.

Data extraction

The following information was extracted from the eligible studies: title, first author's name, year of publication, study design, data origin (country, hospital database/registry), data collection period, inclusion criteria, subgroups, patient number of the subgroups, total patient number, HR (mean ± standard deviation (SD) or median [interquartile range] (IQR)), phase of recording HR values (PH/AD), mortality within 30 days (n, %). In case of studies using overlapping data, the less comprehensive report with the smaller sample size was excluded.

Risk of bias assessment

Quality In Prognostic Studies (QUIPS) tool was used separately by two authors (TH and ZR) to assess the risk of bias for each study.[23] Disagreements were resolved by consensus. QUIPS consists of six main domains: 'Study attrition', 'Study participation', 'Prognostic factor', 'Outcome measurement', 'Study confounding' and 'Statistical analysis and reporting'. A rating for each domain was assigned as carrying 'low', 'moderate' or 'high' risk of bias. Based on the ratings of the individual domains, the overall risk of bias was evaluated by each study.

Statistical analysis

The association between HR and mortality of trauma patients was assessed using meta-regression analysis. A result of $p<0.05$ was considered as significant. As a subgroup analysis, meta-regression was performed on trauma patients who received blood products. Statistical analyses were performed with

Stata 16 (Stata Corp, College Station, TX, USA). To convert median values to means, we used the method of Xiang Wan.[24]

Patient and public involvement

Patients and public were not specifically involved in designing the study.

RESULTS

Results of systematic search and selection

Two thousand and seventeen records were identified through our search strategy on 1 September 2020. One thousand three hundred seventy-three articles were screened on title. Five hundred fifty-seven abstracts were assessed, and 132 publications were enrolled into the final, comprehensive full text analysis. Ultimately, 19 records met our eligibility criteria. The flowchart of study enrollment is shown in Figure 1.

Fig. 1. PRISMA flow diagram

Study characteristics

All publications processed data of trauma patients with suspected hemorrhage from the past 10 years. From 19 studies yielding 3057 patients in total, 13 records collected data retrospectively and 6 prospectively. The number of participants in each dataset ranged from 15 to 428. Ten studies enrolled patients only if they received blood products as a part of the initial management. Seven publications used hemodynamic instability identified mainly by vital parameters as inclusion criteria. One study analyzed patients with a positive result on FAST examination after blunt abdominal trauma. One research enrolled patients with abdominal gunshot injuries. Each of the inclusion criteria listed above entails a strong suspicion for significant bleeding. The main characteristics of the 19 eligible studies are summarized in Table 1. The more comprehensive description of the papers is available in the supplementary material (Table S2).

First author, year	Country	Data collection	Patient characteristics	Patient number	HR mean ± SD (PH/AD)	Mortality n, (%)
Bohonek 2019 [25]	*Czech Republic*	*retrospective*	*received blood products*	*46*	*94.8 ± 59.0 (AD)*	*10 (21.7)*
Boudreau 2019 [26]	*USA*	*retrospective*	*received blood products*	*116*	*101.3 ± 43.0 (PH)*	*27 (23.3)*
Duchesne 2019 [27]	USA	retrospective	hemodynamic instability	279	120.6 ± 27.7 (AD)	89 (32.0)
Montazer 2019 [28]	Iran	prospective	hemodynamic instability	400	110.0 ± 14.0 (AD)	67 (16.7)
Priestley 2019 [29]	*USA*	*retrospective*	*received blood products*	*283*	*104.0 ± 24.0 (PH)*	*88 (31.1)*

