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One-year employment outcome prediction after traumatic brain injury: A CENTER-TBI study

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A B S T R A C T

Background: Traumatic brain injury (TBI) can come with long term consequences for functional outcome that can complicate return to work.
Objectives: This study aims to make accurate patient-specific predictions on one-year return to work after TBI using machine learning algorithms. Within this process, specific research questions were defined: [1] How can we make accurate predictions on employment outcome, and does this require follow-up data beyond hospitalization? [2] Which predictors are required to make accurate predictions? [3] Are predictions accurate enough for use in clinical practice?
Methods: This study used the core CENTER-TBI observational cohort dataset, collected across 18 European countries between 2014 and 2017. Hospitalized patients with sufficient follow-up data were selected for the current analysis (N = 586). Data regarding hospital stay and follow-up until three months post-injury were used to predict return to work after one year. Three distinct algorithms were used to predict employment outcomes: elastic net logistic regression, random forest and gradient boosting. Finally, a reduced model and corresponding ROC-curve was created.
Results: Full models without follow-up achieved an area under the curve (AUC) of about 81 %, which increased up to 88 % with follow-up data. A reduced model with five predictors achieved similar results with an AUC of 90 %.
Conclusion: The addition of three-month follow-up data causes a notable increase in model performance. The reduced model - containing Glasgow Outcome Scale Extended, pre-injury job class, pre-injury employment status, length of stay and age - matched the predictive performance of the full models. Accurate predictions on post-TBI vocational outcomes contribute to realistic prognosis and goal setting, targeting the right interventions to the right patients.

1. Introduction

Prognostication is a key aspect of medicine and can be defined as relating patient and injury features to the patient's outcome.[1] These factors influencing patient outcomes often include demographics, pre-injury health status, severity and mechanism of injury, severity of potential other injuries, and social environment.[2] When empirical data on these features are analyzed and integrated into a prognostic model, individualized predictions can be obtained for use in clinical practice. For patients as well as their relatives, realistic expectations and counseling based on such individualized outcome predictions are highly important.[3]

Traumatic brain injury (TBI) is a condition for which accurate prognostication is particularly relevant. TBI is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force".[4] Apart from substantial mortality, neurological injury is anticipated to be the dominant contributor to impairment from neurological conditions up until today.[5] The complexity of the brain, the nature and severity of damage, and the varying individual response to the specific injury result in a wide-ranging variability of clinical manifestations of TBI.[2] Prognostic models can help clinicians provide individual patients insight into expected outcomes despite this complexity and variability.

In 2017, the Lancet Neurology Commission on TBI published a report on the state of the art of current evidence, of which section 8 highlights the remaining gaps in TBI research.[2] One of their conclusions was that there is a lack of prediction models on other topics than mortality and overall level of disability as measured by the Glasgow Outcome Scale Extended (GOSE). Their 2022 update only showed progress in the prediction of quality of life and post-concussive symptoms.[3]

Return to work is a very relevant outcome for prognostication, both from an individual and a societal point of view. Declining community integration, health-related quality of life and life satisfaction all have been linked to unemployment after TBI.[6–8] On a more global level,

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unemployment after TBI implies a loss of human potential and comes with a considerable cost for society. The indirect costs generated by productivity losses account for a substantial share of the financial burden TBI generates for society.[9]

The current study aims to create a prediction model for employment outcomes at one year after TBI for patients hospitalized with TBI in Europe. In order to create this prediction model, the following research questions were assessed:[1] How can we make accurate predictions on employment outcome, and does this require follow-up data beyond hospitalization?[2] Which predictors are required to make accurate predictions?[3] Are predictions accurate enough for use in clinical practice?

2. Methods

2.1. Data sources and patient selection

This study used data from the CENTER-TBI project, which prospectively collected longitudinal observational data of patients hospitalized with TBI (stratified by severity) across 63 centers in 18 European countries between 2014 and 2017.[10] The CENTER-TBI project with EC grant 602150 was carried out in line with all pertinent EU local legislation of the countries of the recruiting sites.

