PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic factors for recovery of health status after injury: a prospective multicentre cohort study
AUTHORS	de Munter, Leonie; Polinder, Suzanne; Havermans, Roos; Steyerberg, Ewout; de Jongh, M

VERSION 1 – REVIEW

REVIEWER	Alexis Lion Fédération Luxembourgeoise des Associations de Sport de Santé, Luxembourg
REVIEW RETURNED	05-May-2020

GENERAL COMMENTS	General comments The study aimed to evaluate and characterize the recovery of the health status after a trauma. Patients who were admitted to several hospitals in the Noord-Brabant region were followed for two years. They regularly answered questionnaires (EQ-5L) to monitor their health status. Baseline characteristics were collected from a registry and from a posteriori questionnaire. The authors identified the factors which are linked to the recovery of the health status. The introduction is interesting, but the authors should explain the prognostic factors which are already identified and the importance to conduct the present study. The methods section is difficult to follow. It could be clearer with more details. It must be more rigorous (e.g. median, mean, VAS, etc.). The results section is not precise enough. Results were partially reported, and the tables are difficult to understand. All significant results could be highlighted in the tables/figures. The authors could improve the results by checking the health recovery according to the prognostic factors. The prognostic factors should be selected based on the previous results section. Obviously, the location of the injury is very interesting. However, the recovery patters according to the gender, the age, length of stay, comorbidities and pre-injury health status would help the improve the treatment: specific physiotherapy or physical activity prescription for those who will have mobility issues, ergotherapy and home care for those who will have usual activities and self-care issues, psychotherapy for those who will have anxiety/depression, cognitive therapy for those who will have cognition issues, specific treatment (which could include physical activity) for those who will have pain. It could be helpful to know when to start these treatments. The authors have a great

	opportunity to help to improve the treatment after a trauma. It could contribute to improve the personalized treatment. This should be the aim of this study: realize an algorithm of with the characteristics of the patients to propose a tailored treatment. The current discussion is vague. The data should be compared to the data published in the literature. What is a good health status? What were the prognostic factors already known? The discussion should then discuss the treatment possibilities according to the results. The authors should not forget that the most important in clinical research is the patients. What conclusion could be drawn based on the results to lead an optimal and rapid recovery after a trauma. Major comments Title In title, please indicate that the recovery concerns the health status. In addition, based on the results, I suggest to delete the word “poor”. The title could be “Prognostic factors for recovery of health status after trauma: a prospective multicenter cohort study. Should be “injury” used instead of “trauma”? Abstract Page 1, line 28. Please indicate throughout the paper that the recovery concerns the health (status). Page 1, line 36. Is it after injury, trauma, or hospital admission? Page 1, line 37. What is low health status? Page 1, line 40. How were evaluated pre-injury health status and frailty? It should be mentioned in the main outcome measures. Length of stay? Where (at hospital)? Page 1, lines 41 to 43. To be modified if statistics are added (please see my general comments). Introduction Page 3, line 68. Please add also lifelong treatment or lifestyle changes (e.g. physical activity, etc.). Page 3, line 69. “Poor outcome”. Please precise that it is health outcome. Page 3, lines 69 to 73. What did observe these studies? What were the conclusions? What were the identified prognostic factors? Page 3, lines 73 to 76. Why is it important? Page 3, line 79. Why two years after injury? Why not 3 or 5 or 10? Methods Page 4, lines 83 to 101. The BIOS-study should be more explained. What are the variables collected in this study and

	when? What are the variables of the BIOS-study that are used in the present study? Do the authors add other variables (e.g. Trauma data) to the data collected in the BIOS-study? It should be clearly stated. Did the authors use the costs outcome? How was it measured? It is not clear when the participants had to fill which questionnaire. The questionnaire was answered at one week and one month after trauma and the short version of the questionnaire was answered at three, six, 12 and 24 months. Is it correct? Please explain more clearly which the questions of the questionnaire were answered at one week and one month after trauma (i.e. EQ-5D, EQ-VAS, cognition dimension?). A chronological figure presenting the collected data will help the readers. Page 4, line 92. Are the injuries induced by osteoporosis excluded? Page 4, line 96. Please clarify if it is after injury, after trauma, or after hospital admission, or after hospital discharge. Page 4, lines 99 to 101. Please clarify if it was legal/ethical to collect data and use data from non-participating patients. Page 5, line 108. Please clarify. Please use “EQ-5D utility score” consistently in the article. Page 5, line 119. Please confirm that the EQ-VAS was not in the short questionnaire answered at 3, 6, 12 and 24 months. If it is correct, I do not understand the results section. Please check this point. Page 6, line 131. Why did the authors measure frailty only in older adults? There is a high risk of bias in the analysis. Page 6, line 132. There is a recall bias for the data collection of the pre-injury health status. It should be acknowledged at least in the limitations of the article in the discussion. The bias could be even more important after an injury. Obviously, health status was better before an injury. Page 6, line 134. Please explain when and how the clinical variables were collected (Trauma Registry). Page 6, line 142. Please explain if the used injury classification is implemented in the Trauma Registry. If not, why do the authors used this classification instead of the classification of the Trauma Registry? Page 6, line 145. What about fibula fractures? What about knee injuries such as ACL injuries? What about sprain injuries or skin burn? In the table 4, injuries (or trauma) are further regrouped. Please use only one classification consistently in the manuscript. Page 6, line 153. It should be explained before what and why data of non-participants were collected (and if it is ethical). Page 6, line 154. How was tested the normality of the data?

