



Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Physiologic Predictors of Severe Injury: A Systematic Review

Draft review available for public comment from August 16, 2017 to September 12, 2017.

Research Review Citation: Totten AM, Cheney TP, O'Neil ME, Newgard CD, Daya M, Fu R, Wasson N, Hart EL, Chou R. Physiologic Predictors of Severe Injury: Systematic Review. Comparative Effectiveness Review No. 205. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 18-EHC008-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2018. Posted final reports are located on the [Effective Health Care Program search page](https://doi.org/10.23970/AHRQEPCCER205). DOI: <https://doi.org/10.23970/AHRQEPCCER205>.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General Comments	My only general concern is whether the lactate data is being appropriately represented. When all the data is pooled the conclusion is that it performs similarly to SBP and SI but as indicated in Table A, Sensitivity was much higher in the studies that looked at Lactate > 2 or 2.5. The study in table A with the lowest sensitivity is listed as reference 47. I pulled that reference which looks at the combination of lactate with the ACS triage decision rules to predict trauma center need. It does not directly assess the relationship with mortality and so I am not sure how the sensitivity of 23% was derived for this study for Table A and this study was also included in the Combined OH and ED data in the next column. I worry that misinterpretation of this study could be impacting the conclusions and perhaps lactate is superior to traditional vital signs.	We separated the lactate data into out-of-hospital and ED as well as by thresholds for the pooled values so that the differences are clearer. Also, for the pooled results we clarified that outcome is a composite. We calculated the sensitivity from the counts provided in the publication of the number of cases with lactate at each of three levels and the number patients defined as with and without trauma center need in the article. We have also clarified that more studies of out-of-hospital lactate are needed and that one study is insufficient.
TEP Reviewer #2	General Comments	Thank you for the opportunity to review this paper. This is a herculean effort to characterize the literature on current tools for predicting the need for a trauma center. It is well written, comprehensive and meticulous in its identification of its limitations both in the scope of the available literature and the methodology necessary to summarize the data.	Thank you.
TEP Reviewer #3	General Comments	Document and accompanying work is very good and easy to interpret even for a non epidemiologist .The process and content as well as the recommendation's are reasonable and would improve Trauma care as well as prevent unnecessary hospital by-pass .	Thank you.
TEP Reviewer #4	General Comments	typo on page 17 line 24 adequate/adequately	Corrected.
TEP Reviewer #5	General Comments	The overall report is well done.	Thank you.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General Comments	<p>The report is absolutely on target. The target population is the prehospital care provider. The hidden target is the medical providers in all of the hospital EDs that are not trauma centers, which receive trauma patients because EMS cannot cross county lines or because there is no destination determination for trauma patients in the service area. These sites also need some type of triage scheme to determine if a patient needs to go to a higher level of care.</p> <p>Trauma systems are not operational in every state and there remains a potpourri of EMS services across the US. I don't know if we really understand how many services actually use the CDC triage diagram. I believe many providers use their clinical intuition and don't refer to the diagram when they are in the field, even if use of the triage tool is in protocol. I have reviewed papers that say as much. The more complicated you make it, the less likely they are to do it.</p> <p>The key questions get at the initial assessment: ABCD (airway and breathing in Key Questions 2 and 3); circulation in Key Questions 1 and 3; disability in Question 3) and Question 3 also looks at specific combinations/scales/scoring tools.</p>	Thank you.
Peer Reviewer #2	General Comments	Clinically meaningful. Target population and audience identified. Key questions appropriate.	Thank you.
Peer Reviewer #3	General Comments	<p>This is a very thorough and well written evaluation of the existing literature. It is limited primarily by the quality of the existing evidence. My general concern is that there is very little in the results section to support the conclusions made about extremes of age. It is difficult to evaluate exactly how many articles included or excluded children and the elderly in most of the section (particularly for the pooled measures). It seems there was very little. Therefore I am not sure that the statement "Measures used for adults are useful for children and older people....", is well supported. This also makes this document less clinically meaningful as there is no evidence presented or discussion of which of the measures would be applicable at extremes of age and or how they would need to be modified.</p>	We have revised the section on age (pediatrics and older people) to be clearer and to provide more detail.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Introduction	excellent	Thank you.
TEP Reviewer #2	Introduction	Pg 6 Abstract conclusion- How was serious injury defined here (can you be more specific within the limitations of the abstract?)	We have expanded the explanation that we used several indicators for serious injury in this review.
TEP Reviewer #3	Introduction	SEE ABOVE	Thank you.