The total number of patients in the core dataset was 4509. However, the current analysis has some additional selection criteria. First of all, this study was limited to patients in the work force at the time of injury. This was operationalized as an age between 16 and 65 at the time of injury, without being a student, retired, disabled or homemaker at the time of injury. Patients who were unemployed but looking for work, were considered to be in the work force. Second, patients were selected based on the presence of outcome data, as will be elaborated upon in the next section. Finally, in order to be included in this study, patients were required to have a completeness of at least 80 % of the follow-up outcomes data at the three months post-TBI timepoint, to ensure usability of these data as predictors while avoiding a large amount of imputation.

2.2. Study outcome

The outcome of this study was a binary classification of whether an individual was competitively employed at one year after the date of injury. Within the CENTER-TBI study, outcomes were collected through structured phone interviews or mail surveys. At least one variable on employment at one year post-TBI had to be available. Distinct classifications of employment status in the CENTER-TBI dataset were recategorized into one common, broader outcome classification. When multiple potential outcome variables were available, some apparent contradictions were possible, likely due to slightly different nuances in the phrasing of the original question. When this occurred, a majority of indications for a certain category was required to include a patient in the final study dataset. Also, when it was indicated that a patient did not return to work due to a reason unrelated to the injury, this patient was removed from the analysis.

2.3. Data preparation

All data preparation and analysis steps were conducted in R, with most steps being completed within the tidymodels framework (see Digital Supplemental Content 1–3). This study used the CENTER-TBI data subsets on patient demographics, medical history, injury and emergency care, imaging, hospital stay, vitals, surgeries and other medical interventions, follow-up data and outcomes. Variables were removed if they concerned the research process rather than the patient and provided care (e.g., variables related to consent and study participation). Additionally, variables with a data type that is not suitable for modelling (e.g., free-text or large number of categories) were excluded. In case of time-dependency of predictors, only the data points up to three months post-injury were considered. For features related to medical imaging, the information (regarding observed lesions) of the last available scan up to three months post-injury was retained. After consulting a radiologist, MRI findings, when available, were considered dominant over CT evidence in case of inconsistencies. Furthermore, variables with more than 85 % missingness were removed. The remaining features were imputed using a k-nearest neighbors algorithm, using the corresponding function in the recipes package (see Digital Supplementary Content 1). Finally, data were decorrelated with a cutoff of 0.8. When decorrelation led to the removal of features, priority was given to features that can be more intuitively associated with employment outcomes after TBI. Throughout the data preparation, data recoding and/or merging of related features was performed if these could avoid unnecessary removal of features (e.g., due to large number of categories, missingness or correlation).

2.4. Data analysis

Given the large number of features available in the CENTER-TBI dataset and the high degree of complexity of the relation between the various predictors and the outcome to be modelled, machine learning is the preferred modelling approach.[11,12] Additionally, machine learning possesses the capability to effectively manage extensive sets of predictors.

This study compares three machine learning algorithms: elastic net logistic regression, a random forest ensemble and a gradient boosting ensemble.[13] A quasi-random tuning grid (Latin hypercube) was used on 25 bootstrap samples to select the optimal hyperparameter values of each of these three algorithms. The models with the best balanced accuracy were selected, calculated as the average of the sensitivity and the specificity, to account for class imbalance of the outcome variable. The corresponding hyperparameter values were used to finalize the models by refitting them on the entire training dataset. The final estimates of the model performance were obtained using a hold-out test dataset, comprising 25 % of the data stratified by outcome. Area under the curve (AUC) was used for model evaluation. To gain some insight into the features that contribute the most to the obtained predictions, feature importance of ensemble models was quantified using Gini impurity. For the elastic net logistic regression model, feature importance was represented by the magnitude of parameter coefficients.

The dependence of the measured model performance on the data split was assessed by creating twenty different repetitions of the analysis with different data splits and visually summarizing the distribution of performance metrics. For feature importance, pairwise rank correlations were calculated to estimate the consistency between different runs (results are presented in Digital Supplemental Content 2). Finally, a linear mixed model was used to test which condition (i.e. with or without follow-up data) and modelling algorithm was best across all twenty iterations while accounting for the inherent relations in the data. Additionally, contrasts with Tukey correction were calculated to allow direct comparison of all modelling algorithms.