	Page 7, line 158. Missing data were imputed. Please explain if there is a risk. Original data and data after imputation could be presented and compared in an additional table in supplementary materials. Page 7, line 165. Again, please check if EQ-VAS was measured at each time point. Page 7, line 170. Why were all potential prognostic factors entered in the multivariable models? Why not only those which were significant in the univariate analyses? How did the authors manage the type I errors due to the elevated numbers of statistical analyses? What was the p-level for significance for each analysis? What was the criteria of significance of the coefficient correlations? Results Page 9, line 185. It is very helpful to compare the participants with the patients who did not accept to take part of the study. However, the baseline characteristics presented in this section and in the table 1 could mislead the readers. How many patients answered all the questionnaires? Who are the drop-out participants? Why most of the exclusion was observed within the first week? Why are there approximately 1000 patients more who participated at 1 month than at 1 week? Page 9, lines 191 to 195. Please check these lines according to the results presented in the table 1. For the ASA classification, I am wondering why the authors did not use dummy variables to test the differences between each category. Indeed, the significant p-value for the ASA classification means that there is a heterogeneity of the categories. We cannot conclude that there are more class 2 in the responders than in the non-responders. Post-hoc analyses should be performed (using dummy variables). This is the same for the functional capacity index. Why did the authors not perform statistical analyses for the injury classification and the mechanism of injury? In the table 1, please check the values for the length of stay and the injury severity score (same medians and IQR in both groups with significant p-values). Why are the pre-injury health status and the frailty not presented in the table 1? Please try to be more precise in the text (e.g. adding values to “more often”). Page 9, line 197. Why are the pre-injury (or pre-trauma) health status not presented here (and in the corresponding figures)? Page 10, line 211. In the supplementary material, and the tables 2 to 4, please highlight the results which are considered as significant/non-significant (using bold, italic or NS, etc.) and indicate the threshold of significance. It will help the readers. Page 10, line 215. What is higher age? In the table 2, it seems that the category >75 is not associated with self-care. What are the numbers of patients in each age category? What is the rational of these age categories? Page 10, line 218. Female sex is not a significant prognostic factor for self-care (and mobility).

	Page 10, lines 219 to 224. What are “lower extremity injury”, “upper extremity injury”, “spine injury” and “traumatic brain injury”? These groups of injuries were not defined in the methods. Do they author analyze these groups? If yes, please modify the methods section and the table 2. For example, hip fracture (if considered as lower extremity injury) was associated only with EQ-5D mobility dimension. Another example, radius, ulna, or hand fracture were associated with mobility and self-care only. Please check and rewrite this paragraph (lines 212 to 224). Page 10, lines 226 to 232. “Health status over time” paragraph and the first part of the “Recovery patterns” paragraph are similar. I suggest to regroup these paragraphs. The significant improvements presented in the table 3 could be indicated in the figure 2 (consequently, the table 3 could be deleted). The paragraph “recovery patterns” could be renamed “recovery patterns according to the prognostic factors”. Page 10, line 231. Pain/discomfort was not significant 12 to 24 months after trauma. It could be presented in this section that mobility improved until six months, self-care and pain discomfort until 12 months, and usual activities until 24 months. Anxiety improved from one to six months. Page 11, lines 233 to 242. Spine injury showed improved mobility and self-care up to six months. Lower extremity injury did not show less mobility problems in the first month. Spine injury did not show fewer usual activities problems in the first month. According to the table 4, pain/discomfort recovery occurred until 12 months (except for spine between three and six months). Analyses (and figures) of recovery patters of the health status and its dimensions according to selected prognostic factors would be interesting (please see my general comments). Discussion Page 12, line 246. “Health status was especially low” compared to what? What is a low health status? Please add references. The characteristics of the patients and the non-participants should be discussed. Please discuss the injury severity score (or add in the methods section the range of the Injury severity score). The results of the EQ-5D utility scores, the EQ-VAS and the EQ-5D dimensions should be discussed considering the current published literature. It would be interesting to know if the values presenting in the current study are similar to those published in other studies. Or, the “normal” range of these scores could be presented in the methods sections. Minor comments Page 1, line 33. Please do not start the sentence with “4883”. I suggest to change thedot at the end of the previous sentence by colons (:). Page 1, lines 34 to 36. Please rephrase the sentence. It is difficult to follow as it is (too many “and”). Page 1, line 38. Please add a space between the results and the SD.

	Page 2, line 50. Health recovery. Page 3, line 60. How many millions? Please add a reference. Page 3, line 60. Do the authors previse that survivorship concern severe trauma? Page 3, line 62. HS is not consistently used thereafter. Page 4, line 86. Please rephrase “after trauma in injured patients”. Maybe delete “injured patients”. Page 4, line 92. Please define briefly “pathological fractures” or give an example. Page 4, line 94. Is “participating” the correct wording? Page 4, lines 95 and 98. Please change to 12 months. Page 5, line 116. HS? Please use this abbreviation consistently in the manuscript (or do not us it at all). Page 6, line 147. Please add a space after groups. Page 6, line 148-149. Please add space after head and abdomen. Page 7, line 155. Mean and SD were also presented. Page 7, line 156. What is ISS (injury severity score)? Please be careful with all the abbreviations throughout the paper. Page 7, line 172. What is LOS (length of stay)? Please be careful with all the abbreviations throughout the paper. Page 9, line 191, please add the number of non-responders (or non-participants; please choose only determination) Page 9, line 192, what is level 1 trauma center? Please define it. Page 9, line 198. Please see add mean and standard deviation (SD) in the methods. Why mean and SD were used instead of median and IQR? Are the data for health status distributed normally? Page 9, lines 203-205. Please remind the readers that the dimensions were calculated from the EQ-5D questionnaire. Page 9, line 206. Please be consistent throughout the article with the use of the words “injury” and “trauma”. Page 10, line 211. The first sentence of the paragraph is quite vague. Page 10, line 214. Please use EQ-5D utility score and EQ-VAS instead of health status in the results section. Please use a precise wording. Page 10 line 227. “Health status measured with the EQ-5D utility score”, this is the good way to present the results and it should be used throughout the paper.

	Page 10, line 227. “Most recovery occurred … ” is rather imprecise and can mislead the readers. Page 12, line 245. “We found that patients … two years after injury”; this a vague sentence. Page 12, line 249. “dimensions” of what? Page 12, line 250. “less problems”, too vague. Please rephrase. Table 1. Mechanism of injury, "missing" is in bold and add a capital letter. Figures. Where are the legends?

