Predictors of access to rehabilitation in the year following traumatic brain injury: a European prospective and multicenter study

Running title: Rehabilitation after TBI

Louis Jacob, PhD[a,b]; Mélanie Cogné, MD-PhD[c]; Olli Tenovuo, MD-PhD[d,e]; Cecilie Røe, MD[f,g]; Nada Andelic, MD-PhD[f,g]; Marek Majdan, PhD[h]; Jukka Ranta, PhD[i]; Peter Ylen, PhD[i]; Helen Dawes, PhD[j]; Philippe Azouvi, MD-PhD[k,l]; CENTER-TBI Participants and Investigators (**Appendix**)

[a] Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux 78180, France

[b] Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, Barcelona 08830, Spain

[c] University Hospital of Rennes, 2, rue Henri-le-Guilloux, Rennes 35000, France

[d] Turku Brain Injury Centre, Turku University Hospital, Turku, Finland

[e] Department of Clinical Neurosciences, University of Turku, Turku, Finland

[f] Department of Physical Medicine and Rehabilitation, Oslo University Hospital, Oslo, Norway

[g] Research Centre for Habilitation and Rehabilitation Models & Services (CHARM), Faculty of Medicine, University of Oslo, Oslo, Norway

[h] Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia

[i] VTT Technical Research Centre of Finland Ltd, Finland

[j] Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK

[k] Department of Physical Medicine and Rehabilitation, Raymond Poincaré Hospital, AP-HP, 104, boulevard Raymond-Poincaré, Garches 92380, France

[l] Université Paris-Saclay, UVSQ, Laboratoire de Recherches cliniques et en santé publique sur les handicaps psychique, cognitif et moteur, 78035, Versailles, France

Corresponding author:

Dr. Louis Jacob

Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines

2 avenue de la Source de la Bièvre, Montigny-le-Bretonneux 78180

France

Tel.: +33-(0)6-27-88-37-06

louis.jacob.contacts@gmail.com

Number of characters in the title (spaces included): 129

Number of characters in the running title (spaces included): 25

Number of words in the abstract: 245

Number of words in the main body of the article: 4,416

Number of references: 53

Number of figures: 3 [appended at end]

Number of tables: 1 [appended at end]

Number of supplementary files: 3 [appended at end]

Abstract

Background: Although rehabilitation is beneficial for individuals with traumatic brain injury (TBI), a significant proportion of them do not receive adequate rehabilitation after acute care.
Objective: Therefore, the goal of this prospective and multicenter study was to investigate predictors of access to rehabilitation in the year following injury in patients with TBI.
Methods: Data from a large European study (CENTER-TBI) including TBIs of all severities between December 2014 and December 2017 were used (N=4,498 patients). Participants were dichotomized into those who had and those who did not have access to rehabilitation in the year following TBI. Potential predictors included sociodemographic factors, psychoactive substance use, pre-injury medical history, injury-related factors, and factors related to medical care, complications and discharge.
Results: In the year following traumatic injury, 31.4% of patients received rehabilitation services. Access to rehabilitation was positively and significantly predicted by female sex (OR=1.50), increased number of years of education completed (OR=1.05), living in Northern (OR=1.62; reference: Western Europe) or Southern Europe (OR=1.74), lower pre-hospital Glasgow Coma Scale score (OR=1.03), higher Injury Severity Score (OR=1.01), intracranial (OR=1.33) and extracranial surgery (OR=1.99), and extracranial complication (OR=1.75). On contrast, significant negative predictors were lack of pre-injury employment (OR=0.80), living in Central and Eastern Europe (OR=0.42), and admission to hospital ward (OR=0.47; reference: admission to intensive care unit) or direct discharge from emergency room (OR=0.24).
Conclusions: Based on these findings, there is an urgent need to implement national and international guidelines and strategies for access to rehabilitation after TBI.

Keywords: traumatic brain injury; rehabilitation; predictive factors; international prospective study; Europe.

Introduction

Around 12% of people worldwide have a history of traumatic brain injury (TBI).[1] In Europe, the annual incidence of hospital-treated TBI is 262 cases per 100,000 persons, and the two most frequent causes are falls and road traffic accidents.[2] TBI is a leading cause of deaths worldwide,[3–5] and a risk factor for a wide range of chronic physical, cognitive, emotional, and psychiatric problems.[6] Furthermore, TBI is associated with decreased self-care, difficulties with social relationships and diminished quality of life.[7] Therefore, rehabilitation plays a major role in the management of TBI, and multidisciplinary rehabilitation interventions are often needed in the months following injury.