After finalizing the full models, the best reduced model was created using a forward stepwise procedure. The same data splits and metrics as before were used to evaluate performance of reduced models. The classification-ability of the final model was evaluated by calculating accuracy, sensitivity, specificity, positive predictive value and negative predictive value across all thresholds. Additionally, a calibration plot was created to assess how well the probabilities estimated by a model align with the actual probabilities of the events being predicted in the population under examination.

3. Results

3.1. Study sample

Fig. 1 shows a flowchart of the patient selection process. The final study sample contained 586 individuals. An overview of their

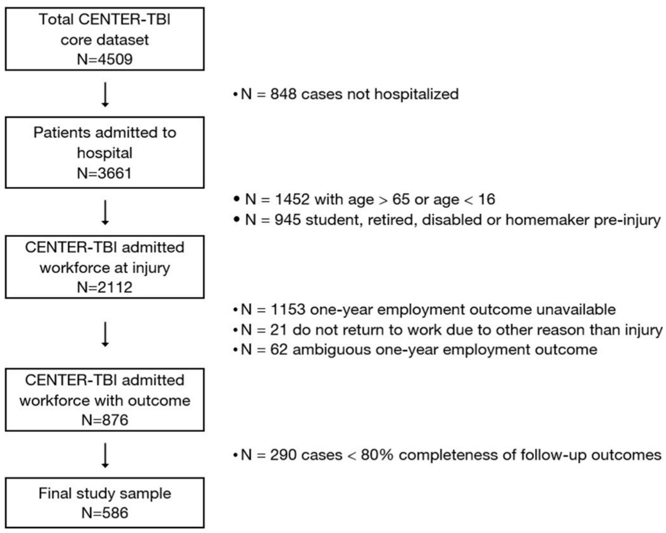

Fig. 1. Patient selection flowchart.

demographics and early outcome characteristics is shown per outcome category in Table 1. The study sample had a mean age of 43 (SD = 13) and consisted of 76 % males. A majority of 63 % of the sample had mild TBI at baseline, 10 % had moderate TBI and 22 % severe TBI. The median acute length of stay (LOS) was 8 days (Q1 = 3; Q3 = 21). As for educational and professional background, half of the sample (49 %) obtained a degree of post-secondary education. Before injury, 75 % worked full-time, 17 % worked part-time, and 8 % was unemployed and looking for work. After one year, 70 % of the study sample were working.

3.2. Full model performance

The first column of Fig. 2 shows the distribution of AUC for each of the twenty data splits, for either the data available at discharge or the follow-up enhanced data. Without follow-up data, the median AUC achieved by the different modelling algorithms is around 81 % across algorithms. With three-month follow-up, this went up to about 88 %. All three modelling algorithms performed similarly. Thus, the logistic regression model was chosen because it has the highest transparency and explainability.

When the AUC values obtained by the twenty repetitions of the three modelling algorithms in two conditions (with vs. without follow-up data) are modelled using a linear mixed effect model, a significant main effect of the condition is found ($p < 0.0001$). Additionally, the AUC values of the gradient boosting model has significantly lower performance than the other two algorithms (see Digital Supplementary Content 2).

Table 1
Overview of study sample characteristics per outcome.

	Employed at 1y post-TBI	Not employed at 1y post-TBI
Demographics		
Age		
18-35	131 (32 %)	48 (28 %)
36-50	137 (33 %)	53 (31 %)
51-65	147 (35 %)	70 (41 %)
Sex		
Male	297 (72 %)	126 (74 %)
Female	118 (28 %)	45 (26 %)
Education		
Higher education	128 (31 %)	32 (19 %)
No higher education	262 (63 %)	132 (77 %)
Cause of Injury		
Road traffic accident	191 (46 %)	95 (56 %)
Incidental fall	148 (36 %)	52 (30 %)
Other non-intentional injury	32 (8 %)	6 (4 %)
Violence	17 (4 %)	7 (4 %)
Suicide	4 (<1 %)	1 (<1 %)
Pre-injury Employment Situation		
Pre-injury Employment Status		
Working full time	321 (77 %)	120 (70 %)
Working part time	65 (16 %)	28 (16 %)
Unemployed	18 (4 %)	26 (15 %)
Pre-injury Job Class		
Manager/Professional	89 (21 %)	17 (10 %)
Technician/Supervisor/Associate	72 (17 %)	17 (10 %)
Clerk/Sales	47 (11 %)	9 (5 %)
Skilled manual worker	61 (15 %)	35 (20 %)
Manual worker	67 (16 %)	42 (25 %)
Acute and Post-acute TBI Severity		
Baseline Glasgow Coma Scale		
Mild	293 (71 %)	74 (43 %)
Moderate	38 (9 %)	18 (11 %)
Severe	64 (15 %)	66 (39 %)
Glasgow Outcome Scale at 3 mo post-TBI		
Good recovery	235 (57 %)	16 (9 %)
Moderate disability	158 (38 %)	74 (43 %)
Severe disability	19 (5 %)	80 (47 %)