Barmparas 2018 [30]	*USA*	*retrospective*	*received blood products*	*120*	*101.1 ± 39.7 (AD)*	*59 (49.2)*
Chaochan kit 2018 [31]	*Thailand*	*retrospective*	*received blood products*	*15*	*113.0 ± 22.1 (AD)*	*12 (80.0)*
Moore 2018 [32]	USA	prospective	hemodynamic instability	125	110.0 ± 15.9 (PH)	16 (12.8)
Ng 2018 [33]	Canada	retrospective	hemodynamic instability	117	112.0 ± 35.0 (AD)	22 (19.0)
Guo 2017 [34]	China	prospective	hemodynamic instability	428	111.3 ± 17.9 (AD)	104 (23.4)
Heidari 2017 [35]	Iran	prospective	blunt abdominal trauma with positive FAST	168	105.3 ± 23.4 (AD)	57 (33.9)
Luehr 2017 [36]	*USA*	*retrospective*	*received blood products*	*115*	*133.3 ± 21.4 (PH)*	*20 (17.4)*
Naumann 2017 [37]	*UK*	*retrospective*	*received blood products*	*17*	*108.0 ± 16.2 (AD)*	*3 (17.6)*
Savage 2017 [38]	*USA*	*retrospective*	*received blood products*	*330*	*108.2 ± 55.3 (AD)*	*82 (24.8)*
Day 2016 [39]	*USA*	*retrospective*	*received blood products*	*116*	*98.0 ± 24.0 (PH)*	*13 (11.0)*
Ordoñez 2016 [40]	Colombia	retrospective	hemodynamic instability	171	112.6 ± 23.5 (AD)	26 (15.2)
Shah 2015 [41]	Pakistan	retrospective	isolated abdominal gunshot wound	70	99.8 ± 30.3 (AD)	11 (15.7)
Thurston 2015 [42]	South Africa	prospective	hemodynamic instability	50	123.3 ± 13.1 (AD)	11 (22.0)
Sisak 2013 [43]	*Australia*	*prospective*	*received blood products*	*91*	*100.0 ± 30.1 (AD)*	*13 (14.0)*

Table 1. Baseline characteristics of the included studies. The majority of the papers enrolled trauma patients who received blood products (italics) 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.
*only cohort B consisted of trauma patients with active bleeding
PH=prehospital, AD=upon admission, FAST=focused assessment with sonography for trauma

Study quality

The methodological quality of the enrolled papers was investigated with QUIPS tool. The domain 'Study attrition' was not suitable for the retrospective studies. In 5 prospective studies, a moderate risk for study attrition bias was identified. All papers were judged to carry a low risk of bias in 'Study participation' and 'Prognostic factor measurement' domains. In contrast, almost half of the records were accompanied by a moderate risk of bias with regards to 'Study confounding', since the role of important confounders was not clarified in these reports. The results of the QUIPS assessment are shown in Figure 2.

Fig. 2 Risk of bias assessment

Primary meta-regression

Our primary meta-regression investigated the relation between HR and mortality in trauma patients with hemorrhage based on all 19 datasets. We found no significant relation between HR and the outcome (p=0.847); thus, a linear association could not be confirmed. The results with the regression line are demonstrated in Figure 3.

Fig. 3 Relation between HR and mortality of bleeding trauma patients

Subgroup analysis

Due to the relative heterogeneity of the patient enrollment criteria of the individual papers, a subgroup of 10 studies utilizing the use of blood products in the initial management as inclusion criteria was formed and analyzed separately. Again, our findings demonstrated no significant relation and linear association between HR and mortality rate (Fig. 4).

Fig. 4 Subgroup analysis of studies on trauma patients who received blood products

DISCUSSION

Interpretation of results

The present study was designed to investigate and update current knowledge on the relation between HR and mortality in bleeding trauma patients. We identified 19 studies providing early HR and mortality data on trauma patients with hemorrhage from the past 10 years through database search. Due to the relative heterogeneity of the patient enrollment criteria of the individual papers, a subgroup of 10 records was created. Each of these 10 studies provided data on trauma patients who received blood products. Meta regressions were conducted on the data of all records and the subgroup, respectively.

No significant relation was found between HR and mortality in our meta regressions. This result supports the evidence provided by studies doubting the value of HR in the initial assessment of potentially bleeding trauma patients. Additionally, our findings raise further concerns over the validiy of HR in the ATLS classification of hypovolemic shock.

HR is an easily accessible vital parameter that indubitably reacts to circulatory volume depletion [5,6]. However, the complexity of this reaction seems to contain too many possibilites for misinterpretation to be used in the simplified scheme presented by ATLS. The current classification of hypovolemic shock suggests that HR increases continuously parallel to the severity of bleeding. The increase can stagnate between class I-II and III-IV according to ATLS.[3] This scheme seems to be incongruent with the existing literature on the physiology of HR change during intravascular volume depletion. The HR response tends to follow a biphasic or triphasic pattern instead of continuous increase [8,10,11]. If it comes to a decrease or stagnation in HR value, it is likely to occur at two separate stages of hemorrhage. First, due to increased vagal activity caused by a Bezold-Jarisch-like reflex just around 30% blood loss,[5,10] between shock classes II and III, where ATLS suggests a clear increase in HR. Secondly, at the end stage of hemorrhage, bradycardia appears preceding cardiac arrest.[15,44,45] Based on these

observations, the pattern of HR alterations during hemorrhage suggested by ATLS may reflect the clinical condition more accurately after minor modifications (Table 2).