TEP Reviewer #4	Introduction	Pg 27, line 19 I would include the risk of injury due to rapid transport. Helicopter transport results in both increased costs and increased risk, while transport by ground using lights and sirens increases injury risk.	We have added the fact that transportation involves risks to the text.
TEP Reviewer #5	Introduction	Very well done.	Thank you.
Peer Reviewer #1	Introduction	<p>I searched the document for the 2006 IOM report on the Future of Emergency Care. I really believe this was the impetus for much of the increase in prehospital and emergency medicine research subsequent to the report, as well as increases in funding research in these arenas. The report pointed out the significant gaps in evidence based knowledge, particularly in the prehospital environment.</p> <p>An increase in relevant publications in the last decade is mentioned in the manuscript. I think you would be remiss not to mention the IOM report as part of the reason for this.</p> <p>The Trauma chain of survival is mentioned. Figure 1 comes from the British Journal of Surgery. I am used to framing this as the trauma "Continuum of Care" that begins with education and prevention and continues with the provision of scene care, ED, acute care, rehabilitation and reentry into the community.</p>	Thank you. We have added the IOM reference to the introduction. We agree that the concepts of the chain of survival and continuum of care overlap. We chose to use the former because it is more focused around when triage measures are used and the implications of triage decisions.
Peer Reviewer #2	Introduction	Pg 2, Para 1. Change from "...the transport decision..." to "...transport destination decision..."	edited, p. 2



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Introduction	<p>ES page 7 I do not understand the following sentence is general meant to be generalizable? The consistent message across studies is that adult triage approaches are general but that thresholds may need to be different</p> <p>ES page 9 should this table be in the results section?</p> <p>P2 In 36 details vs detailed?</p>	edited, p. 2 (detailed)
TEP Reviewer #1	Methods	Methods appear appropriate	Thank you.
TEP Reviewer #2	Methods	<p>The studies included were justifiable and the strategies for inclusion were explained. The outcome measures varied widely between studies but this is detailed in the methods and as a limitation</p> <p>Pg 35 In 38 Difficult to interpret this pooled risk estimates for combined endpoints. These metrics will favor specificity at these cut points, sensitivity analyses and Youden indices have been done on BP and Lactate. The differences in AUROC will be small but if the intent is to use these as prehospital screening tools then we may be focusing on the wrong thing. If looking for incremental benefits are Net Reclassification Indices available?</p>	We agree that there are several different approaches to assessing measures and they serve different purposes. We focused on sensitivity/specificity and AUROCs because we were able to pool the data for several measures, adding estimates across several studies as a way to summarize this evidence. We agree that other approaches would be valuable and could be applied in future work.
TEP Reviewer #3	Methods	SEE ABOVE	Thank you.
TEP Reviewer #4	Methods	I strongly encourage you to consider including under and over-triage rates. It is much more common to talk about field triage in these terms rather than sensitivity and specificity.	We considered several different approaches and discussed them and decided to focus on measures that would allow comparisons across studies and populations. We agree that other approaches would be useful in future work.
TEP Reviewer #5	Methods	Well done.	Thank you.
Peer Reviewer #1	Methods	All yes	Thank you.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	<p>Inclusion/exclusion criteria: "Abstracts identified 650 articles that appeared to meet the inclusion criteria. The full text of these articles was reviewed and we included 100 articles." Including only a 100 seems like too much of a round number/convenience/practical number rather than a number that was reached through rigorous exclusion process.</p> <p>Re: inclusion criteria. Disaster triage criteria should be excluded. Purpose of disaster triage criteria is to prioritize who needs care/who doesn't need care along with those who are "expectant" (expected to die) in order to do greatest good for greatest number of patients. Very different from triage of daily occurring injuries where focus is on a single patient.</p>	<p>We have update the search and the number of articles included is now 138.</p> <p>We included some studies of disaster triage criteria because they use similar measures and several were tested on data from trauma registries as data from disasters are limited. While their intended use may be different, the data are relevant.</p>
Peer Reviewer #3	Methods	<p>In general the answer to all of above is yes given the status of the existing literature However although age extremes are addressed in the sub questions the methodology lumps together studies with populations of different ages and therefore does not answer the specific questions in the sub questions Ie What age ranges and values for different age ranges are supported by the evidence</p>	<p>We have revised the section on age to provide more information and included the studies that focus on pediatrics or older people in this section.</p>
TEP Reviewer #1	Results	no concerns	Thank you.