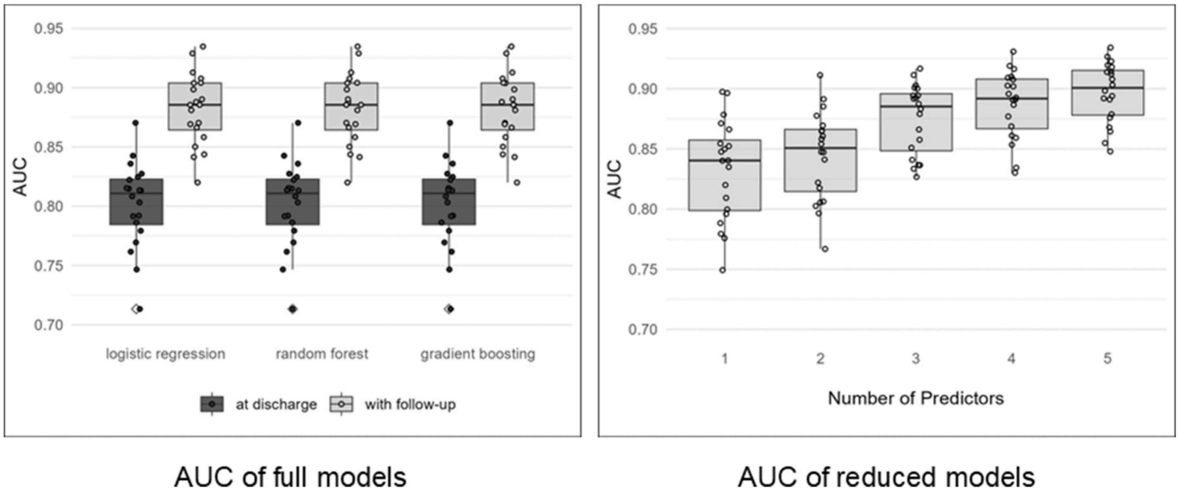

Fig. 2. Aggregated Area Under the Curve (AUC) of full (left) and reduced models (right).
Each dot on the graphs represents a different data split, with diamonds indicating outliers.

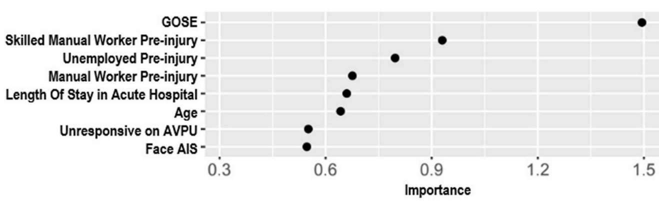

Fig. 3. Feature importance of elastic net logistic regression model with follow-up data.
(GOSE = Glasgow Outcome Scale Extended; AVPU = Alert, Voice, Pain, Unresponsive; AIS = Abbreviated Injury Scale).

3.3. Feature importance

Without follow-up, LOS showed up as the most important predictor, across all algorithms. Other consistently important predictors include age, pre-injury employment status, total injury severity and some vital parameters (heart rate, blood pressure and oxygen saturation). With three-month follow-up, GOSE became the most important predictor in each of the algorithms.