REVIEWER	Elton R Edwards Alfred Health & Monash University Australia
REVIEW RETURNED	08-Jun-2020

GENERAL COMMENTS	**BMJ open review** GENERAL: This is a detailed review of factors associated with outcomes following trauma in The Netherlands. A large sample is utilized. Several prognostic factors are identified for various subgroups. The population studied needs to be carefully recognized and considered. The population is relatively old with mean age 68yrs and the injury level is low with mean ISS=5. Hence this is a specific population of older persons with a lesser degree of injury. The low level of injury is also demonstrated by the low admission rate to ICU of only 7%. Given that the population studied had low level trauma, it is anticipated that recovery will be substantial during the first 6 mths as identified by the researchers. However they demonstrated that even with the lesser degree of injury studied, full recovery does not occur with EQ-5D utility at 0.79 after 2 years and EQ-VAS at 75.58 at 2 yrs. Approaching 50% of participants reported problems with mobility, pain and usual activities at 2yrs. This is useful information demonstrating the ongoing impact of this level of injury and the fact that its effects extend beyond 2 years. The paper “paints a picture” of the pathway to recovery in the group studied and provides knowledge upon which advice can be provided to patients and family in a clinical setting.

	SPECIFIC COMMENTS: Lines 34-36 the text is poorly constructed and requires revision. Suggest remove parentheses and change, “and were collected……” To: This data was collected….. Line 73 states: “Last, pre-injury health status was not measured or taken into account by determining the prognostic factors for health status in previous studies.” It is not clear the meaning of “by determining the prognostic factors” – please clarify, revise or delete this sentence. Line 78 suggest remove(I) and (II) – not necessary / confusing Line 145 the AIS injury groupings outlined do not include femur fracturs (other than hip) or knee injuries. These injuries were presumably present. Please clarify where they fitted into the subgroups created for the study. ALSO with spine injury, where did the unstable vertebral fracture fit within your 2 subgroups Line 249 states “reporting problems in the dimensions” Does this mean “reporting problems in the same dimensions”? If not, which dimensions are referred to here? Please clarify. Line 261 states “……..prognostic factor for problems with mobility and self-care but showed to be a negative associated with other dimensions of the EQ-5D.” This is unclear, “a negative” what? Please rewrite and clarify. Line 262 states “The latter is in line with a recent study, stating that the relationship between age and the dimensions of EQ-5D differed4.” This is an important point but requires clarity. Please expand a little to make clear the meaning of this statement. Table 1 & 2 consider placing at end in an appendix – not vital to the reader whilst reading the bulk of the study – i.e. used more for reference and further evaluation of results by a reader.

	The following lines require revision based on grammatical errors: Line 55: Change “injured patients were more likely to participated” TO injured patients were more likely to participate Line 60-61: Change “The number of survivors after trauma increased the last decades, due to the improvement of trauma care” TO The number of survivors after trauma has increased over several decades, due to the improvement of trauma care1 Line 70: Change “previous studies on prognostic factors for poor recovery were conducted in major or severe trauma patients population” TO previous studies of prognostic factors for poor recovery studied major or severe trauma patient populations Line 75: Change “that take into account the total clinical” TO that takes into account the total clinical Line 112: Change “Cognition was added as additional dimension” TO Cognition was added as an additional dimension Line 216: Change “for less problems on self-care” TO for less problems of self-care Line 219: Change “Lower extremity injury showed to be a prognostic factor” TO Lower extremity injury was a prognostic factor Line 221: Change “Spine injury showed to be a prognostic” TO Spine injury was a prognostic Line 223: Change “Traumatic brain injury showed to be a prognostic” TO Traumatic brain injury was a prognostic

	Line 266: Change “patients with TBI were at risk on developing cognitive” TO patients with TBI were at risk of developing cognitive Line 305: Change “patients showed to be recovered after six months” TO patients demonstrated recovery after six months

REVIEWER	Julie Agel Harborview Medical Center, USA
REVIEW RETURNED	27-Aug-2020

GENERAL COMMENTS	I have a few overarching concerns about this work. 1. For a trauma population where ISS ranges from 0-75 you have a median of 4 which is one injury of mild severity in one system - this is not trauma in the true sense of the word 2. Your age median is also very high 68 - Please explain these two factors as they impact your entire paper Do you have an analysis for the group of patients who completed all the surveys so we can see how they did compared to the mix of participants at each time point presented? Is there a difference between the proxy and self completed responses? Do you know why proxies were needed? Please modify your conclusions - you only collected data through two years -- it is possible that improvement continues up to five years - you just didn't measure that so you don't know that. Is the shorter version of the survey validated - who decided which questions to ak in the shorter version? How were the prognostic factors chosen? You address the limitation that some patients under 65 are frail - can you explain why everyone over 65 is frail? I think your data mapping recovery is interesting - but a better understanding of the sample it represents is required. What were the time windows around each time point? Please indicate somewhere if you are involved in the project from which this data came or if you just had access to the data.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Alexis Lion
Fédération Luxembourgeoise des Associations de Sport de Santé, Luxembourg

The study aimed to evaluate and characterize the recovery of the health status after a trauma. Patients who were admitted to several hospitals in the Noord-Brabant region were followed for two years. They regularly answered questionnaires (EQ-5L) to monitor their health status. Baseline characteristics were collected from a registry and from a posteriori questionnaire. The authors identified the factors which are linked to the recovery of the health status.

The introduction is interesting, but the authors should explain the prognostic factors which are already identified and the importance to conduct the present study.
The methods section is difficult to follow. It could be clearer with more details. It must be more rigorous (e.g. median, mean, VAS, etc.).

The results section is not precise enough. Results were partially reported, and the tables are difficult to understand. All significant results could be highlighted in the tables/figures. The authors could improve the results by checking the health recovery according to the prognostic factors. The prognostic factors should be selected based on the previous results section. Obviously, the location of the injury is very interesting. However, the recovery patters according to the gender, the age, length of stay, comorbidities and pre-injury health status would help the improve the treatment: specific physiotherapy or physical activity prescription for those who will have mobility issues, ergotherapy and home care for those who will have usual activities and self-care issues, psychotherapy for those who will have anxiety/depression, cognitive therapy for those who will have cognition issues, specific treatment (which could include physical activity) for those who will have pain. It could be helpful to know when to start these treatments. The authors have a great opportunity to help to improve the treatment after a trauma. It could contribute to improve the personalized treatment. This should be the aim of this study: realize an algorithm of with the characteristics of the patients to propose a tailored treatment.