<p>TEP Reviewer #2</p>	<p>Results</p>	<p>Pg 12 Results: I would have to understand the methodology better here. Changing the combined outcome will alter the performance characteristics drastically.</p> <p>There will also be great variability with respect to subgroups of patients (penetrating, blunt, TBI, age, mode, distance), and when and how the data was sampled.</p> <p>Pg 14 Table A All of the in-hospital studies are likely to be biased based on the following, survival bias, selection bias (those in extremis might be taken to the closest hospital, those not thought to be severely injured may not be taken to a trauma center), and a treatment bias those who have meet inclusion criteria for transport to a trauma center will be treated with fluids and hemorrhage control measures which may improve physiologic parameters by the time the patient arrives at the hospital. There may also be temporal trends among VS even in patients who have severe injuries to regress to the mean, or clear lactate assuming they are in compensated shock.</p> <p>Pg 16 Para 1 These metrics will favor specificity at these cut points, sensitivity analyses and Youden indices have been done on BP and Lactate. The differences in AUROC will be small but if the intent is to use these as prehospital screening tools then we may be focusing on the wrong thing.</p> <p>Pg 44 In 44 Although several studies have demonstrated the limitations of this as a screening tool. Including demonstrating that SBP<110 are associated with increased incidence of death, and sub populations including patients at the extremes of age and patients with TBI are more likely to suffer severe and ongoing injury at SBP >90. (This is partially addressed in subsequent paragraphs)</p> <p>Pg 46 Table 4 While there is some overlap, the outcomes of these studies are all very different. Hypotension (SBP<90) will be more sensitive for the composite outcomes like RC (includes death, operative intervention and blood transfusion) as compared to studies which only address mortality or LSI.</p>	<p>We agree that using different indicators of serious injury effects the performance and we included subtotals by type as well as the overall estimated in the plots so people could see this.</p> <p>We agree that the patients vary and this is reflected in the heterogeneity estimates. We included this in the discussion.</p> <p>We separated ED and out-of-hospital estimates because we agree there are differences and we wanted to be able to present whether these differences effect the performance of the measures.</p> <p>There are several different approaches to assessing measures and they serve different purposes. We focused on sensitivity/specificity and AUROCs because we were able to pool the data for several measures and adding estimates across several studies provides an additional type of information to be considered.</p> <p>We agree and have included the studies with different thresholds to illustrate this point.</p>
<p>TEP Reviewer #3</p>	<p>Results</p>	<p>SEE ABOVE</p>	<p>Thank you.</p>



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Results	<p>I question using the multi-casualty papers for this analysis. The Garner and Gebhart papers in particular, while they did look at trauma patients the intention was to look at mass casualty triage schemes which use physiologic parameters but have a very different goal. I would consider excluding ref 37 in executive summary and 129 in main references.</p> <p>I would consider reporting under and over triage rates as defined in the MMWR on field triage. That is the more common way to discuss triage accuracy then sensitivity and specificity and there was ACS guidance on goal values although it is no longer in their optimal care book.</p>	<p>We have added a label indicating that measures are designed for mass casualty incidents, but we kept this information because in some studies these were evaluated on trauma registry data, so they provided information about measure performance with trauma patients.</p> <p>We considered under and over triage as potential outcomes but decided to focus on sensitivity and specificity and AUROC as more data were available and these could be combined across populations/studies.</p>
TEP Reviewer #5	Results	<p>Regarding the presentation of the resulting positive and negative likelihood ratios....the authors should offer an explanatory sentence that would frame their use. A sentence would be helpful on page 75 line 31. The authors do a great job of illustrating the interpretation of sensitivity and specificity in many locations (e.g., Page 45, Line 6). No such offering is made for likelihood ratios.</p>	<p>Based on suggestions from others, we have limited the use of the likelihood ratios to examples in the discussion and we have revised the text.</p>
Peer Reviewer #1	Results	<p>I am used to seeing evidence based reports that look like this. I predict that many readers will look at only the Executive Summary. For those who wish to dig deeper, there are many relevant figures and tables. Personally, I thought the sensitivity and specificity data most fascinating. The review is extensive and thorough. I did not appreciate any studies that were overlooked.</p>	<p>Thank you.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	Per above, the disaster triage studies should be excluded.	We have added a label indicating measures are designed for mass causality incidences, but we kept this information because in some studies these were evaluated on trauma registry data, so they provided information about measure performance with trauma patients.
Peer Reviewer #3	Results	I would like to see the pediatric and elder population studies analyzed separately This is particularly an issue for the pooled measure figures (4 -11) The reader does not have any information on the population evaluated in each study For the non- pooled measures, the tables do indicate in some cases if a study was "pediatric" or "elderly" It may be better presented with a separate column for the population studied in the table	We have substantially revised the text regarding children and older adults. The studies that included analysis of age groups are included in that section of results. In the overall results the label indicates the population was limited to that age group, while the other studies included all ages or did not specific.