Severity classes / *Estimated blood loss*		*Class I* *<15%*	*Class II* *15-30%*	*Class III* *31-40%*	*Class IV* *>40%*
Physiologic variables	HR	↔	↔/↑	↑	↑/↑↑
	HR*	**↔**	**↑**	**↔/↑**	**↓/↑**
	SBP	↔	↔	↔/↓	↓
	GCS	↔	↔	↓	↓
	Pulse pressure	↔	↓	↓	↓
	Respiratory rate	↔	↔	↑	↑
	Urine output	↔	↔	↓	↓↓
	BD	0-2 mEq	2-6 mEq	6-10 mEq	≥10 mEq
Transfusion		Monitor	Possible	Yes	Massive transfusion

Table 2. Advanced Trauma Life Support (ATLS) classification of hypovolemic shock including suggested modifications in the pattern of heart rate (HR) derangements. The table is based on the 10th edition of ATLS. Estimated blood loss is shown as percentage of total blood volume.
*The suggested modifications are highlighted in bold: possible stagnation in HR value is indicated around 30% blood loss due to increased vagal activity. The possibility of bradycardia in profound bleeding in Class IV is highlighted
HR=heart rate, SBP=systolic blood pressure, GCS=Glasgow Coma Scale, BD=base deficit

Despite criticism, HR is a promptly available vital sign that may lead physicians in the right direction in a relatively high percentage of cases when it comes to the initial management of potentially bleeding trauma patients. However, the question remains if it is effective enough to be taken into consideration when we can also rely on parameters with higher sensitivity and specificity for bleeding – such as base deficit. Multiple studies have presented the inferiority of HR as compared to other predictors included in the ATLS criteria such as systolic blood pressure (SBP), Glasgow Coma Scale (GCS) and base deficit (BD).[46,47] Based on these concerns, the role of HR in the classification of hypovolemic shock and the initial management of the severely injured should be re-evaluated.

Strenghts and limitations

Our study focuses on injury-related severe hemorrhage, a condition carrying high clinical importance. In the previous decades, trauma care has gone through remarkable development. On that note, we decided to use scientific data only from January 2010 – September 2020 (date of database search). The included papers were judged to carry a relatively low risk of bias.

Naturally, our study also has its limitations. Although mortality is a highly objective outcome and we included patients only with significant hemorrhage, the direct cause of death may be difficult to determine in some cases. 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. Prehospital measures may have affected the HR values registered upon admission. There is a notable difference in patient number among some of the included studies. The characteristics of the patient population by the individual records show a significant heterogeneity. To minimize this, a subgroup analysis was performed on patients who received blood products during initial in-hospital trauma care. These limitations prevented us from performing an adequate meta-analysis; however, we believe that we managed to raise attention on a clinically important issue.

Conclusions

The legitimity of HR in the initial assessment of hypovolemic shock seems to be obvious, but in fact, its usefulness is questionable due to unsatisfactory sensitivity and specificity. The complexity of HR response during hemorrhage leads to the possibility of misinterpretation, false sense of hemodynamic stability and consequent delay in adequate therapy.

Further research is required to reappraise HR as a physiologic variable in the ATLS classification of hypovolemic shock. As a reaction frequently associated with bleeding, tachycardia should raise suspicion for hemorrhage, but it might not be appropriate as one of the determining factors of therapeutic decisions, such as administration of blood products. In addition to the literature demonstrating the multi-phasic response of HR to bleeding, our study presents the lack of linear association with mortality. Considering these, modifying the pattern of HR derangements in the ATLS shock classification may make this pragmatic guide even more precise.

