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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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3 1 **TACHYCARDIA DOES NOT IMPLY AN INCREASED RISK OF MORTALITY IN**
4 **TRAUMA-RELATED HEMORRHAGIC SHOCK - A SYSTEMATIC REVIEW AND**
5 **2 META-REGRESSION**
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26 ABSTRACT

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

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

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

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

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

48 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 49 • The study summarizes and analyzes scientific data from the past 10 years to investigate trauma-
50 related hemorrhage, an issue with high clinical importance.
- 51 • The paper provides a systematic search of EMBASE, MEDLINE (via PubMed), Cochrane
52 Controlled Register of Trials (CENTRAL) and Web of Science databases, utilizes rigorous
53 study selection criteria, assesses each enrolled paper for bias, and performs meta-regression
54 analyses.
- 55 • Studies focusing on special populations including pregnant, pediatric (<18 years of age),
56 geriatric (≥ 55 years), burned and traumatic spinal- or brain injured patients were excluded from
57 the study.
- 58 • The heterogeneity and the difference in patient number among the included studies prevented
59 us from performing an adequate meta-analysis.

60 INTRODUCTION

61 Hypovolemia caused by hemorrhage is the most common cause of shock in trauma. Delay in the
62 recognition of shock has been linked to unfavorable outcomes such as organ dysfunction and
63 mortality.[1,2] The initial assessment of trauma-related hypovolemic shock is based on derangements
64 of physiologic variables (including base deficit) according to the recommendations of Advanced Trauma
65 Life Support (ATLS).[3] Among these variables, heart rate (HR) is one of the most controversial when
66 it comes to blood loss.[4-7] As commonly criticized, HR is not only influenced by hemodynamic
67 changes, but also by several other factors such as anxiety, pain, and medications resulting in a low
68 specificity for hemorrhage.[4,8,9] Furthermore, ATLS suggests the continuously increasing tendency of
69 HR in accordance with the severity of bleeding.[3] However, in clinical reality, the HR response to
70 hemorrhage is rather biphasic or triphasic than linear.[8,10,11] Consequently, the utility of HR in the
71 early management of bleeding trauma patients was called into doubt during the past decades.[4,5,8,9]
72 The reliability of HR was already questioned in the early 2000s by a retrospective analysis on 14325
73 trauma patients. According to the results of this study, HR displayed insufficient sensitivity and
74 specificity in predicting hypotension after trauma.[9] A few years later, a registry analysis denoted
75 further doubts in HR, as it had performed poorly in predicting the need for an emergent intervention and
76 administration of packed red blood cells (pRBC) in the first 24 hours post-injury.[4] Additionally, as
77 ATLS was progressively widespread, the role of HR in the classification of hypovolemic shock sparked
78 controversy. In 2013, 16305 patients from the German Trauma Register (DGU®) were allocated into shock
79 classes according to ATLS guidance.[12] Ultimately, no significant alterations in mean HR were found
80 within the four classes. According to these data, expecting tachycardia in case of hypovolemia can be
81 misleading in many instances. Moreover, a false sense of hemodynamic stability based on normal HR
82 can lead to fatal consequences, since the lack of tachycardia in hypoperfusion is associated with poor
83 prognosis.[13]

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

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

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

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3 96 loss presented by ATLS is questionable.[8,15] Due to the development of trauma care and a paradigm
4 97 shift in the initial fluid resuscitation approach in the past decades,[16,19] we aimed to update current
5 98 knowledge on the effectivity of HR as predictor of mortality post-injury. For this purpose, a
6 99 comprehensive database search has been conducted, data has been extracted and analyzed through meta-
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9 100 regressions. As a primary outcome, the relationship between HR and mortality has been assessed. Since
10 101 the severity of bleeding has a close relation to the risk for adverse outcomes including increased organ
11 102 dysfunction and mortality, our study may be able to initiate further research reappraising the validity of
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13 103 HR in the ATLS classification of hypovolemic shock.
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17 18 104 **MATERIALS AND METHODS**

19 20 105 **Protocol and search strategy**

21 106 The present review is reported in accordance with Preferred Reporting Items for Systematic Reviews
22 107 and Meta-Analyses (PRISMA).[20] The PRISMA checklist for our work is available in the supporting
23 108 information (Table S1). The review protocol was registered in the Open Science Framework (OSF)
24 109 system under registration DOI: 10.17605/OSF.IO/HJWYR.

25 110 A systematic search of EMBASE, MEDLINE (via PubMed), Cochrane Controlled Register of Trials
26 111 (CENTRAL) and Web of Science databases was performed with the following search terms: "trauma"
27 112 AND ("heart rate" OR "pulse rate" OR "tachycardia" OR "bradycardia" OR "vital sign" OR "vital signs"
28 113 OR "vital parameter" OR "vital parameters") AND "mortality" AND ("bleeding" OR "haemorrhage"
29 114 OR "hemorrhage" OR "haemodynamic" OR "hemodynamic").
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36 115 **Eligibility criteria**

37 116 Records on bleeding trauma patients were considered for eligibility only if they provided initial HR
38 117 values (prehospital (PH) or upon admission (AD)) in addition to mortality data covering a time interval
39 118 not exceeding 30 days from the time of injury. If the inclusion criteria of the individual studies included
40 119 transfusion of blood products and/or positive focused assessment with sonography for trauma (FAST)
41 120 examination and/or hemodinamical instability after trauma and/or abdominal gunshot injury, the patient
42 121 cohort was considered hemorrhagic.

43 122 Non-English language reports, records on special populations such as pregnant, pediatric (<18 years of
44 123 age) or geriatric (≥ 55 years) were not considered. Studies on patients suffering burns, traumatic spinal
45 124 or- brain injuries were excluded.

46 125 Taking the development of trauma care in the past decade into consideration (e.g.: introduction of
47 126 TXA,[16] and paradigm shift in fluid resuscitation [19]) all studies that included data on patients who
48 127 received treatment before 2010 were also excluded.

49 128 **Study selection**

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3 129 After having duplicates removed with the help of a reference manager software (EndNote X7), articles
4 130 published before 2010 were also discarded. On the remaining studies, title and abstract screenings were
5 131 performed by two review authors (PJ, IG). Thereafter, the full texts of the potentially eligible records
6 132 were obtained and assessed based on the criteria described above. Disagreements were resolved by
7 133 consensus.

11 134 **Data extraction**

13 135 The following information was extracted from the eligible studies: title, first author's name, year of
14 136 publication, study design, data origin (country, hospital database/registry), data collection period,
15 137 inclusion criteria, subgroups, patient number of the subgroups, total patient number, HR (mean \pm
16 138 standard deviation (SD) or median [interquartile range] (IQR)), phase of recording HR values (PH/AD),
17 139 mortality within 30 days (n, %). In case of studies using overlapping data, the less comprehensive report
18 140 with the smaller sample size was excluded.