The current discussion is vague. The data should be compared to the data published in the literature. What is a good health status? What were the prognostic factors already known? The discussion should then discuss the treatment possibilities according to the results. The authors should not forget that the most important in clinical research is the patients. What conclusion could be drawn based on the results to lead an optimal and rapid recovery after a trauma.

Major comments

Title

In title, please indicate that the recovery concerns the health status. In addition, based on the results, I suggest to delete the word “poor”. The title could be “Prognostic factors for recovery of health status after trauma: a prospective multicenter cohort study. Should be “injury” used instead of “trauma”?
Thank you for the suggestions, we changed the title in: ‘Prognostic factors for recovery of health status after injury: a prospective multicentre cohort study’.

Abstract

Page 1, line 28. Please indicate throughout the paper that the recovery concerns the health (status).
We changed ‘recovery’ throughout the paper to ‘health status’, when appropriate.

Page 1, line 36. Is it after injury, trauma, or hospital admission?
The questionnaire is collected at the specific time points after injury.

Page 1, line 37. What is low health status?
We changed the line to: ‘Health status increased mostly during the first six months after injury’.

Page 1, line 40. How were evaluated pre-injury health status and frailty? It should be mentioned in the main outcome measures. Length of stay? Where (at hospital)?
We added a sentence to the abstract: ‘potential prognostic factors were based on literature and clinical experience (e.g. age, sex, pre-injury frailty (Groningen Frailty Index), pre-injury health status (EQ-5D)).

Page 1, lines 41 to 43. To be modified if statistics are added (please see my general comments).
The abstract is adjusted according to the revisions in the main paper.

Introduction

Page 3, line 68. Please add also lifelong treatment or lifestyle changes (e.g. physical activity, etc.).
We added these suggestions to line 68.

Page 3, line 69. “Poor outcome”. Please precise that it is health outcome.
In line with an earlier comment, we changed outcome and recovery to health status.

Page 3, lines 69 to 73. What did observe these studies? What were the conclusions? What were the identified prognostic factors?
We included several prognostic factors from the conducted studies.

Page 3, lines 73 to 76. Why is it important?
Because recovery is not only dependent on injury severity or on injury in specific body regions, research should also focus on the more comprehensive clinical trauma population. This makes it possible to determine different patterns between several injury groups. We added the following sentence: ‘Although recovery after injury is not only determined by injury severity or injury in specific body regions, research that takes into account the total clinical trauma population during their recovery is scarce.’

Page 3, line 79. Why two years after injury? Why not 3 or 5 or 10?
The BIOS-study was based on guidelines from van Beeck et al. The authors advise assessment of injury-related disability at 1, 2, 4 and 12 months. To make assessments more manageable for the research team, outcome assessment was performed at 1 week, 1, 3, 6, 12 and 24 months. However, we acknowledge that this does not correspond to the previous lines in the introduction. We deleted ‘the first two years of’ from this line.
Reference:
Van Beeck EF, Larsen CF, Lyons RA, Meerding WJ, Mulder S, Essink-Bot ML. Guidelines for the conduction of follow-up studies measuring injury-related disability. J Trauma. 2007;62(2):534-550.

Methods

Page 4, lines 83 to 101. The BIOS-study should be more explained. What are the variables collected in this study and when? What are the variables of the BIOS-study that are used in the present study? Do the authors add other variables (e.g. Trauma data) to the data collected in the BIOS-study? It should be clearly stated. Did the authors use the costs outcome? How was it measured?
Collection of the data, prognostic variables and outcome measurements were described in the following subheadings. A more detailed description of the BIOS-study is described elsewhere (see reference 17 for the BIOS-study protocol).

It is not clear when the participants had to fill which questionnaire. The questionnaire was answered at one week and one month after trauma and the short version of the questionnaire was answered at three, six, 12 and 24 months. Is it correct? Please explain more clearly which the questions of the questionnaire were answered at one week and one month after trauma (i.e. EQ-5D, EQ-VAS, cognition dimension?). A chronological figure presenting the collected data will help the readers.
We understand the lines are not clear to the readers. We changed the descriptions and added some information to the collection of the data.

Page 4, line 92. Are the injuries induced by osteoporosis excluded?
Yes, we added this example to the exclusion criteria.

Page 4, line 96. Please clarify if it is after injury, after trauma, or after hospital admission, or after hospital discharge.
As stated in the methods section, we collected the questionnaires at 1 week, 1, 3, 6, 12 and 24 months after injury.

Page 4, lines 99 to 101. Please clarify if it was legal/ethical to collect data and use data from non-participating patients.
The study was approved by the Medical Ethics Committee Brabant. The BIOS-study is project number NL50258.028.14 and the short questionnaire is NW2016-09. We added this information to the method section.

Page 5, line 108. Please clarify. Please use "EQ-5D utility score" consistently in the article.
We checked whether EQ-5D utility score is consistently used in the paper and changed the wording if needed.

Page 5, line 119. Please confirm that the EQ-VAS was not in the short questionnaire answered at 3, 6, 12 and 24 months. If it is correct, I do not understand the results section. Please check this point.
We understand this was not clearly stated. We changed the lines and added more information throughout the method section.

Page 6, line 131. Why did the authors measure frailty only in older adults? There is a high risk of bias in the analysis.
The BIOS-study incorporated multiple measurements into one questionnaire. Patients had to complete questionnaires six times during follow-up consisting of >120 questions. The Groningen Frailty Index consists of 15 questions. To reduce the amount of questions, we decided to only collect the frailty measure in patients who were most likely to be frail (i.e. patients 65 years or older). We discussed this issue in the limitation section of the discussion.

Page 6, line 132. There is a recall bias for the data collection of the pre-injury health status. It should be acknowledged at least in the limitations of the article in the discussion. The bias could be even more important after an injury. Obviously, health status was better before an injury.
We agree with the reviewer and added recall bias and response shift as a limitation in the discussion: 'In addition, retrospectively collected preinjury health status scores are prone to recall bias and response shift[34]. However, they are considered more appropriate compared to general population norm scores[35].'