LIST OF ABBREVIATIONS

CENTRAL - Cochrane Controlled Register of Trials
ATLS - Advanced Trauma Life Support
HR - heart rate
pRBC - packed red blood cells
TXA - tranexamic acid
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PH - prehospital
AD - on admission
FAST - focused assessment with sonography for trauma
SD - standard deviation
IQR - interquartile range
QUIPS - Quality In Prognostic Studies
SBP- systolic blood pressure
GCS - Glasgow Coma Scale

BD - base deficit

STATEMENTS

Conflict of Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

PJ: preparation of the draft of the manuscript, contribution in study design, selection of studies, data extraction; LH: statistical analysis, interpretation of data; PHe: expert in the field of internal medicine, provided revisions to the scientific content of the manuscript; EC: expert in the field of traumatology, substantial contribution in study design and interpretation of data, provided revisions to the scientific content of the manuscript; EB: data extraction, preparation of the standardized data collection sheet; TH: risk of bias assessment, stylistic and grammatical revision of the manuscript; IG: substantial contribution in study design, selection of studies, data extraction; AL: formatting the manuscript, stylistic revision of the manuscript; AS: statistical analysis, interpretation of data; ZR: risk of bias assessment, preparation of the manuscript; EP: participation in the design of the study and its coordination; JT: provided revisions to the scientific content of the manuscript, validation of data extraction; PHa: study design, preparation of the manuscript, provided revisions to the scientific content of the manuscript

Hereby, all authors certify that they have participated sufficiently in the work to take public responsibility for the content.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Our study uses published data only. The original contributions presented in the study are included in the article and supplementary material, further inquiries can be directed to the corresponding author.

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FIGURE LEGENDS

Fig. 1. PRISMA flow diagram. Our search strategy resulted 2017 papers. 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
*heart rate (HR) was not provided in mean or median, only the number of patients in ranges of HR (e.g., 100-120 bpm) was given

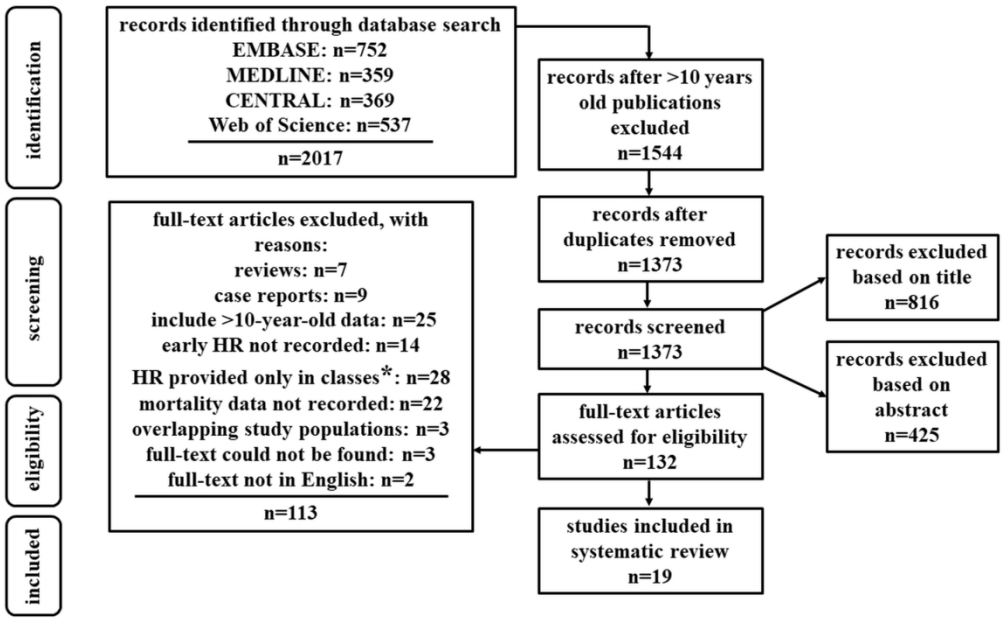
Fig. 2. Risk of bias assessment.
a: The figure shows the risk of bias in the 6 main domains of the Quality In Prognostic Studies (QUIPS) assessment, in each paper. 'Study attrition' was not suitable for the retrospective studies. In 5 prospective studies, there was a moderate risk for study attrition bias. All studies were judged to carry a low risk of bias in 'Study participation' and 'Prognostic factor measurement' domains. 'Study confounding' was the worst rated domain: a moderate risk appeared in almost half of the records, in which the role of important confounders was not reported thoroughly. Based on the assessment of the 6 main domains, the overall risk of bias was determined for each study
b: The summarized risk of bias is illustrated in percentages in the main domains

Fig. 3. Relation between heart rate (HR) and mortality of bleeding trauma patients. Linear association between HR and mortality could not be identified.