23 141 **Risk of bias assessment**

24 142 Quality In Prognostic Studies (QUIPS) tool was used separately by two authors (TH and ZR) to assess
25 143 the risk of bias for each study.[21] Disagreements were resolved by consensus. QUIPS consists of six
26 144 main domains: 'Study attrition', 'Study participation', 'Prognostic factor', 'Outcome measurement',
27 145 'Study confounding' and 'Statistical analysis and reporting'. A rating for each domain was assigned as
28 146 carrying 'low', 'moderate' or 'high' risk of bias. Based on the ratings of the individual domains, the
29 147 overall risk of bias was evaluated by each study.

35 148 **Statistical analysis**

36 149 The association between HR and mortality of trauma patients was assessed using meta-regression
37 150 analysis. A result of $p < 0.05$ was considered as significant. As a subgroup analysis, meta-regression was
38 151 performed on trauma patients who received blood products. Statistical analyses were performed with
39 152 Stata 16 (Stata Corp, College Station, TX, USA). To convert median values to means, we used the
40 153 method of Xiang Wan.[22]

46 154 **RESULTS**

49 155 **Results of systematic search and selection**

50 156 Two thousand and seventeen records were identified through our search strategy on 1 September 2020.
51 157 One thousand three hundred seventy-three articles were screened on title. Five hundred fifty-seven
52 158 abstracts were assessed, and 132 publications were enrolled into the final, comprehensive full text
53 159 analysis. Ultimately, 19 records met our eligibility criteria. The flowchart of study enrollment is shown
54 160 in Figure 1.

58 161 **Fig. 1.** Study flowchart

162 Study characteristics

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

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

184 Study quality

185 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.

191 **Fig. 2** Risk of bias assessment

192 Primary meta-regression

193 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.

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

198 Subgroup analysis

199 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).

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

204 DISCUSSION

205 Interpretation of results

206 The present study was designed to investigate and update current knowledge on the relation between
 207 HR and mortality in bleeding trauma patients. We identified 19 studies providing early HR and mortality
 208 data on trauma patients with hemorrhage from the past 10 years through database search. Due to the
 209 relative heterogeneity of the patient enrollment criteria of the individual papers, a subgroup of 10 records
 210 was created. Each of these 10 studies provided data on trauma patients who received blood products.
 211 Meta regressions were conducted on the data of all records and the subgroup, respectively.
 212 No significant relation was found between HR and mortality in our meta regressions. This result supports
 213 the evidence provided by studies doubting the value of HR in the initial assessment of potentially
 214 bleeding trauma patients. Additionally, our findings raise further concerns over the validity of HR in the
 215 ATLS classification of hypovolemic shock.
 216 HR is an easily accessible vital parameter that indubitably reacts to circulatory volume depletion [5,6].
 217 However, the complexity of this reaction seems to contain too many possibilities for misinterpretation to
 218 be used in the simplified scheme presented by ATLS. The current classification of hypovolemic shock
 219 suggests that HR increases continuously parallel to the severity of bleeding. The increase can stagnate
 220 between class I-II and III-IV according to ATLS.[3] This scheme seems to be incongruent with the
 221 existing literature on the physiology of HR change during intravascular volume depletion. The HR
 222 response tends to follow a biphasic or triphasic pattern instead of continuous increase [8,10,11]. If it
 223 comes to a decrease or stagnation in HR value, it is likely to occur at two separate stages of hemorrhage.
 224 First, due to increased vagal activity caused by a Bezold-Jarisch-like reflex just around 30% blood
 225 loss,[5,10] between shock classes II and III, where ATLS suggests a clear increase in HR. Secondly, at
 226 the end stage of hemorrhage, bradycardia appears preceding cardiac arrest.[15,23,24] Based on these
 227 observations, the pattern of HR alterations during hemorrhage suggested by ATLS may reflect the
 228 clinical condition more accurately after minor modifications (Table 2).

<i>Severity classes</i>		<i>Class I</i>	<i>Class II</i>	<i>Class III</i>	<i>Class IV</i>
<i>Estimated blood loss</i>		<15%	15-30%	31-40%	>40%
<i>Physiologic variables</i>	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

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3 **Table 2.** Advanced Trauma Life Support (ATLS) classification of hypovolemic shock including
4 suggested modifications in the pattern of heart rate (HR) derangements. The table is based on the 10th
5 edition of ATLS. Estimated blood loss is shown as percentage of total blood volume.

6 *The suggested modifications are highlighted in bold: possible stagnation in HR value is indicated
7 around 30% blood loss due to increased vagal activity. The possibility of bradycardia in profound
8 bleeding in Class IV is highlighted

9 HR=heart rate, SBP=systolic blood pressure, GCS=Glasgow Coma Scale, BD=base deficit

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

244 **Strengths and limitations**

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

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

257 **Conclusions**

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

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

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3 266 phasic response of HR to bleeding, our study presents the lack of linear association with mortality.
4 267 Considering these, modifying the pattern of HR derangements in the ATLS shock classification may
5 268 make this pragmatic guide even more precise.
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10 269 **STATEMENTS**

11 270 **Conflict of Interests**

12 271 The authors declare that the research was conducted in the absence of any commercial or financial
13 272 relationships that could be construed as a potential conflict of interest.

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20 279 **Authors' contributions**

21 280 PJ: preparation of the draft of the manuscript, contribution in study design, selection of studies, data
22 281 extraction; LH: statistical analysis, interpretation of data; PH: expert in the field of internal medicine,
23 282 provided revisions to the scientific content of the manuscript; EC: expert in the field of traumatology,
24 283 substantial contribution in study design and interpretation of data, provided revisions to the scientific
25 284 content of the manuscript; EB: data extraction, preparation of the standardized data collection sheet; TH:
26 285 risk of bias assessment, stylistic and grammatical revision of the manuscript; IG: substantial contribution
27 286 in study design, selection of studies, data extraction; AL: formatting the manuscript, stylistic revision of
28 287 the manuscript; AS: statistical analysis, interpretation of data; ZR: risk of bias assessment, preparation
29 288 of the manuscript; EP: participation in the design of the study and its coordination; JT: provided revisions
30 289 to the scientific content of the manuscript, validation of data extraction; PH: study design, preparation
31 290 of the manuscript, provided revisions to the scientific content of the manuscript
32 291 Hereby, all authors certify that they have participated sufficiently in the work to take public
33 292 responsibility for the content.

34 293 **Ethics approval and consent to participate**

35 294 Not applicable.