There was a high degree of consistency in the rank of the feature importance for different data splits (see Digital Supplemental Content 2). This is shown for the elastic net logistic regression model in Fig. 3. The highest ranking features for this model in terms of importance, are shown in Digital Supplemental Content 2 as well.

3.4. Reduced model

Based on the feature importance of the full elastic net logistic regression model, a forward stepwise procedure adding features in order of importance resulted in the performance shown in the right panel of Fig. 2. With the GOSE as the only predictor in a univariable model, a decent AUC of 84 % is observed. The stepwise addition of pre-injury occupation, pre-injury employment status, LOS and age results in further improvement to the model performance. Model coefficients are presented in Table 2, with the corresponding metric curves in Fig. 4. Digital Supplemental Content 4 contains the full table of sensitivity, specificity, PPV, NPV and accuracy values per threshold. Fig. 5 presents the calibration curve of the model, showing no systematic over- or underestimation of the probability of returning to work.

A reduced model was created as well for the dataset with discharge data only. This can be consulted in Digital Supplemental Content 3.

Table 2
(Exponentiated) coefficients of reduced model.

Variable	Coefficients			Odds Ratios		
	B	LCL	UCL	Exp(B)	Exp(LCL)	Exp(UCL)
Intercept	−1.82	−3.50	−0.19	0.16	0.03	0.82
GOSE	1.06	0.85	1.30	2.89	2.34	3.65
Pre-Injury Job Class (ref = Manager/Professional)						
Technician/Supervisor/Associate Professional	−0.25	−1.16	0.66	0.78	0.31	1.94
Clerk/Sales	0.11	−0.94	1.20	1.12	0.39	3.32
Skilled manual worker	−1.25	−2.10	−0.44	0.29	0.12	0.65
Manual worker	−1.14	−1.99	−0.32	0.32	0.14	0.73
Other	−0.97	−1.85	−0.12	0.38	0.16	0.89
Pre-Injury Employment Status (ref = Working Full-Time)						
Unemployed, looking for work	−2.96	−3.93	−2.03	0.05	0.02	0.13
Working Part-Time (20–34 h/week)	0.16	−0.65	0.99	1.17	0.52	2.70
Working Part-Time (<20 h/week)	−0.54	−1.71	0.73	0.58	0.18	2.07
Length Of Stay	−0.04	−0.05	−0.02	0.96	0.95	0.98
Age at Injury	−0.04	−0.06	−0.02	0.96	0.94	0.98

B = estimate; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit; Exp = Exponentiated; ref = reference category; GOSE = Glasgow Outcome Scale Extended.

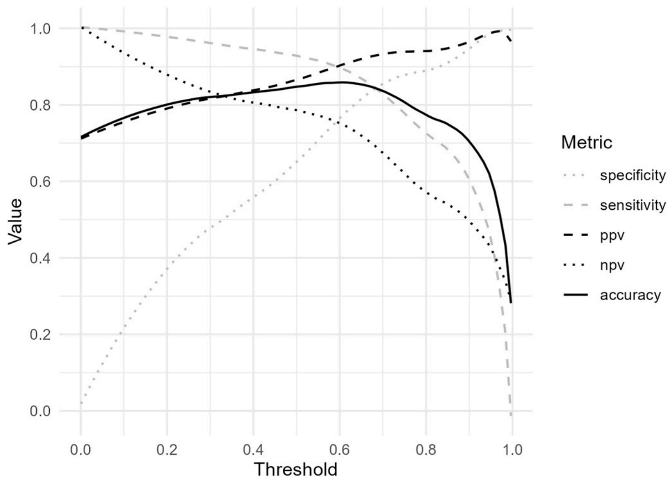

Fig. 4. Performance metrics across all possible thresholds (with slight LOESS smoothing).
PPV = Positive Predictive Value; NPV = Negative Predictive Value.