HR=heart rate

Fig. 4. Subgroup analysis of studies on trauma patients who received blood products. Linear association between early heart rate (HR) and mortality rate of patients could not be identified.

HR=heart rate



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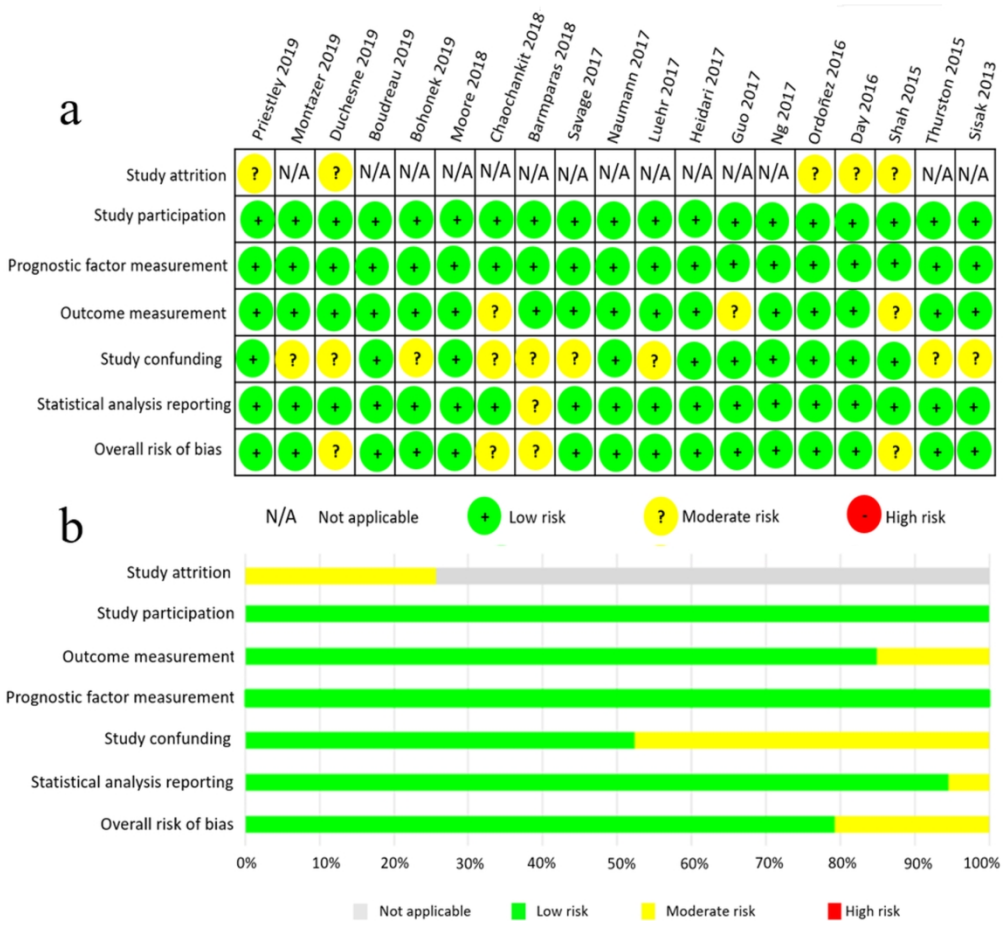