36 295 **Consent for publication**

37 296 Not applicable.

38 297 **Availability of data and materials**

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3 298 Our study uses published data only. The original contributions presented in the study are included in the
4 299 article and supplementary material, further inquiries can be directed to the corresponding author.

300 **Patient and public involvement**

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

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432 **FIGURE LEGENDS**

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

436 *heart rate (HR) was not provided in mean or median, only the number of patients in ranges of HR (e.g.,
 437 100-120 bpm) was given

438 **Fig. 2.** Risk of bias assessment.

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

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

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

449 HR=heart rate

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

452 HR=heart rate

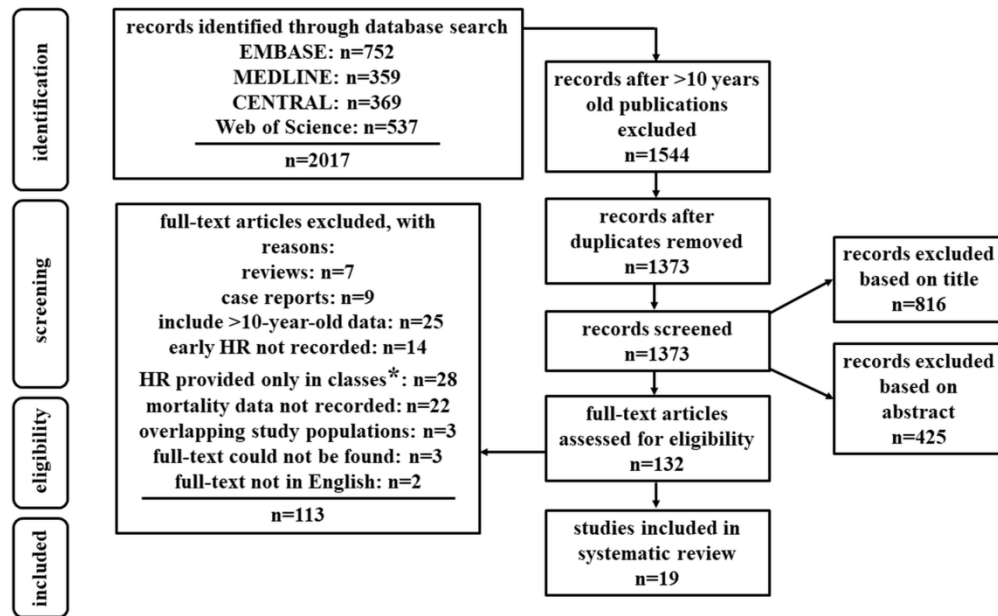


Fig. 1. PRISMA flow diagram. Our search strategy resulted 2017 papers. After excluding articles published before 2010 and duplicates, 1373 papers were screened based on title and abstract. In 79 cases the title clearly indicated non-eligible study design such as review or systematic review. Twenty-four 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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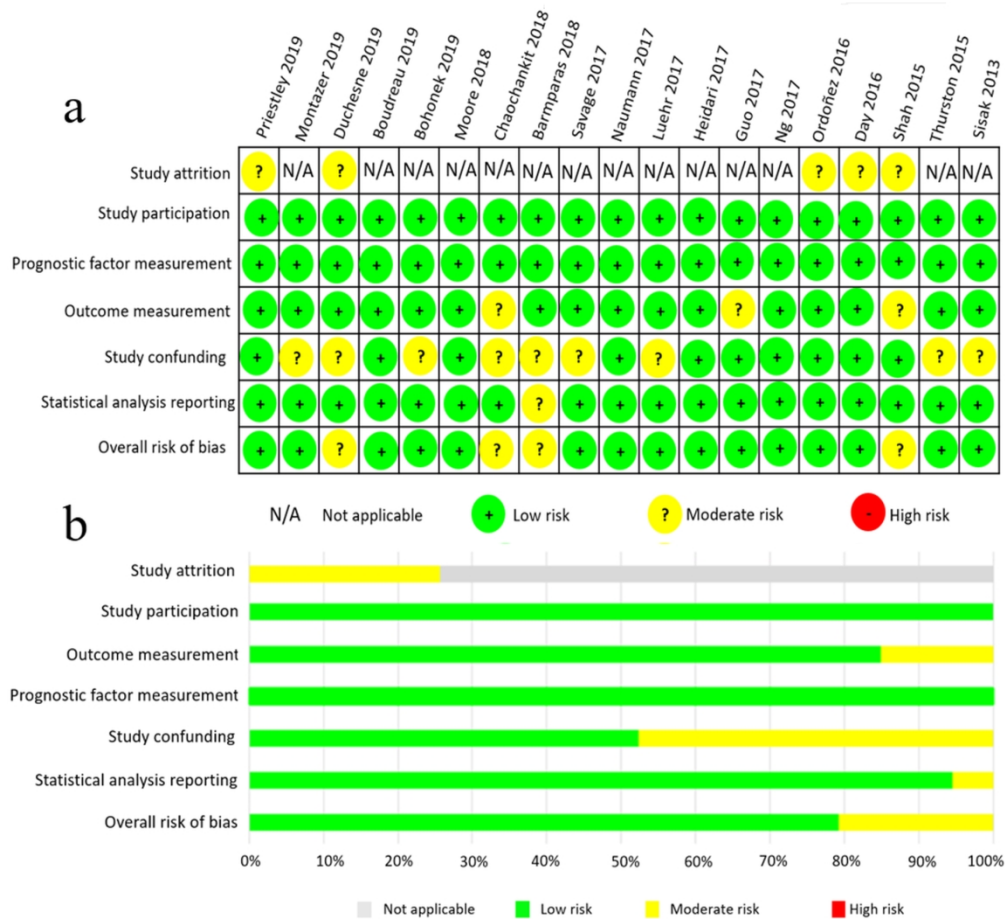


Fig. 2. Risk of bias assessment.