Peer Reviewer #3	Results	Base deficit : Its unclear why this was included as it is not a test available to most prehospital providers when making triage decisions	This statement has been removed and the text edited.
Peer Reviewer #3	Results	Pediatric and older individual section To better address the sub questions it may be helpful to have comparison between performance of the measures in the different age ranges	We expanded the discussion to report more key results.
Peer Reviewer #3	Results	This statement is not well supported by the results "Across all studies there is general agreement that adult studies are relevant to children....." "It also probably does not belong in the results section	We have revised the introduction to lactate to clarify this and we have added these references.
TEP Reviewer #1	Discussion/ Conclusion	in light of my comment under general concern may want to add a paragraph specifically addressing lactate	We expanded the discussion to report more key results.
TEP Reviewer #2	Discussion/ Conclusion	Pg 49 Para 1 "Lactate is produced from anaerobic metabolism..." this is only partly true, and the elevations in lactate following traumatic injury are not solely the result of anaerobic metabolism and decreased hepatic clearance but also by increased production from exogenous catecholamine and aerobic glycolysis. This is all well described in (Kraut and Madias NEJM 2014)	We have revised the introduction to lactate to clarify this and we have added these references.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/Conclusion	Pg 49 Ln 9 the period after 4mmol/L(.) is intentional?	The period has been removed
TEP Reviewer #2	Discussion/Conclusion	Pg 49 Ln 40 Interventions and time from injury particularly in patient who are able to clear the lactate, the deltas may be of even greater value in terms of evaluating patients who have had adequate field hemorrhage control or volume resuscitation.	The use of lactate clearance as a measure was added to the text of this section as well as reference to the included study that evaluated its ability to predict mortality.
TEP Reviewer #2	Discussion/Conclusion	Pg 50 Figure 7 Guyette 2015 is an enriched population as all the patients had a SBP <100 which influenced the performance characteristics.	We have revised this section and added text describing more about the studies of out-of-hospital lactate.
TEP Reviewer #2	Discussion/Conclusion	Pg 51 Figure 8 Shah 2013 was air medical, again a higher specificity likely due to a combination of differences in metabolism in children and the preselected population	We have revised this section and added text describing more about the studies of out-of-hospital lactate.
TEP Reviewer #2	Discussion/Conclusion	Guyette 2015 was multi center ground	We now indicate in Table 2 that Guyette, 2015 was a multicenter ground study. Given that it was part of the ROC Data Coordinating Center the "Type of Data Source" has also been corrected.
TEP Reviewer #2	Discussion/Conclusion	Pg 63 Ln 22 The study referenced in 49 concludes that HRV does not add additional value to vital signs	We have included a discussion of this study in the text, including a summary of these findings.
TEP Reviewer #2	Discussion/Conclusion	Pg 68 Ln 8 The RR papers were judged to have a low risk of bias but these metrics (particularly when collected in the field) are rarely accurately recorded.	The risk of bias assessment includes several criteria and studies do not have to meet all criteria to be considered low risk of bias, though we agree that the reliability of the measurement is important and in this case could be improved.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/Conclusion	Pg 71 Ln 18 Guyette J of Trauma 2012 evaluated prehospital StO2 in trauma patients AUROC 0.71 but used the slope of the deoxygenation curve instead of the raw value which was highly dependent on the individual patient and varied significantly with environmental conditions in the helicopter.	We have added this study to this table.
TEP Reviewer #2	Discussion/Conclusion	Pg 92 Ln2 Was Shah Pediatric Emergency Care 2013 Pediatric Lactate evaluated in this group?	We have incorporated this study and report results in the table.
TEP Reviewer #2	Discussion/Conclusion	Pg 98 Ln24 terrible for screening, current tools are not able to rule out patients (Authors address this in the implications and	We have revised the discussion and conclusions to clarify the interpretation of sensitivity and specificity and performance of measures included in this review.
TEP Reviewer #3	Discussion/Conclusion	SEE ABOVE	Thank you.
TEP Reviewer #4	Discussion/Conclusion	I think it is important to explicitly state that there are risks to over triage as well as under triage. You want patients to get to the care they need but you also don't want to talk people out of their communities who don't need it. Doing so increases costs and risks to personal safety. This point is missing from the executive summary and not very strong in main paper.	We have added the idea that there are risks to over and under triage to the text.