Based on the definition of the World Health Organization, rehabilitation is “a set of interventions designed to optimize functioning and reduce disability in individuals with a health condition who experience some form of limitation in functioning, across the continuum of care and throughout the lifespan”.[8] Rehabilitation may be undergone in inpatient (e.g., general rehabilitation unit, geriatric unit) and outpatient settings (e.g., community, outpatient clinic). Although rehabilitation is widely considered as beneficial for survivors of TBI,[9] a substantial proportion of patients do not receive adequate rehabilitation after acute care.[10,11] For example, a study including 508 patients with moderate-to-severe TBI from the Netherlands showed that discharge was home for 49% of the sample.[10] In the past years, several studies have investigated predictors of referral to rehabilitation in survivors from TBI.[12–17] A French study of 254 cases of severe TBI showed that living alone, low socioeconomic status, pre-injury alcohol abuse, low TBI severity [e.g., high Glasgow Outcome Scale (GOS) scores at acute care discharge], and transfer through a non-specialized medical ward before discharge were significant predictors for non-referral to rehabilitation.[13]

Another prospective study including 566 patients with severe TBI from Switzerland found that lower scores on the Glasgow Coma Scale (GCS) at admission and at 14 days, higher injury severity scores, and older age were positively associated with inpatient rehabilitation.[16] These previous studies have several limitations that need to be acknowledged. First, without an international setting,[12–17] the generalization of these previous findings may be limited. Second, the majority of these studies did not include patients with mild or moderate TBI,[13–16] and thus little is known about the predictors of access to rehabilitation in these populations. Third, previous research has failed to adjust for several factors that may impact the odds for rehabilitation [e.g., alcohol use,[12,15] psychiatric disorders,[12,15] area of injury (i.e., rural or urban)[12–17]]. Considering these limitations, new research is needed to gain a better understanding of predictors of access to rehabilitation in patients with TBI.

The present study is part of a larger European international prospective study, the CENTER-TBI study.[18] Our main objective was to investigate predictors of access to rehabilitation in the year following TBI. Because TBI is a major public health concern in Europe,[19] identifying factors that may impact access to rehabilitation in this region might help reduce the associated burden.

Methods

Study participants

Data from a large European project that aims to improve the care for patients with TBI (CENTER-TBI) were used.[18] Briefly, this was a prospective longitudinal observational study including 4,509 patients with TBI of all severities from countries across Europe and Israel.[18] As the present study focused on rehabilitation in European countries, patients from Israel were excluded (N=11), and the final sample consisted of 4,998 participants aged between 0 and 96 years (**Supplementary Figure 1**). Inclusion criteria were: i) presentation to one of the study sites (mostly level-1 trauma centers) within 24 hours of TBI; and ii) need for head computed tomography (decision based on standard clinical practices of the participating centers). TBI diagnosis was made at the discretion of the participating centers, and relied on the anamnesis, the clinical evaluation and paraclinical investigations. Exclusion criteria were severe pre-existing neurological disorders that would confound outcome assessments. Care pathways included three severity strata: intensive care unit (ICU) stratum (patients admitted to an ICU), admission stratum (patients admitted to a hospital ward) and emergency room (ER) stratum (patients directly discharged from ER). Lengths of follow-up differed between ICU and admission strata (i.e., 12 months) and ER stratum (i.e., six months). Data were collected between December 2014 and December 2017. Details about ethics approval can be found in previous CENTER-TBI publications.[20,21] Finally, the study followed STROBE guidelines (**Supplementary Table 1**), while the study registration number was NCT02210221 (https://clinicaltrials.gov/).

Data collection, handling and storage

Demographic and clinical data were collected using an online electronic form, and data were de-identified and stored on a secure database.[20] Data curation was done by a multidisciplinary data curation task force and the members of the Work Package 14. All CENTER-TBI variables are available at https://www.center-tbi.eu/data/dictionary (Data Dictionary).

Access to rehabilitation (dependent variable)

Access to inpatient or outpatient rehabilitation was assessed at 3, 6 and 12 months after injury. For the purpose of this study, patients were dichotomized into those who received and those who did not receive rehabilitation care (inpatient and/or outpatient rehabilitation) within the year following TBI (i.e., at 3, 6 or 12 months). Inpatient rehabilitation facilities included units specialized in TBI rehabilitation, general rehabilitation units, general long-term acute care units, and geriatric units. Outpatient rehabilitation included physical therapy, occupational therapy, psychological services, cognitive remediation, speech therapy, social work, recreational therapy, nursing services, independent living training, vocational services, peer mentoring, comprehensive day treatment, and home health. Outpatient rehabilitation was undergone in a variety of different settings (e.g., community, outpatient clinic) that were not documented in the database. Finally, neither inpatient nor outpatient rehabilitation included tele-rehabilitation.