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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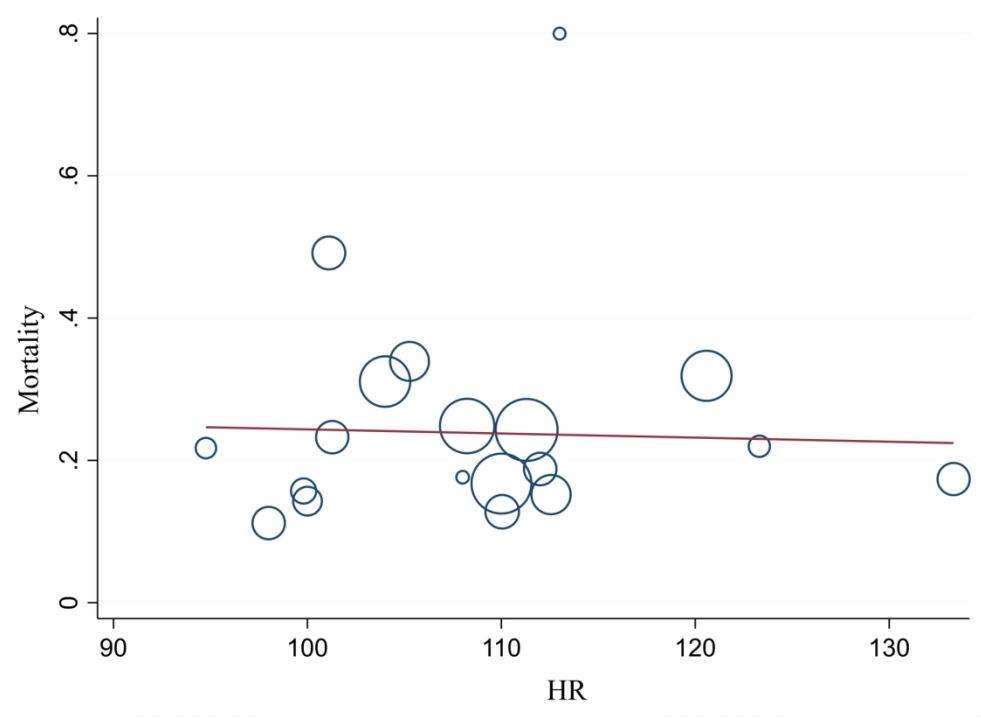


Fig. 3. Relation between heart rate (HR) and mortality of bleeding trauma patients. Linear association between HR and mortality could not be identified.
HR=heart rate

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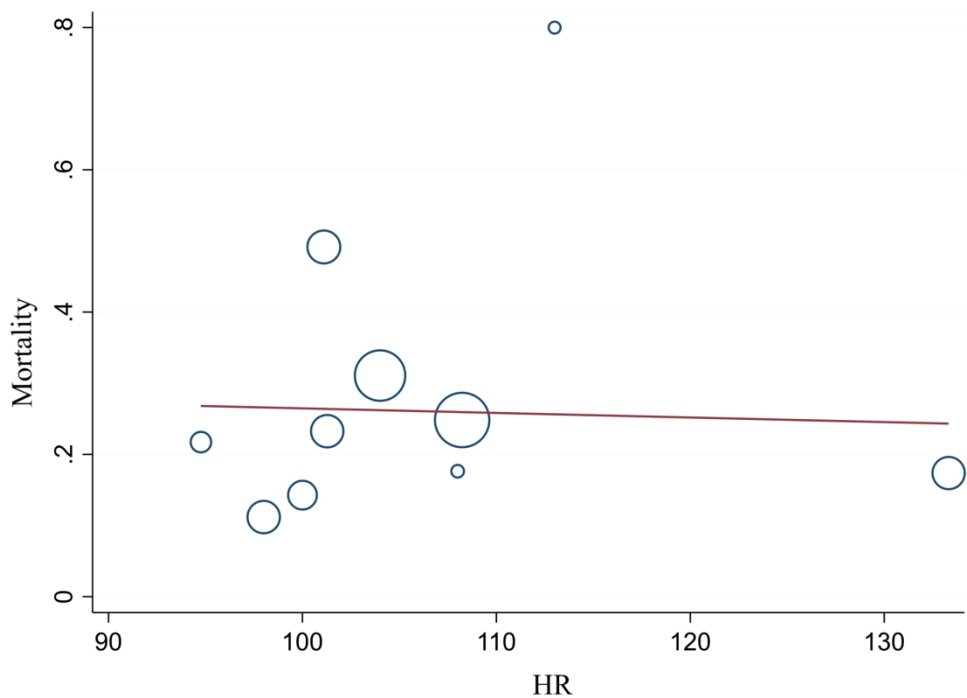


Fig. 4. Subgroup analysis of studies on trauma patients who received blood products. Linear association between early heart rate (HR) and mortality rate of patients could not be identified.
HR=heart rate

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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

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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/>

For peer review only

Study: first author, year of publication	Data origin: institute, country	Data collection: type, date	Patient characteristics	Patient number	HR mean \pm 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 \pm 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 \pm 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 \leq 90 mmHg and/or HR \geq 120 bpm and/or BD \geq 5 mEq	279	120.6 \pm 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 \pm 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 \pm 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 \pm 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 \pm 22.1 (AD)	12 (80.0)
Moore 2018	Denver Health Medical Center, Denver, CO, USA	prospective, single-center, April 2014 – March 2017	SBP \leq 70 mmHg or 71-90 mmHg with HR \geq 108 bpm	125	110.0 \pm 15.9 (PH)	16 (12.8)
Ng 2018	British Columbia Trauma Registry, Canada	retrospective, single-center, April 2012 – June 2015	SBP \leq 90 mmHg and/or HR \geq 110 bpm	117	112.0 \pm 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 \pm 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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3 1 **THE PREDICTIVE VALUE OF TACHYCARDIA FOR MORTALITY IN TRAUMA-**
4 **RELATED HEMORRHAGIC SHOCK: A SYSTEMATIC REVIEW AND META-**
5 2 **REGRESSION**
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10 4 **Péter Jávor¹, Lilla Hanák², Péter Hegyi^{2;3}, Endre Csonka¹, Edina Butt¹, Tamara Horváth⁴, István**
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26 ABSTRACT

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

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

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

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

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

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

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

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

54 STRENGTHS AND LIMITATIONS OF THIS STUDY

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

- 59 • Studies focusing on special populations including pregnant, pediatric (<18 years of age),
60 geriatric (≥ 55 years), burned and traumatic spinal- or brain injured patients were excluded from
61 the study.
- 62 • The heterogeneity and the difference in patient number among the included studies prevented
63 us from performing an adequate meta-analysis.
- 64 • Although mortality is a highly objective outcome, the fact that in some cases hemorrhage might
65 not been the direct cause of death even if bleeding was present is an important limitation of the
66 study.