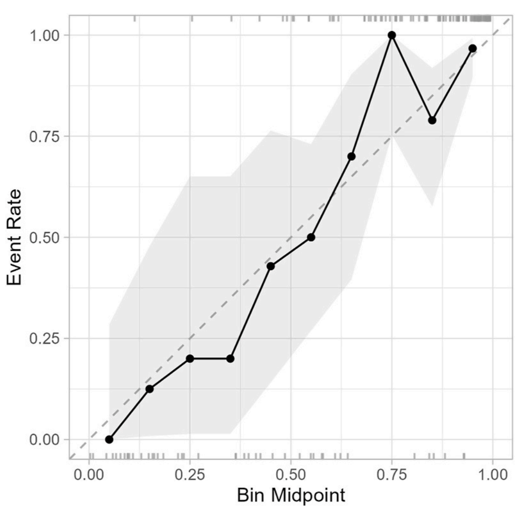

Fig. 5. Calibration plot. Interpretation aid: Among the individuals who had a predicted probability of X% to return to work, Y% actually returned to work.

4. Discussion

4.1. How can we make accurate predictions on employment outcome, and does this require follow-up data beyond hospitalization?

In general, it can be observed that the addition of three-month follow-up data to the full model is associated with a significant improvement of model performance across all modelling algorithms (see Digital Supplementary Content 2). Among the modelling algorithms tested in this study, the best predictions can be obtained by an elastic net logistic regression or a random forest algorithm. Preference was given to the logistic regression model over the random forest because of more transparency of the prediction mechanism. Surprisingly, the development of the reduced model showed that good predictions do not require a large number of predictors.

4.2. Which predictors are required to make accurate predictions?

Among acute hospitalization variables, LOS is the most important predictor. LOS is known to be affected by social determinants, which could also be relevant in this context.[14,15] However, the main explanation for the importance of LOS is that it can be considered a proxy variable for medical complexity and injury severity. The latter is also a highly important feature in our models. Similarly, acute injury severity is also represented in vital parameters (heart rate, blood pressure and oxygen saturation), whose feature importance ranks highly as well.

Older age is considered to be a barrier for return to work across different pathologies.[16] Specifically for TBI, a majority of studies found age to be associated with employment outcomes.[17] On the one hand, this can be explained by the general societal tendency towards a negative relation between employability and advancing age.[18,19] On the other hand, age is also associated with slower recovery and worse outcomes after TBI.[20,21]

The importance of pre-injury employment status to predict post-injury employment status is self-explanatory. As for pre-injury occupation, the fact that higher job levels are predictive of better outcomes has previously been explained by workers without stable qualifications or work experience pre-injury having more difficulty to reintegrate onto the labor market post-injury.[22]

When three-month follow-up is added, total GOSE score systematically becomes the most important predictor of one-year employment outcome. The feature importance of the full model and the substantial predictive accuracy of the univariable model, and the odds ratio (increase with factor 2.89 per point increase in GOSE) indicate the importance of the GOSE as a predictor for return to work. This is unsurprising, as return to work is only possible for the upper levels for the GOSE. General disability level can also be quantified using different scales, including the DRS, the FIM and the GOSE. Though measurements of these scales were not available in this study, other studies found evidence for each of these scales to be associated with employment outcomes after TBI.[17]

4.3. Are predictions accurate enough for use in clinical practice?

The calibration plot shows that the predicted probabilities match the actual probabilities of returning to work well. Given the relatively small hold-out dataset the plot was based on, some occasional deviations are less concerning than the general trend, which aligns well with the diagonal. This indicates that there is no systematic over- or underestimation of the actual probability of returning to work.

Fig. 4 shows that if a health practitioner wants to give a prognosis to a patient that is as predictive as possible (i.e., PPV + NPV as high as possible), the probability of the prediction being correct is somewhat over 80 % at a threshold of about 0.33. While this is far from a perfect prediction, this has some indicative value. Thus, the model can be used in a supportive role in clinical practice, as long as the characteristics of the sample of the current study can be considered similar to those of the target patient population and, therefore, generalizable. Fig. 4 and Digital Supplemental Content 4 allow the determination of a different optimal decision threshold if the health practitioner has another preference regarding the metrics to be maximized.

4.4. Limitations and suggestions for future research

A first limitation of this study concerns the fact that the hospitals where the CENTER-TBI data collection took place were mostly specialized trauma centers. Therefore, we have no information on the performance of our models for patients in more local hospitals. Despite the relatively large sample size of the complete CENTER-TBI project, the combination of the study inclusion criteria and the incompleteness of the follow-up data led to a substantial decrease in the available number of observations for this analysis. Given this limited number of patients, our robustness analysis showed a range for different model performance metrics depending on the data split. Additionally, a larger sample size would have resulted in more consistent model performance estimates.