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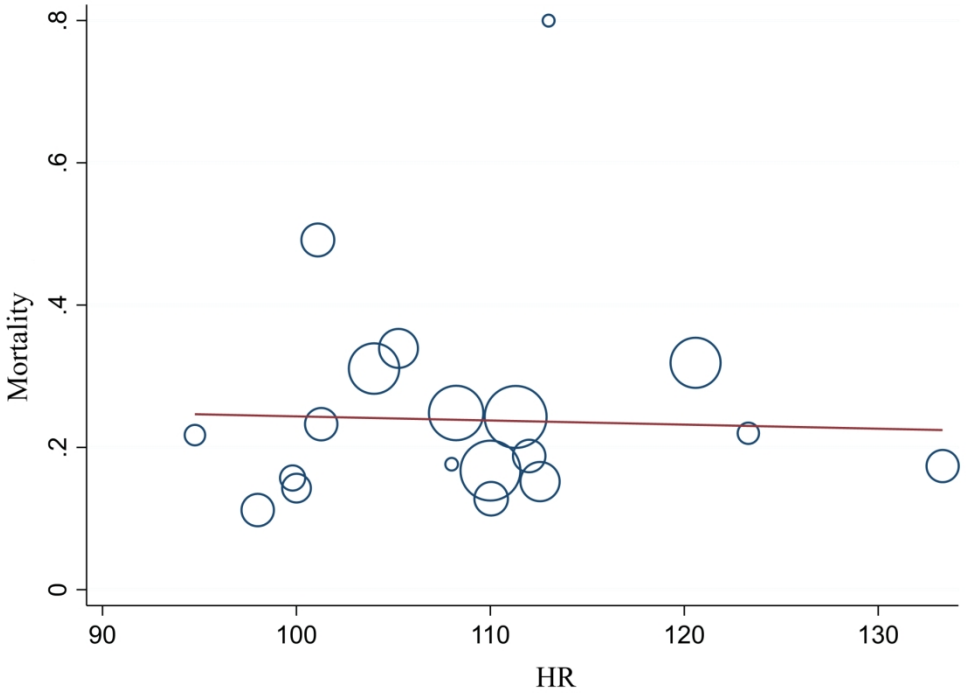

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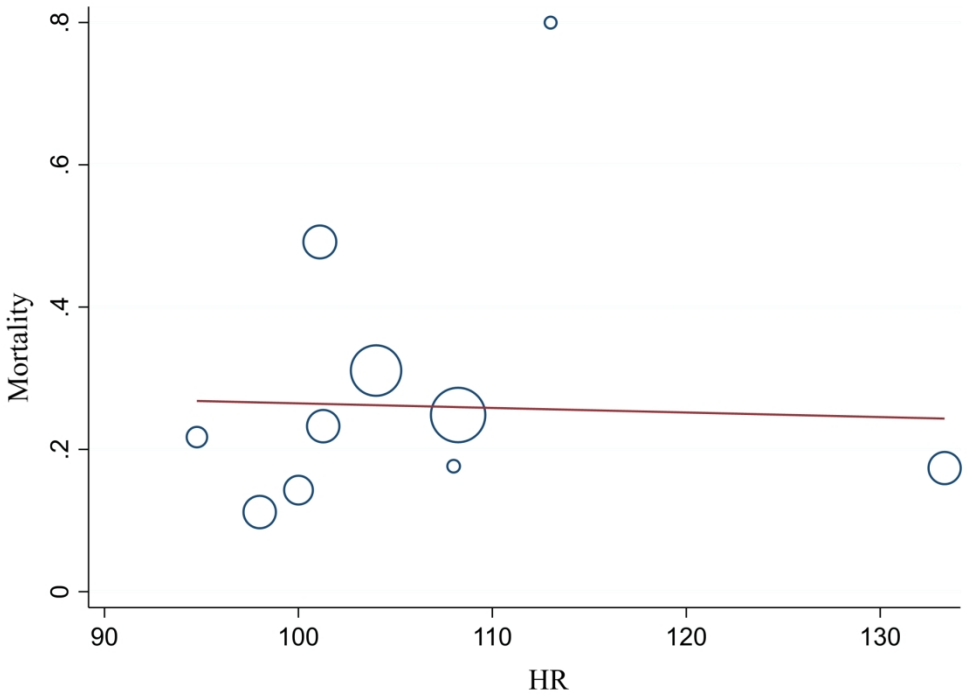

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported (Page nr.)
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4, 10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported (Page nr.)
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	-
Study characteristics	17	Cite each included study and present its characteristics.	6 (Table 1)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6-7 (Fig. 2)
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7 (Fig 3-4)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6-7, (Fig. 2)
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7-8
	23b	Discuss any limitations of the evidence included in the review.	9
	23c	Discuss any limitations of the review processes used.	9
	23d	Discuss implications of the results for practice, policy, and future research.	9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	9
Competing interests	26	Declare any competing interests of review authors.	9
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	10