67 INTRODUCTION

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

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

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

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3 94 and validate a prognostic model to predict death due to bleeding. Although HR showed a significant
4 95 relation to mortality, the curve was U-shaped as opposed to the linear model presented by ATLS.[15]
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6 96 A notable limitation of previous studies is that trauma protocols have undergone several changes, which
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8 97 makes recent information incomparable with data from the past. In 2010, the CRASH-2 trial brought
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10 98 one of the most prominent findings of the past decades with the validation of the safeness and effectivity
11 99 of tranexamic acid (TXA).[16-18]
12
13 100 The present systematic review investigates the role of HR in the initial assessment of trauma patients
14 101 with hemorrhage. Regarding the efficiency of HR as a predictor of outcome in trauma, there is
15 102 contradictory data in the literature.[4,5,15] Furthermore, the linear association between HR and blood
16 103 loss presented by ATLS is questionable.[8,15] Due to the development of trauma care and a paradigm
17 104 shift in the initial fluid resuscitation approach in the past decades,[16,19] we aimed to update current
18 105 knowledge on the effectivity of HR as predictor of mortality post-injury. For this purpose, a
19 106 comprehensive database search has been conducted, data has been extracted and analyzed through meta-
20 107 regressions. As a primary outcome, the relationship between HR and mortality has been assessed. Since
21 108 the severity of bleeding has a close relation to the risk for adverse outcomes including increased organ
22 109 dysfunction and mortality, our study may be able to initiate further research reappraising the validity of
23 110 HR in the ATLS classification of hypovolemic shock.

111 **MATERIALS AND METHODS**

112 **Protocol and search strategy**

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

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

123 **Eligibility criteria**

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

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3 129 of TXA,[16] and paradigm shift in fluid resuscitation [19]) all studies that included data on patients
4 130 treated before 2010 were also excluded.

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7 131 To consider a patient cohort hemorrhagic, the inclusion criteria of the individual studies had to include
8 132 transfusion of blood products and/or positive focused assessment with sonography for trauma (FAST)
9 133 examination and/or hemodynamical instability after trauma and/or abdominal gunshot injury. Records
10 134 on special populations such as pregnant, pediatric (<18 years of age) or geriatric (≥ 55 years) were not
11 135 considered. Studies on patients suffering burns, traumatic spinal or- brain injuries were excluded.

12 136 With excluding special populations and pediatric and older age groups we aimed to reduce the influence
13 137 of confounding factors. Since studies of geriatric trauma patients have used age cutoffs ranging from 55
14 138 to 80 years and there is no clear consensus in the literature,[21,22] we decided to exclude study
15 139 populations of 55 years of age or older to diminish the effects of age-related confounding factors.

21 140 **Study selection**

22 141 After having duplicates removed with the help of a reference manager software (EndNote X7), articles
23 142 published before 2010 were also discarded. On the remaining studies, title and abstract screenings were
24 143 performed by two review authors (PJ, IG). Thereafter, the full texts of the potentially eligible records
25 144 were obtained and assessed based on the criteria described above. Disagreements were resolved by
26 145 consensus.

31 146 **Data extraction**

32 147 The following information was extracted from the eligible studies: title, first author's name, year of
33 148 publication, study design, data origin (country, hospital database/registry), data collection period,
34 149 inclusion criteria, subgroups, patient number of the subgroups, total patient number, HR (mean \pm
35 150 standard deviation (SD) or median [interquartile range] (IQR)), phase of recording HR values (PH/AD),
36 151 mortality within 30 days (n, %). In case of studies using overlapping data, the less comprehensive report
37 152 with the smaller sample size was excluded.

43 153 **Risk of bias assessment**

44 154 Quality In Prognostic Studies (QUIPS) tool was used separately by two authors (TH and ZR) to assess
45 155 the risk of bias for each study.[23] Disagreements were resolved by consensus. QUIPS consists of six
46 156 main domains: 'Study attrition', 'Study participation', 'Prognostic factor', 'Outcome measurement',
47 157 'Study confounding' and 'Statistical analysis and reporting'. A rating for each domain was assigned as
48 158 carrying 'low', 'moderate' or 'high' risk of bias. Based on the ratings of the individual domains, the
49 159 overall risk of bias was evaluated by each study.

55 160 **Statistical analysis**

56 161 The association between HR and mortality of trauma patients was assessed using meta-regression
57 162 analysis. A result of $p < 0.05$ was considered as significant. As a subgroup analysis, meta-regression was
58 163 performed on trauma patients who received blood products. Statistical analyses were performed with

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3 164 Stata 16 (Stata Corp, College Station, TX, USA). To convert median values to means, we used the
4 165 method of Xiang Wan.[24]
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8 166 **Patient and public involvement**

9 167 Patients and public were not specifically involved in designing the study.
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13 168 **RESULTS**

14 169 **Results of systematic search and selection**

15 170 Two thousand and seventeen records were identified through our search strategy on 1 September 2020.
16 171 One thousand three hundred seventy-three articles were screened on title. Five hundred fifty-seven
17 172 abstracts were assessed, and 132 publications were enrolled into the final, comprehensive full text
18 173 analysis. Ultimately, 19 records met our eligibility criteria. The flowchart of study enrollment is shown
19 174 in Figure 1.
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25 175 **Fig. 1.** PRISMA flow diagram
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28 176 **Study characteristics**

29 177 All publications processed data of trauma patients with suspected hemorrhage from the past 10 years.
30 178 From 19 studies yielding 3057 patients in total, 13 records collected data retrospectively and 6
31 179 prospectively. The number of participants in each dataset ranged from 15 to 428. Ten studies enrolled
32 180 patients only if they received blood products as a part of the initial management. Seven publications
33 181 used hemodynamic instability identified mainly by vital parameters as inclusion criteria. One study
34 182 analyzed patients with a positive result on FAST examination after blunt abdominal trauma. One
35 183 research enrolled patients with abdominal gunshot injuries. Each of the inclusion criteria listed above
36 184 entails a strong suspicion for significant bleeding. The main characteristics of the 19 eligible studies are
37 185 summarized in Table 1. The more comprehensive description of the papers is available in the
38 186 supplementary material (Table S2).
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46 47 First author, year	48 Country	49 Data collection	50 Patient characteristics	51 Patient number	52 HR mean ± SD (PH/AD)	53 Mortality n, (%)
54 <i>Bohonek 2019 [25]</i>	55 <i>Czech Republic</i>	56 <i>retrospective</i>	57 <i>received blood products</i>	58 46	59 94.8 ± 59.0 (AD)	60 10 (21.7)
<i>Boudreau 2019 [26]</i>	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)
<i>Priestley 2019 [29]</i>	USA	retrospective	received blood products	283	104.0 ± 24.0 (PH)	88 (31.1)

<i>Barmparas 2018 [30]</i>	<i>USA</i>	<i>retrospective</i>	<i>received blood products</i>	120	101.1 ± 39.7 (AD)	59 (49.2)
<i>Chaochan kit 2018 [31]</i>	<i>Thailand</i>	<i>retrospective</i>	<i>received blood products</i>	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)
<i>Luehr 2017 [36]</i>	<i>USA</i>	<i>retrospective</i>	<i>received blood products</i>	115	133.3 ± 21.4 (PH)	20 (17.4)
<i>Naumann 2017 [37]</i>	<i>UK</i>	<i>retrospective</i>	<i>received blood products</i>	17	108.0 ± 16.2 (AD)	3 (17.6)
<i>Savage 2017 [38]</i>	<i>USA</i>	<i>retrospective</i>	<i>received blood products</i>	330	108.2 ± 55.3 (AD)	82 (24.8)
<i>Day 2016 [39]</i>	<i>USA</i>	<i>retrospective</i>	<i>received blood products</i>	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)
<i>Sisak 2013 [43]</i>	<i>Australia</i>	<i>prospective</i>	<i>received blood products</i>	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

196 Study quality

197 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.