Page 6, line 134. Please explain when and how the clinical variables were collected (Trauma Registry).
We added the line: 'all clinical variables were extracted from the trauma registry.'

Page 6, line 142. Please explain if the used injury classification is implemented in the Trauma Registry. If not, why do the authors used this classification instead of the classification of the Trauma Registry? Page 6, line 145. What about fibula fractures? What about knee injuries such as ACL injuries? What about sprain injuries or skin burn? In the table 4, injuries (or trauma) are further regrouped. Please use only one classification consistently in the manuscript.
We added supplemental file 1 for detailed description of the injury classification, which is based on the AIS code used in the trauma registry. The trauma registry includes all different AIS codes, but does not use or apply injury classifications. The AIS codes describes over 2000 different injuries. Because of the wide range of injuries and because outcomes after injuries widely differ, we created this classification in close collaboration with a clinician. We only created specific injury classifications for the most common types of injuries.

Page 6, line 153. It should be explained before what and why data of non-participants were collected (and if it is ethical).
Data from the non-respondents was extracted from the trauma registry. We did not collect or use any data from the non-responders which we extracted from their medical file. The study was approved by the Medical Ethics Committee Brabant (project number BIOS-study: NL50258.028.14 and short questionnaire: NW2016-09).

Page 6, line 154. How was tested the normality of the data?
Normality of the data was assessed visually with a normal Q-Q Plot. This information was added to the subheading data analysis in the method section.

Page 7, line 158. Missing data were imputed. Please explain if there is a risk. Original data and data after imputation could be presented and compared in an additional table in supplementary materials.
Proportions of missing data in the dataset were minimal. Although it is possible that missingness was not at random, resulting in biased imputation values, we did not report differences in analyses between complete cases and the imputation set. Previous research from our study group showed no differences between analyses with the imputation set and the complete cases. However, we acknowledge this information could be mentioned in the paper. Therefore, the following lines were added: 'Detailed description of the imputation model and imputed values were previously published[23]. No large differences were found between imputed data analyses and complete case analyses.'
Reference:
Kruithof N, Polinder S, de Munter L, van de Ree, Cornelis LP, Lansink KW, de Jongh MA, et al. Health status and psychological outcomes after trauma: A prospective multicenter cohort study. PLoS one 2020; 15(4): e0231649.

Page 7, line 165. Again, please check if EQ-VAS was measured at each time point.
As discussed before, the EQ-VAS was only collected in the BIOS-study. This is also demonstrated in the flow diagram (Figure 1).

Page 7, line 170. Why were all potential prognostic factors entered in the multivariable models? Why not only those which were significant in the univariate analyses? How did the authors manage the type I errors due to the elevated numbers of statistical analyses? What was the p-level for significance for each analysis? What was the criteria of significance of the coefficient correlations?
We selected the prognostic variables based on previous literature and clinical experience, according to previous literature[1]. We did not select variables based on significance from the univariate analyses, so we did not adjust for multiple testing to select variables. We added the following line to the methods: 'A p-value of ≤.05 was considered statistically significant.'
References:

Results

Page 9, line 185. It is very helpful to compare the participants with the patients who did not accept to take part of the study. However, the baseline characteristics presented in this section and in the table 1 could mislead the readers. How many patients answered all the questionnaires? Who are the drop-out participants? Why most of the exclusion was observed within the first week? Why are there approximately 1000 patients more who participated at 1 month than at 1 week?
Patients who did not respond to a questionnaire were considered a non-responder for that time point, but could participate again in the following questionnaires. Also, proxy questionnaires were send from 1 month onwards and were non-responders for the 1 week measurement. We added this information in the methods section. Because our analyses (linear mixed models)

takes into account all participants, also patients who did not complete all questionnaires, we chose to show characteristics of the participants (at least one completed questionnaire) and non-responders. However, we understand the need for explanation. Therefore, we added some extra information in the baseline characteristics section: 'A total of 1,105 participants (22.6% of the study population) completed all BIOS questionnaires at each time point. The main reason for lost to follow-up was that completing the questionnaire was too time consuming. Patients who reported to be fully recovered and patients aged 18-24 were most likely to be lost to follow-up.'

Page 9, lines 191 to 195. Please check these lines according to the results presented in the table 1. For the ASA classification, I am wondering why the authors did not use dummy variables to test the differences between each category. Indeed, the significant p-value for the ASA classification means that there is a heterogeneity of the categories. We cannot conclude that there are more class 2 in the responders than in the non-responders. Post-hoc analyses should be performed (using dummy variables). This is the same for the functional capacity index. Why did the authors not perform statistical analyses for the injury classification and the mechanism of injury? In the table 1, please check the values for the length of stay and the injury severity score (same medians and IQR in both groups with significant p-values). Why are the pre-injury health status and the frailty not presented in the table 1? Please try to be more precise in the text (e.g. adding values to "more often").
We checked the results according to table 1. We made some changes in text and table. The values for length of stay and ISS are correct. Although the medians are the same for the two groups, significant results can be found because the Mann-Whitney test is a rank sum test and not a median test. We included pre-injury health status and frailty in the table. Furthermore, mechanism of injury is excluded from the table to reduce the number of variables and in line with the paper.

Page 9, line 197. Why are the pre-injury (or pre-trauma) health status not presented here (and in the corresponding figures)?
Pre-injury health status is retrospectively collected. It is not presented in the figures because it is a different measurement compared to the prospectively collected follow-up health status measurements. We agree it could be mentioned in the characteristics table. We added the values to table 1.

Page 10, line 211. In the supplementary material, and the tables 2 to 4, please highlight the results which are considered as significant/non-significant (using bold, italic or NS, etc.) and indicate the threshold of significance. It will help the readers.
We changed the tables according to the suggestions.

Page 10, line 215. What is higher age? In the table 2, it seems that the category >75 is not associated with self-care. What are the numbers of patients in each age category? What is the rational of these age categories?
The numbers of patients for categories for age and length of stay were added to table 1. The age categories were chosen based on clinical relevance and experience.