TEP Reviewer #5	Discussion/Conclusion	<p>Even though the overall study findings seem to suggest that "combined measures" outperform individual measures....the authors do not discuss this? I could be overemphasizing this point....but I was surprised to see that the only conclusion mentioning the value of combined measures was Page 78, Line 55.</p> <p>The Conclusions and Future Research Needs seem to emphasize the limitation (and need) for studies that control for instrumentation and timing, yet, in other locations of the manuscript, the authors acknowledge the extreme unpredictability of the out of hospital setting. Again, I may be overemphasizing this point, but asking for studies with control for timing and instrumentation do not seem to be the most pressing future directions (i.e., first item listed under Future research Needs).</p>	We have expanded the discussion of combined measures. We have also revised the discussion of future research needs. In this section we have outlined what we found to be missing in the literature but we are not in a position to prioritize future research needs. We hope identifying gaps will help others with that task.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/Conclusion	<p>All yes.</p> <p>I am particularly gratified that the report gives due diligence to two relatively overlooked populations: children and the elderly. Children are often overtriaged, as was mentioned. This is not only because of lack of attention to children in the literature or inclusion in clinical trials. It is because everyone is afraid of them except for those of us in regional centers.</p> <p>The elderly (boomers) are frequent trauma victims and some attention should be paid to patient and family centered care and what this population actually wants and needs. This is a conversation with multiple levels of complexity and should consider advanced directives (if available), and a thoughtful approach to who actually needs to go to the trauma center when many want to exercise the personal choice of staying "at or near home", even if the best trauma care won't be provided. These two extremes of age need some intentional research to better define need for transfer to trauma centers.</p>	Thank you.
Peer Reviewer #2	Discussion/Conclusion	Much more discussion is needed re: the issues of the practical application of the findings. Barriers and solutions to overcome them re: use of shock index and lactate in the field need more in depth discussion. Given financial constraints (and financial model) for EMS systems, cost benefit re: use of point of care lab testing for lactate/other potential labs in field should be discussed.	We have clarified that more research and testing are needed to assess feasibility of use of measures in the field. Assessing technology and cost benefit analyses are outside the scope of this report.
Peer Reviewer #3	Discussion/Conclusion	Limitations are clearly stated for the most part However I think that there should be a clearer statement regarding the ability of the evidence to address the suggestions regarding age extremes. Future research section is clear and well written	Thank you, we have revised the section on the performance of measures in pediatrics and older people to provide more detail and be clearer.
TEP Reviewer #1	Clarity and Usability	excellent	Thank you.
TEP Reviewer #2	Clarity and Usability	The review is clear, usability is limited only by source documents	Thank you, we have noted in the discussion the need for future research to provide better research



Comment ator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Clarity and Usability	SEE ABOVE	Thank you.
TEP Reviewer #4	Clarity and Usability	fine	Thank you.
TEP Reviewer #5	Clarity and Usability	There is an inconsistent use of "e.g.," This method of offering an example is used often in the latter sections of the document...but not in early sections. Spelling: Page 78, Line 42 Page 77, Line 46 Page V, Line 23	Thank you, we have made the suggested copy edits and corrections.
Peer Reviewer #1	Clarity and Usability	Yes to all. The report is intentionally long by design. You could consider publishing the Executive Summary separately as well as the entire report. I think many will be more inclined to download and read the Executive Summary and less likely to download the lengthier document.	The Executive Summary and full report will be published separately.
Peer Reviewer #2	Clarity and Usability	Structured as a federal report, likely in already approved format. Problem is that doesn't translate into it being user friendly for EMS audience. For this to be used to effect change in EMS, will need a companion document very user friendly for that audience, and an associated communications campaign.	The Systematic Review will be used to assist in the revision of EMS guidelines. We have revised the summary to be clearer and we will consider other formats for publication.
Peer Reviewer #3	Clarity and Usability	In general this report is well structured and organized However, I am concerned that the wording of the conclusions about subpopulation may be misleading and are not necessarily supported by the evidence review results	We have revised the conclusions and discussion so the evidence is summarized, and options, possibilities, and opinions are in the discussion.
TEP Reviewer #1	Quality of the Report	Superior	Thank you for reviewing our report.
TEP Reviewer #2	Quality of the Report	Superior	Thank you for reviewing our report.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Quality of the Report	Good	Thank you for reviewing our report.
TEP Reviewer #4	Quality of the Report	Good	Thank you for reviewing our report.
TEP Reviewer #5	Quality of the Report	Good	Thank you for reviewing our report.
Peer Reviewer #1	Quality of the Report	Superior	Thank you for reviewing our report.
Peer Reviewer #2	Quality of the Report	Good	Thank you for reviewing our report.
Peer Reviewer #3	Quality of the Report	Good	Thank you for reviewing our report.