The fact that the vastly reduced models perform at least as well as the full models indicates slight overfitting. Therefore, potential improvement of model performance could have been achieved through more customization of the used prediction algorithms rather than the use of off-the-shelf algorithms and the standard data science workflow. While this was beyond the scope of the current study, fine-tuning the desired behavior of the algorithms could potentially have improved the predictive performance by avoiding overfitting.

Despite good predictive performance, the models created in this work do not fully capture the underlying patterns related to unemployment one year after TBI. It is likely that this is in part caused by the limitations of the predictor set. CENTER-TBI contains an extensive and detailed collection of variables measured during hospitalization. It also comes with follow-up data, though in this analysis only an overall indication of functioning seemed to come forward. Furthermore, clinical datasets such as CENTER-TBI contain little to no information on more environmental factors, which are important when considering return to work outcomes. These can be specific to the direct environment of the patient, such as their support system and workplace characteristics.[23–25] Additionally, factors related to the economic circumstances as well as the services, systems and policies in the country of the individual are highly relevant as well.[23,24,26,27] Particularly in this study, where the utilized data were collected in 18 different countries, this is likely to have caused some of the remaining unexplained variation. Future research should explore these environmental factors further.

Finally, as this is a first modelling attempt, patients who did not have data on the outcome variable at one year post-injury were removed from the analysis which may have introduced bias.

5. Conclusion

This study highlights the predictive value of the GOSE for return to work. Though this scale is often not routinely administered in a care context, this work shows its value for prediction of employment outcomes. Therefore, it may be worthwhile the 10–15 min time it takes to fill out the GOSE questions for patients with TBI who are in the labor force pre-injury.

The reduced prediction model presented in this study can be used to make predictions on employment outcome with an AUC of 90 %. Depending on the goal of the predictions as well as the corresponding cost of false-negatives and false-positives, an appropriate decision threshold can be chosen based on Fig. 4 and the Digital Supplemental Content 4.

Return to work is often a key objective for rehabilitation as employment is an important aspect of community integration. Precise predictions about post-TBI vocational outcomes are therefore particularly relevant as a means of realistic goal setting. Adequate expectations are essential for the patient to be sufficiently informed to participate in the decision-making process concerning his or her treatment. Solid probability estimates provide the opportunity to target resources and efforts in terms of labor market integration programs towards those who have either the best chances of reaching stable employment or those who require extra support in order to obtain this goal.

Ethical approval statement

The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws of the country where the Recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the “Privacy Law”), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) (“ICH GCP”) and the World Medical Association Declaration of Helsinki entitled “Ethical Principles for Medical Research Involving Human Subjects”. Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. Ethical approval was obtained for each recruiting site. The list of sites, Ethical Committees, approval numbers and approval dates can be found on the website: https://www.center-tbi.eu/project/ethical-approval.

Methodology statement

Data for the CENTER-TBI study has been collected through the Quesgen e-CRF (Quesgen Systems Inc, USA), hosted on the INCF platform and extracted via the INCF Neurobot tool (INCF, Sweden). Version of July 2022 of the CENTER-TBI dataset was used in this manuscript.

Poster presentation disclosure

A premature version of the analysis in this article was presented at the ISPOR USA Conference 2023 and the NNS Neurotrauma Conference 2023.

Declaration of generative AI in scientific writing

During the preparation of this work the author(s) used ChatGPT and Quillbot in order to help with phrasing. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

CRediT authorship contribution statement

Helena Van Deynse: Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Wilfried Cools:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation. **Viktor-Jan De Deken:** Writing – review & editing, Validation, Methodology, Data curation. **Bart Depreitere:** Writing – review & editing, Validation, Supervision, Data curation. **Ives Hubloue:** Writing – review & editing, Validation, Supervision, Data curation. **Ellen Tisseghem:** Writing – review & editing, Validation, Data curation. **Koen Putman:** Writing – review & editing, Validation, Supervision, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dhjo.2024.101716.

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