Page 10, line 218. Female sex is not a significant prognostic factor for self-care (and mobility).
We adjusted the text according to this suggestion.

Page 10, lines 219 to 224. What are "lower extremity injury", "upper extremity injury", "spine injury" and "traumatic brain injury"? These groups of injuries were not defined in the methods. Do they author analyze these groups? If yes, please modify the methods section and the table 2. For example, hip fracture (if considered as lower extremity injury) was associated only with EQ-5D mobility dimension. Another example, radius, ulna, or hand fracture were associated with mobility and self-care only. Please check and rewrite this paragraph (lines 212 to 224).

We understand this confusion. Although we describe the injury groups separate in the subheading injury classifications in the method section, we tried to clarify this within table 2 and supplemental table 2.

Page 10, lines 226 to 232. “Health status over time” paragraph and the first part of the “Recovery patterns” paragraph are similar. I suggest to regroup these paragraphs. The significant improvements presented in the table 3 could be indicated in the figure 2 (consequently, the table 3 could be deleted). The paragraph “recovery patterns” could be renamed “recovery patterns according to the prognostic factors”.
We thank the reviewer for this suggestion and changed the results according to this comment. We adjusted figure 2 and included table 3 as a supplemental table.

Page 10, line 231. Pain/discomfort was not significant 12 to 24 months after trauma. It could be presented in this section that mobility improved until six months, self-care and pain discomfort until 12 months, and usual activities until 24 months. Anxiety improved from one to six months.
We changed the whole result section, including this statement. Thank you for the suggestions.

Page 11, lines 233 to 242. Spine injury showed improved mobility and self-care up to six months. Lower extremity injury did not show less mobility problems in the first month. Spine injury did not show fewer usual activities problems in the first month. According to the table 4, pain/discomfort recovery occurred until 12 months (except for spine between three and six months). Analyses (and figures) of recovery patters of the health status and its dimensions according to selected prognostic factors would be interesting (please see my general comments).
We thank the reviewer for this suggestion. However, the aim of this study was to assess the different recovery patterns among all injury classifications. Although the proposed analyses are potentially interesting and useful, we chose to focus on the injury classifications, adjusted for all other factors.

Discussion

Page 12, line 246. “Health status was especially low” compared to what? What is a low health status? Please add references.
Following good statistical practice, health status was analysed as much as possible as a continuous variable[1]. Hence, higher health status refers to having a higher utility score, not to a specific health status cut-off, which is biologically implausible to exist.
Reference
Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med. 2006;25(1):127-41.

The characteristics of the patients and the non-participants should be discussed. Please discuss the injury severity score (or add in the methods section the range of the Injury severity score).
We added the range of the injury severity score in the methods section. Differences between characteristics of patients and non-responders were discussed in the limitations.

The results of the EQ-5D utility scores, the EQ-VAS and the EQ-5D dimensions should be discussed considering the current published literature. It would be interesting to know if the values presenting in the current study are similar to those published in other studies. Or, the “normal” range of these scores could be presented in the methods sections.
Thank you, we added a comparison with literature for the prevalence of problems in the dimensions of health status to the discussion.

Minor comments

Page 1, line 33. Please do not start the sentence with “4883”. I suggest to change the dot at the end of the previous sentence by colons (:).
Page 1, lines 34 to 36. Please rephrase the sentence. It is difficult to follow as it is (too many “and”).
Page 1, line 38. Please add a space between the results and the SD.
Page 2, line 50. Health recovery.
Page 3, line 60. How many millions? Please add a reference.
Page 3, line 60. Do the authors previse that survivorship concern severe trauma?
Page 3, line 62. HS is not consistently used thereafter.
Page 4, line 86. Please rephrase “after trauma in injured patients”. Maybe delete “injured patients”.
Page 4, line 92. Please define briefly “pathological fractures” or give an example.
Page 4, line 94. Is “participating” the correct wording?
Page 4, lines 95 and 98. Please change to 12 months.
Page 5, line 116. HS? Please use this abbreviation consistently in the manuscript (or do not us it at all).
Page 6, line 147. Please add a space after groups.
Page 6, line 148-149. Please add space after head and abdomen.
Page 7, line 155. Mean and SD were also presented.
Page 7, line 156. What is ISS (injury severity score)? Please be careful with all the abbreviations throughout the paper.
Page 7, line 172. What is LOS (length of stay)? Please be careful with all the abbreviations throughout the paper.
Page 9, line 191, please add the number of non-responders (or non-participants; please choose only determination)
Page 9, line 192, what is level 1 trauma center? Please define it.
Page 9, line 198. Please see add mean and standard deviation (SD) in the methods. Why mean and SD were used instead of median and IQR? Are the data for health status distributed normally?
Page 9, lines 203-205. Please remind the readers that the dimensions were calculated from the EQ-5D questionnaire.
Page 9, line 206. Please be consistent throughout the article with the use of the words “injury” and “trauma”.
Page 10, line 211. The first sentence of the paragraph is quite vague.
Page 10, line 214. Please use EQ-5D utility score and EQ-VAS instead of health status in the results section. Please use a precise wording.
Page 10 line 227. “Health status measured with the EQ-5D utility score”, this is the good way to present the results and it should be used throughout the paper.
Page 10, line 227. “Most recovery occurred … ” is rather imprecise and can mislead the readers.
Page 12, line 245. “We found that patients … two years after injury”; this a vague sentence.
Page 12, line 249. “dimensions” of what?
Page 12, line 250. “less problems”, too vague. Please rephrase.
Table 1. Mechanism of injury, "missing" is in bold and add a capital letter.
Figures. Where are the legends?
We thank the reviewer for the corrections and suggestions. We changed the lines according to the comments.