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Study: first author, year of publication	Data origin: institute, country	Data collection: type, date	Indicators of hemorrhage	Patient number (n)	Age (y) mean ± SD or median [IQR]	Male gender n (%)	HR mean ± SD (PH/AD)	Mortality n, (%)	Main outcome(s)
Bohonek 2019	*Military University Hospital Prague, Czech Republic*	*retrospective, single-center, 2014-2018*	*received blood products (fresh apheresis platelets or cryopreserved platelets)*	*46*	*53 [20–80]; 50 [27–66]**	*32 (69.6)*	*94.8 ± 59.0 (AD)*	*10 (21.7)*	*mortality, blood products administered, adverse effects following platelet transfusion, laboratory parameters such as aPTI*
Boudreau 2019	*University of Cincinnati Medical Center, Cincinnati, Ohio, USA*	*retrospective, single-center, April 2014 – October 2015*	*received blood products and tranexamic acid*	*116*	*45 [24-61]; 33 [23-45]**	*90 (77.6)*	*101.3 ± 43.0 (PH)*	*27 (23.3)*	*mortality, thromboembolic events, transfusion requirements*
Duchesne 2019	11 level I trauma centers, 1 level II trauma center from the USA	retrospective, multi-center, *January 2011 – December 2016*	pelvic fracture with SBP ≤ 90 mmHg and/or HR ≥ 120 bpm and/or BD ≥ 5 mEq	279	40 [28–54]	172 (62.0)	120.6 ± 27.7 (AD)	89 (32.0)	mortality, frequency of each hemorrhage intervention adjunct used, time to definitive bleeding control
Montazer 2019	Imam Khomeini Hospital, Sari, Iran	prospective, single-center, March 2014 – February 2015	multiple trauma with hemodynamic instability (not defined)	400	42 ± 20	333 (83.3)	110.0 ± 14.0 (AD)	67 (16.7)	mortality
Priestley 2019	*LAC+USC Medical Center, LAC+USC blood bank database, University of*	*retrospective, single-center, January 2010 – October 2014*	*received 3 units of pRBC in any 60-minute period within 24 hours of admission and received interventional*	*283*	*34 [24-48]*	*244 (86.2)*	*104.0 ± 24.0 (PH)*	*88 (31.1)*	*mortality, days on ventilator, length of hospitalization*

	Southern California, Los Angeles, CA, USA		*radiology or surgery for definitive hemorrhage control*						
Barmparas 2018	*Cedars-Sinai Medical Center Los Angeles, CA, USA*	*retrospective, single-center January 2011 – October 2016*	*received massive transfusion (defined as 3 units of pRBC within the first hour from admission)*	*120*	*39.0 [27.0-54.8]*	*92 (76.7)*	*101.1 ± 39.7 (AD)*	*59 (49.2)*	*mortality*
Chaochankit 2018	*Songklanagarind Hospital, Hat Yai, Thailand*	*retrospective, single-center, January 2014 – December 2014*	*received massive transfusion, met trauma team activation criteria*	*15*	*35 [22-44.5]*	*13 (86.7)*	*113.0 ± 22.1 (AD)*	*12 (80.0)*	*need for massive transfusion*
Moore 2018	Denver Health Medical Center, Denver, CO, USA	prospective, single-center, April 2014 – March 2017	SBP ≤ 70 mmHg or 71-90 mmHg with HR ≥ 108 bpm	125	33 [25-47]	103 (82.4)	110.0 ± 15.9 (PH)	16 (12.8)	mortality
Ng 2018	British Columbia Trauma Registry, Canada	retrospective, single-center, April 2012 – June 2015	SBP ≤ 90 mmHg and/or HR ≥ 110 bpm	117	43 ± 19	96 (82.0)	112.0 ± 35.0 (AD)	22 (19.0)	meeting the indication criteria for TXA
Guo 2017	33 academic hospitals in 16 Chinese provinces, China	prospective, multi-center, December 2013 – April 2014	new-onset hypotension unexplained by any other cause than hemorrhage (SBP < 90 mmHg, DBP < 60 mmHg, or MAP < 65 mmHg or decreased SBP with more than 40 mmHg from baseline in a hypertensive patient), and signs of tissue hypoperfusion (tachycardia, oliguria, mottled skin, altered mental state)	428	52 ± 18	296 (69.2)	111.3 ± 17.9 (AD)	104 (23.4)	mortality
Heidari 2017	4 level I trauma centers from Iran	prospective, multi-center, April 2015 – September 2015	blunt abdominal trauma with positive FAST	168	38 ± 17	129 (76.8)	105.3 ± 23.4 (AD)	57 (33.9)	positive FAST, mortality