203 Fig. 2 Risk of bias assessment

204 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 validity 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 possibilities 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

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

<i>Severity classes</i>		<i>Class I</i>	<i>Class II</i>	<i>Class III</i>	<i>Class IV</i>
<i>Estimated blood loss</i>		<15%	15-30%	31-40%	>40%
<i>Physiologic variables</i>	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

241 **Table 2.** Advanced Trauma Life Support (ATLS) classification of hypovolemic shock including
242 suggested modifications in the pattern of heart rate (HR) derangements. The table is based on the 10th
243 edition of ATLS. Estimated blood loss is shown as percentage of total blood volume.

244 *The suggested modifications are highlighted in bold: possible stagnation in HR value is indicated
245 around 30% blood loss due to increased vagal activity. The possibility of bradycardia in profound
246 bleeding in Class IV is highlighted

247 HR=heart rate, SBP=systolic blood pressure, GCS=Glasgow Coma Scale, BD=base deficit

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

256 **Strengths and limitations**

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

261 Naturally, our study also has its limitations. Although mortality is a highly objective outcome and we
262 included patients only with significant hemorrhage, the direct cause of death may be difficult to
263 determine in some cases. Although studies on special populations have been excluded from our analysis,

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3 264 it is important to emphasize that the presence of potential confounding factors affecting HR values could
4 265 not be ruled out completely. Prehospital measures may have affected the HR values registered upon
5 266 admission. There is a notable difference in patient number among some of the included studies. The
6 267 characteristics of the patient population by the individual records show a significant heterogeneity. To
7 268 minimize this, a subgroup analysis was performed on patients who received blood products during initial
8 269 in-hospital trauma care. These limitations prevented us from performing an adequate meta-analysis;
9 270 however, we believe that we managed to raise attention on a clinically important issue.

15 271 **Conclusions**

16 272 The legitimacy of HR in the initial assessment of hypovolemic shock seems to be obvious, but in fact, its
17 273 usefulness is questionable due to unsatisfactory sensitivity and specificity. The complexity of HR
18 274 response during hemorrhage leads to the possibility of misinterpretation, false sense of hemodynamic
19 275 stability and consequent delay in adequate therapy.

20 276 Further research is required to reappraise HR as a physiologic variable in the ATLS classification of
21 277 hypovolemic shock. As a reaction frequently associated with bleeding, tachycardia should raise
22 278 suspicion for hemorrhage, but it might not be appropriate as one of the determining factors of therapeutic
23 279 decisions, such as administration of blood products. In addition to the literature demonstrating the multi-
24 280 phasic response of HR to bleeding, our study presents the lack of linear association with mortality.
25 281 Considering these, modifying the pattern of HR derangements in the ATLS shock classification may
26 282 make this pragmatic guide even more precise.

36 283 **LIST OF ABBREVIATIONS**

37
38 284 CENTRAL - Cochrane Controlled Register of Trials
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40 285 ATLS - Advanced Trauma Life Support
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42 286 HR - heart rate
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44 287 pRBC - packed red blood cells
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46 288 TXA - tranexamic acid
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48 289 PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
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50 290 PH - prehospital
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52 291 AD - on admission
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54 292 FAST - focused assessment with sonography for trauma
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56 293 SD - standard deviation
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58 294 IQR - interquartile range
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60 295 QUIPS - Quality In Prognostic Studies
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62 296 SBP- systolic blood pressure
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64 297 GCS - Glasgow Coma Scale

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3 298 BD - base deficit
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7 299 **STATEMENTS**
8

9 300 **Conflict of Interests**

10 301 The authors declare that the research was conducted in the absence of any commercial or financial
11 302 relationships that could be construed as a potential conflict of interest.

13
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15
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19 307 content of our paper in any way.

22
23 308 **Authors' contributions**

24 309 PJ: preparation of the draft of the manuscript, contribution in study design, selection of studies, data
25 310 extraction; LH: statistical analysis, interpretation of data; PHe: expert in the field of internal medicine,
26 311 provided revisions to the scientific content of the manuscript; EC: expert in the field of traumatology,
27 312 substantial contribution in study design and interpretation of data, provided revisions to the scientific
28 313 content of the manuscript; EB: data extraction, preparation of the standardized data collection sheet; TH:
29 314 risk of bias assessment, stylistic and grammatical revision of the manuscript; IG: substantial contribution
30 315 in study design, selection of studies, data extraction; AL: formatting the manuscript, stylistic revision of
31 316 the manuscript; AS: statistical analysis, interpretation of data; ZR: risk of bias assessment, preparation
32 317 of the manuscript; EP: participation in the design of the study and its coordination; JT: provided revisions
33 318 to the scientific content of the manuscript, validation of data extraction; PHa: study design, preparation
34 319 of the manuscript, provided revisions to the scientific content of the manuscript
35 320 Hereby, all authors certify that they have participated sufficiently in the work to take public
36 321 responsibility for the content.

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45 322 **Ethics approval and consent to participate**

46 323 Not applicable.

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49 324 **Consent for publication**

50 325 Not applicable.

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53 326 **Availability of data and materials**

54 327 Our study uses published data only. The original contributions presented in the study are included in the
55 328 article and supplementary material, further inquiries can be directed to the corresponding author.