VERSION 2 – REVIEW

REVIEWER	Alexis Lion Fédération Luxembourgeoise des Associations de Sport de Santé
REVIEW RETURNED	01-Oct-2020

GENERAL COMMENTS	The authors improved considerably the manuscript which is easier to read and to understand. However, it remains some issues to fix/clarify. Abstract: Page 1, line 28. The authors may consider deleting « poor ». Page 1, line 32. Adult “injured” patients? Page 1, line 40. The authors replied they changed the sentence using the adverb « mostly » but in the text, it is written « strongly ». Please be consistent. Maybe, it would be better to write that « Health status improved mainly ». Page 1, line 46. The authors may consider rephrasing « problems with cognition » which sounds awkward. Introduction Page 3, line 63. The author could add “However,” at the beginning of the third sentence to contrast and link with the previous one. It will highlight that the impairments are the consequence of the injury (and its treatment). Page 3, line 73. “Most previous study … studied”. The authors may consider using “evaluated” instead of “studied”. Page 3, line 82. Please delete “after injury” or “during the first two years after injury”. Methods Page 4, line 97. “Proxy informant use” should be read. Page 4, line 102. “response rate” should be read. Page 4, line 102. “if patient …” should be more to the beginning to the sentence. I am wondering if the long and the short versions of the questionnaires were sent to the participants at the same time or if they were sent with a delay (if yes, what was the delay?). Patients could therefore answer the long or the short version of the questionnaires. Page 4, line 106. Participants who did not provide informed consent (N = 4891) were also called non-responders in the Table 1 and in the results section. Please use an appropriate wording to identify clearly the two populations. Page 5, line 131. Please correct “Botch”. Page 5, line 132. Please delete one point at the end of the sentence. Page 7, line 169. Add a point before “Normality …”. Page 9, line 212. A total of 762 participants of patients “aged-over 65” reported to be frail. Percentage should relate only on the participants aged over 65.

	Page 9, line 213. Here, the so-called non-responders are patients (N=4891) who did not provide informed consent and who did not participate to the study. Please clarify this point here and in the methods and use an appropriate wording. I am still wondering how it is possible to use personal (clinical) data from individuals who did not provide informed consent… Page 9, lines 217-218. How do the authors know that the main reason for lost to follow-up was the lack of time? In addition, “lost to follow-up” maybe not the correct wording as some of them answered a subsequent questionnaire. “Lost to follow-up” should be changed to “participants who did not answer all questionnaires”. Discussion Page 12, line 267. The authors have the possibility to discuss the factors that will influence the health status after an injury. Previous studies showed that physical activity levels before an injury/surgery can predict the recovery: e.g. : - Parietti-Winkler et al. Prediction of Balance Compensation After Vestibular Schwannoma Surgery. Neurorehabil Neural Repair. 2016 Jun;30(5):395-401. doi: 10.1177/1545968315600270. - Tew et al. Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery. Anaesthesia. 2018 Jun;73(6):750-768. doi: 10.1111/anae.14177.

REVIEWER	Julie Agel Harborview Medical Center USA
REVIEW RETURNED	05-Oct-2020

GENERAL COMMENTS	Thank you for your reviewer responses. Please remove or reword line 165 - you do not know that all patients < 65 were not frail - you are making an assumption. I remain concerned about your sample. Your data represents half the potential population. Line 218 - At what point did these patients report they were fully recovered. I think your conclusions are biased by this loss of your enrolled sample. Everything you report has to be conditional - i.e. based on those who responded ... Please explain what FIgure 1 non-survivors means Did everyone respond to the follow-ups - is that how you determined the not interested group? Please explain why if out of 4883 you only got 3366 pre-injury surveys - are there participants who did not do the pre-injury survey who did later surveys -- if so - and based on the title of Table 1 - what was the latest someone did their first survey IN table 3 - are patients with multiple injuries represented in both the upper and lower extremity analysis? In Table S1 I don't think there is usually a decimal point when reporting the injury severity. I think you have a lot of data here and it is possible that the larger sample size reflects true findings but without a better understanding of your sample at each time it is hard to judge.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Alexis Lion
Fédération Luxembourgeoise des Associations de Sport de Santé

The authors improved considerably the manuscript which is easier to read and to understand. However, it remains some issues to fix/clarify.

Abstract:

Page 1, line 28. The authors may consider deleting « poor ».
'Poor' was deleted.

Page 1, line 32. Adult "injured" patients?
'Injury' was changed into 'injured'.

Page 1, line 40. The authors replied they changed the sentence using the adverb « mostly » but in the text, it is written « strongly ». Please be consistent. Maybe, it would be better to write that « Health status improved mainly ».
We deleted 'strongly', and changed it into 'mainly'.

Page 1, line 46. The authors may consider rephrasing « problems with cognition » which sounds awkward.
We rephrased the sentence to: 'cognitive problems'.

Introduction

Page 3, line 63. The author could add "However," at the beginning of the third sentence to contrast and link with the previous one. It will highlight that the impairments are the consequence of the injury (and its treatment).
We added 'however' to the third sentence.

Page 3, line 73. "Most previous study … studied". The authors may consider using "evaluated" instead of "studied".
We rephrased the sentence according to this suggestion.

Page 3, line 82. Please delete "after injury" or "during the first two years after injury".
We deleted 'during the first two years after injury'.

Methods

Page 4, line 97. "Proxy informant use" should be read.
We added 'informant' to the sentence.

Page 4, line 102. "response rate" should be read.
We rephrased the sentence to: 'response rate'.

Page 4, line 102. "if patient …" should be more to the beginning to the sentence. I am wondering if the long and the short versions of the questionnaires were sent to the participants at the same time or if they were sent with a delay (if yes, what was the delay?). Patients could therefore answer the long or the short version of the questionnaires.
We rephrased the sentence according to this suggestion. The questionnaires were sent to the participants at the same time, without delay.

Page 4, line 106. Participants who did not provide informed consent (N = 4891) were also called non-responders in the Table 1 and in the results section. Please use an appropriate wording to identify clearly the two populations.

We agree with the reviewer this could be confusing. We rephrased the sentence and added an explanation of the meaning of a non-responder.

Page 5, line 131. Please correct “Botch”.
‘Botch’ was corrected into ‘both’.

Page 5, line 132. Please delete one point at the end of the sentence.
The second point was deleted.

Page 7, line 169. Add a point before “Normality …”.
We added a point before ‘Normality’.

Page 9, line 212. A total of 762 participants of patients “aged-over 65” reported to be frail. Percentage should relate only on the participants aged over 65.
We changed the percentage, according to this suggestion.