Luehr 2017	*Mercy Hospital-Springfield, Springfield, MO, USA*	*retrospective, single-center, 2013 - 2016*	*received blood products and tranexamic acid*	*115*	*42 ± 18*	*78 (67.8)*	*133.3 ± 21.4 (PH)*	*20 (17.4)*	*mortality*
Naumann 2017	*University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK*	*retrospective, single-center, July 2015 – January 2017*	*received blood products, required intensive care and had a lactate value >2 mmol/l (cohort B**)*	*17*	*40 ± 18*	*16 (94.0)*	*108.0 ± 16.2 (AD)*	*3 (17.6)*	*mortality, thromboembolic events, hospital-free and ICU-free days (calculated as 30 minus the number of days in hospital and ICU respectively)*
Savage 2017	*Indiana University School of Medicine, Indianapolis IN, USA; The University of Tennessee Health Science Center, Memphis, TN, USA*	*retrospective, multi-center, September 2013 – May 2015*	*received at least one unit of pRBC within the first 24 hours of admission*	*330*	*35 [25-54]*	*251 (76.0)*	*108.2 ± 55.3 (AD)*	*82 (24.8)*	*mortality*
Day 2016	*The Queen's Medical Center, Honolulu, Hawaii, USA*	*retrospective, single-center, September 2011 – March 2013*	*received at least one unit of pRBC in the first 6 hours, met trauma team activation criteria*	*116*	*no data*	*no data*	*98.0 ± 24.0 (PH)*	*13 (11.0)*	*multiple transfusions*
Ordoñez 2016	Fundación Valle del Lili, University Hospital, Cali, Colombia	retrospective, single-center, January 2012 – December 2013	ISS > 15 with hemodynamic instability (SBP < 100 mmHg and/or HR > 100 bpm and/or the need for at least 4 units of packed red blood cells in the trauma bay)	171	32 ± 14	154 (90.0)	112.6 ± 23.5 (AD)	26 (15.2)	mortality
Shah 2015	Aga Khan University Hospital, Karachi, Pakistan	retrospective, single-center, January 2011 – December 2012	isolated abdominal gunshot wound	70	35 ± 11	68 (97.1)	99.8 ± 30.3 (AD)	11 (15.7)	mortality, complications

Thurston 2015	Trauma Center, Groote Schuur Hospital and Faculty of Health Sciences, University of Cape Town, South Africa	prospective, single-center, September 2013 – November 2013	SBP < 90 mmHg and/or HR >110 bpm at any time from admission to 3 hours after injury	50	32 ± 13	47 (94.0)	123.3 ± 13.1 (AD)	11 (22. 0)	mortality
Sisak 2013	*John Hunter Hospital and University of Newcastle, Newcastle, NSW, Australia*	*prospective, single-center, January 2010 – January 2011*	*received blood products within the first 24 hours from admission*	*91*	*38 [22–59]*	*68 (74.7)*	*100.0 ± 30.1 (AD)*	*13 (14. 0)*	*mortality, need for emergent surgery, ICU admission , length of ICU-and hospital stay*

Table S2. Detailed description of the characteristics of the included studies. Most papers enrolled trauma patients receiving blood products and/or showing 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 is a significant heterogeneity in mortality between datasets. The need for massive transfusion is accompanied by a prominently high mortality rate. A mean heart rate (HR) > 120 bpm does not entail an outstanding mortality rate.
*the study population was divided into two groups, median [IQR] age values were provided separately for the groups
**only cohort B consisted of trauma patients with active bleeding
SD=standard deviation, IQR=interquartile range, aPTI=activated partial thromboplastin time, ICU=intensive care unit, PH=prehospital, AD=upon admission, pRBC=packed red blood cells, RCT=randomized controlled trial, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, ISS=injury severity score, HR=heart rate, bpm=beats per minute, BD=base deficit, FAST=focused assessment with sonography for trauma, TXA=tranexamic acid