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14 15 464 **FIGURE LEGENDS**

16
17 465 **Fig. 1.** PRISMA flow diagram. Our search strategy resulted 2017 papers. After excluding articles
18 466 published before 2010 and duplicates, 1373 papers were screened based on title and abstract. In 79 cases
19 467 the title clearly indicated non-eligible study design such as review or systematic review. Twenty-four
20 468 title pointed out that the paper is a case report of a sole case. In 124 cases, the title clearly indicated non-
21 469 eligible study population such as pregnant or pediatric. Five hundred sixteen titles revealed that the study
22 470 is not closely related to our research topic. In 73 cases the title clearly indicated an animal experiment.
23 471 Twenty-one records were excluded based on abstract due to a non-eligible study design such as review
24 472 or systematic review. The abstract indicated a non-eligible study population such as pregnant or pediatric
25 473 in 94 cases. In 110 cases, the abstract indicated that the study is not closely related to our research topic.
26 474 Thirty-nine animal experiments were filtered out based on abstract. Eight studies did not have an English
27 475 language abstract. In 112 cases, the abstract revealed that the study includes data that is more than 10
28 476 years old. Forty-one case reports with a patient number <10 were excluded based on abstract.
29 477 After excluding a total of 816 papers based on title and 425 based on abstract, 132 full-texts were
30 478 assessed for eligibility. Reasons for non-inclusion of full-text articles are detailed above in the Figure.
31 479 Ultimately, 19 studies were enrolled to our meta-regression
32 480 *heart rate (HR) was not provided in mean or median, only the number of patients in ranges of HR (e.g.,
33 481 100-120 bpm) was given
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45 482 **Fig. 2.** Risk of bias assessment.

46 483 **a:** The figure shows the risk of bias in the 6 main domains of the Quality In Prognostic Studies (QUIPS)
47 484 assessment, in each paper. ‘Study attrition’ was not suitable for the retrospective studies. In 5 prospective
48 485 studies, there was a moderate risk for study attrition bias. All studies were judged to carry a low risk of
49 486 bias in ‘Study participation’ and ‘Prognostic factor measurement’ domains. ‘Study confounding’ was
50 487 the worst rated domain: a moderate risk appeared in almost half of the records, in which the role of
51 488 important confounders was not reported thoroughly. Based on the assessment of the 6 main domains,
52 489 the overall risk of bias was determined for each study

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56 490 **b:** The summarized risk of bias is illustrated in percentages in the main domains
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3 491 **Fig. 3.** Relation between heart rate (HR) and mortality of bleeding trauma patients. Linear association
4 492 between HR and mortality could not be identified.

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6 493 HR=heart rate
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8 494 **Fig. 4.** Subgroup analysis of studies on trauma patients who received blood products. Linear association
9 495 between early heart rate (HR) and mortality rate of patients could not be identified.

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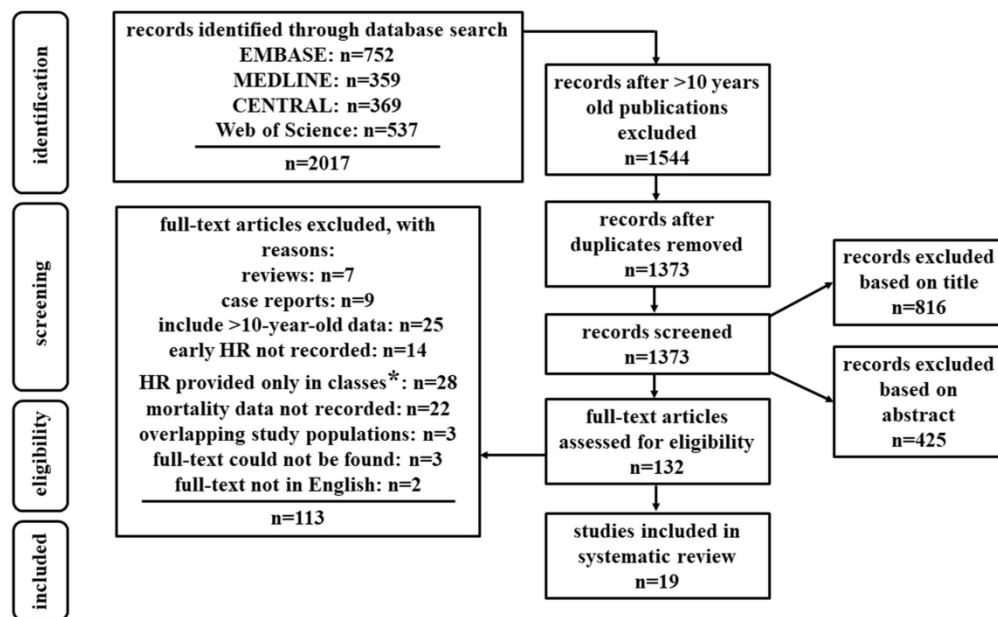


Fig. 1. PRISMA flow diagram. Our search strategy resulted 2017 papers. After excluding articles published before 2010 and duplicates, 1373 papers were screened based on title and abstract. In 79 cases the title clearly indicated non-eligible study design such as review or systematic review. Twenty-four 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

170x105mm (300 x 300 DPI)

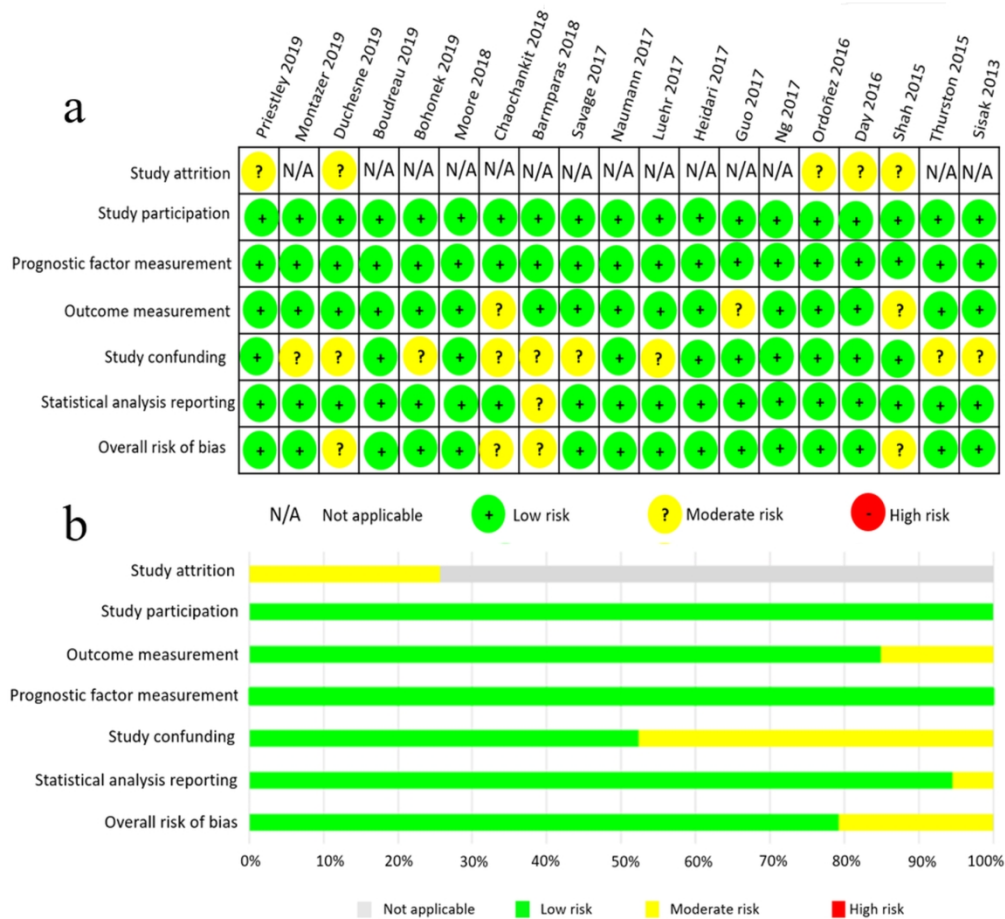


Fig. 2. Risk of bias assessment.