Page 9, line 213. Here, the so-called non-responders are patients (N=4891) who did not provide informed consent and who did not participate to the study. Please clarify this point here and in the methods and use an appropriate wording. I am still wondering how it is possible to use personal (clinical) data from individuals who did not provide informed consent…
I added an explanation about non-responders in the method section, in line with a previous comment.

Page 9, lines 217-218. How do the authors know that the main reason for lost to follow-up was the lack of time? In addition, “lost to follow-up” maybe not the correct wording as some of them answered a subsequent questionnaire. “Lost to follow-up” should be changed to “participants who did not answer all questionnaires”.
We send questionnaires to the patients and called them by telephone to inform them about the study. If patients responded not to complete the questionnaire, we asked for the reason of non-participation. This is how we determined the reason of non-responding (i.e. not interested, fully recovered, too time consuming etc.). This comment is in line with a comment of reviewer 3, we added this information to the methods.

Discussion

Page 12, line 267. The authors have the possibility to discuss the factors that will influence the health status after an injury. Previous studies showed that physical activity levels before an injury/surgery can predict the recovery:
e.g. :
- Parietti-Winkler et al. Prediction of Balance Compensation After Vestibular Schwannoma Surgery. Neurorehabil Neural Repair. 2016 Jun;30(5):395-401. doi: 10.1177/1545968315600270.
- Tew et al. Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery. Anaesthesia. 2018 Jun;73(6):750-768. doi: 10.1111/anae.14177.
Pre-operative exercise is indeed a factor that will influence the health status after injury. However, most patients that are included in this study are acute patients, with minimal delay to treatment. Exercise before operation is not the main target here and could not be induced with these prediction models. However, we agree we could inform the reader more about the implications of such models. Therefore we included a paragraph in the discussion.

Reviewer: 3
julie agel
Harborview Medical Center USA

Thank you for your reviewer responses.
Please remove or reword line 165 - you do not know that all patients < 65 were not frail - you are making an assumption.
We deleted the sentence.

I remain concerned about your sample. Your data represents half the potential population.

We acknowledge that 'only' 50% of the eligible patients participated. This is also stated in the discussion as a limitation, and is a well-known problem for prospective cohort studies. Participation in a longitudinal cohort study is frequently correlated with cultural or lifestyle factors, possibly inducing selection bias. It is well known that the lower the response rate, the higher the risk of a biased sample. For that reason, we tried to increase the response rate in this study by allowing patients to flow in at each measure point up until 1 year post-trauma.

Line 218 - At what point did these patients report they were fully recovered. I think your conclusions are biased by this loss of your enrolled sample. Everything you report has to be conditional - i.e. based on those who responded ...
At every follow-up point we asked patients to complete the questionnaires. If we did not receive the answers, we called them to inform them about the questionnaire and, if necessary, about the reason of not participating. Several patients responded that they did not want to participate because they feel they were fully recovered. However, because we do not know what there actually health status was, we reported them as missings. However, we agree with the reviewer that the conclusions are conditional. Although we already mentioned this in the limitations, we also rephrased the first sentence of the conclusion.

Please explain what Figure 1 non-survivors means. Did everyone respond to the follow-ups - is that how you determined the not interested group?
The non-survivors are participants who died during the follow-up period. For example, at 3 months there are 61 non-survivors, meaning that of the total group of participants (who completed an informed consent, 61 patients died during the 3 months follow-up. We included this explanation in the figure legends.
We send questionnaires to the patients and called them by telephone to inform them about the study. If patients responded not to complete the questionnaire, we asked for the reason of non-participation. This is how we determined the reason of non-responding (i.e. not interested, fully recovered, too time consuming etc.). This was also included in the methods.

Please explain why if out of 4883 you only got 3366 pre-injury surveys - are there participants who did not do the pre-injury survey who did later surveys -- if so - and based on the title of Table 1 - what was the latest someone did their first survey.
In the BIOS-study, the retrospectively collected pre-injury EQ-5D-3L was used to interpret the change from HS prior to the trauma to post-trauma HS. However, retrospectively collected pre-injury HS is prone to recall bias and response shift. Up to 1 month after injury we retrospectively asked patients to complete their pre-injury assessment. However, we did not find it reliable to ask patients from the 3 month follow-up onwards about their pre-injury status (due to recall bias and response shift). That is why only patients who participated in the 1 week and 1 month follow-up questionnaire completed the pre-injury assessment. The latest someone completed the pre-injury assessment was 6 weeks after injury.

In table 3 - are patients with multiple injuries represented in both the upper and lower extremity analysis?
Patients who have both upper and lower extremity injury are represented in both groups.

In Table S1 I don't think there is usually a decimal point when reporting the injury severity.
Injury severity is reported according to the abbreviated injury score. For example: the corresponding AIS code for Tibia fracture is 854000.2 . In supplemental file 1 we reported the first 3 numbers related to the region, type and structure of the region (i.e. 854). The second value corresponds to the injury severity of the tibia fracture (i.e. .2). We included the '.' to make clear it corresponds to this last number of the AIS code.

I think you have a lot of data here and it is possible that the larger sample size reflects true findings but without a better understanding of your sample at each time it is hard to judge.
We thank the reviewer for the comments.

VERSION 3 – REVIEW

REVIEWER	Alexis Lion Fédération Luxembourgeoise des Associations de Sport de Santé
REVIEW RETURNED	17-Nov-2020

GENERAL COMMENTS	The authors improved considerably the manuscript which is easier to read and to understand. However, it remains some minor issues to fix/clarify. Page 5, line 101. The authors should consider modifying the sentence as follow: “Participants, patients or proxy informants were asked to sign an informed consent”. Page 5, line 108. The authors should consider modifying the sentence as follow: “were considered as a non-participant” Page 5, line 111. The authors should consider modifying the sentence as follow: “sign informed consent nor complete no follow-up questionnaire.” Page 13, line 247. The authors should consider modifying the sentence as follow: “up to”

REVIEWER	Julie Agel Harborview Medical Center USA
REVIEW RETURNED	17-Nov-2020

GENERAL COMMENTS	Thank you for your responses.