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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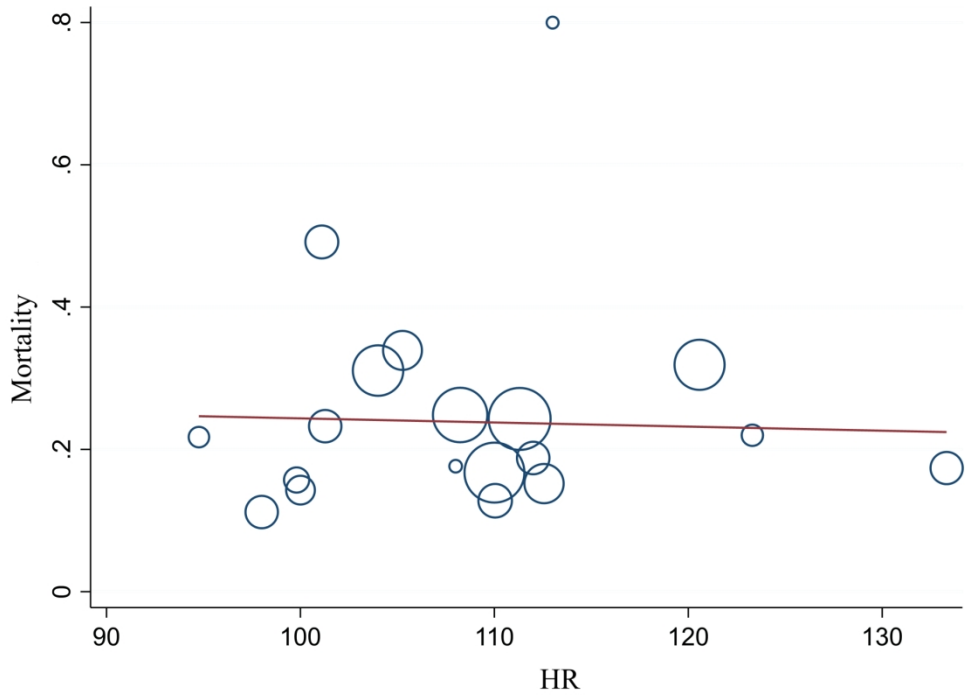


Fig. 3. Relation between heart rate (HR) and mortality of bleeding trauma patients. Linear association between HR and mortality could not be identified.
HR=heart rate

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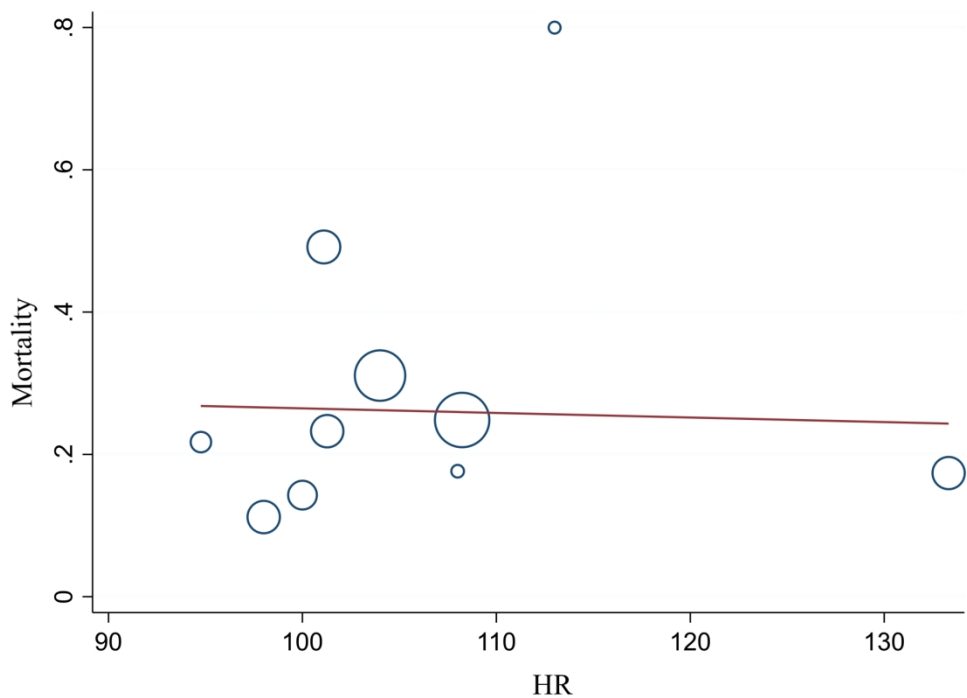


Fig. 4. Subgroup analysis of studies on trauma patients who received blood products. Linear association between early heart rate (HR) and mortality rate of patients could not be identified.
HR=heart rate

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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.	-



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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



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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/>

For peer review only

Study: first author, year of publication	Data origin: institute, country	Data collection: type, date	Indicators of hemorrhage	Patient number (n)	Age (y) mean \pm SD or median [IQR]	Male gender n (%)	HR mean \pm 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 \pm 59.0 (AD)	10 (21.7%)	mortality, blood products administered, adverse effects following platelet transfusion, laboratory parameters such as aPTT
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 \pm 43.0 (PH)	27 (23.3%)	mortality, thrombotic 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 \leq 90 mmHg and/or HR \geq 120 bpm and/or BD \geq 5 mEq	279	40 [28–54]	172 (62.0%)	120.6 \pm 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 \pm 20	333 (83.3%)	110.0 \pm 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 \pm 24.0 (PH)	88 (31.1%)	mortality, days on ventilator, length of hospitalization

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

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, thromboe mbolic events, hospital- free and ICU-free days (calculate d as 30 minus the number of days in hospital and ICU respective ly)
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 transfusio ns
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, complicat ions

Thurston 2015	Trauma Center, Groote Schoor 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