Predictors of access to rehabilitation (independent variables)

Sociodemographic factors

Sociodemographic factors included sex (male or female), age (in years), marital status (not married/separated/divorced/widowed/other or married/living together), number of years of education completed, pre-injury employment (yes or no), and region (i.e., Western, Northern, Southern, Central and Eastern Europe). Following the EuroVoc classification,[22] Western Europe (N=2,308) included Austria (N=109), Belgium (N=315), France (N=115), Germany (N=185), Netherlands (N=1006), and the United Kingdom (N=578); Northern Europe (N=1,090) included Denmark (N=15), Finland (N=372), Latvia (N=105), Lithuania (N=45), Norway (N=419), and Sweden (N=134); Southern Europe (N=973) included Italy (N=560) and Spain (N=413); and Central and Eastern Europe (N=127) included Hungary (N=43), Romania (N=21) and Serbia (N=63).

Psychoactive substance use

Psychoactive substances included tobacco, alcohol, sedative drugs, cannabis, and other illicit drugs (current use of each of these substances: yes or no).

Pre-injury medical history

Factors related to pre-injury medical history were the American Society of Anaesthesiologists (ASA) Physical Status score,[23] any neurological condition (yes or no), any other somatic condition (yes or no), any psychiatric condition (yes or no), previous TBI (yes or no), use of beta-blockers (yes or no), and use of anticoagulants or platelet aggregation inhibitors (yes or no). The ASA score included four categories: I (a normal healthy patient), II (a patient with mild systemic disease), III (a patient with severe systemic disease), and IV (a patient with a severe systemic disease that is a constant threat to life). Any neurological condition included neurological diseases and neuropathic pain. Any other somatic condition included cardiovascular, developmental, endocrine, gastrointestinal, haematological, hepatic, musculoskeletal, oncologic, otorhinolaryngological, pulmonary, renal, and other diseases. Regarding previous TBI, patients were dichotomized in those with at least one previous TBI and those without any previous TBI.

Injury-related factors

Injury-related factors included geographical area of injury (urban or rural), injury intention (i.e., unintentional, intentional, undetermined), pre-hospital GCS score, and Injury Severity Score (ISS). The ISS is calculated as the sum of the squares of the three highest Abbreviated Injury Scale (AIS) scores.[24] The AIS, a scale used to describe patients' needs for treatment, has the following categories: minor (1; no treatment required), moderate (2;

requires outpatient treatment only), serious (3; requires inpatient treatment outside ICU), severe (4; requires observation and/or basic inpatient treatment inside ICU), critical (5; requires intubation, mechanical ventilation or vasopressors for blood pressure support), and unsurvivable (6; not survivable).[18] The ISS ranges from 0 to 75 with higher scores indicating more severe injuries, and the ISS is automatically assigned 75 if there is any injury with an AIS of 6.

Medical care, complications and discharge

The variables related to medical care, complications and discharge were stratum (i.e., admitted to ICU, admitted to hospital ward, directly discharged from ER), intracranial surgery (yes or no), extracranial surgery (yes or no), intracranial complication (yes or no), extracranial complication (yes or no), and GCS score at discharge. Stratum is a variable that depicts pathways of care following TBI but also an overall measure of injury severity. Patients were allocated to each stratum based on the initial medical decision, and they remained in the same stratum throughout the study. However, because of potential clinical worsening, it remains possible that individuals who had been initially discharged from ER were later admitted to hospital ward or ICU.

Statistical analyses

As there were approximatively 13% of missing data in the database, missing data were imputed using multiple imputation by chained equations (MICE).[25] Multiple imputation was preferred over single imputation because it allows the estimation of the distribution of plausible values for missing data.[26] It was hypothesized that missing data were missing at random (MAR), meaning that the propensity for a value to be missing was related to observed data but not missing data.[27] The number of imputed datasets was estimated using the prevalence of incomplete cases.[26] Thus, 80 and 70 datasets were imputed for the analyses including the overall sample and patients who had access to outpatient rehabilitation, respectively.

Differences in the sample characteristics between those who had and those who did not have access to rehabilitation in the year following injury were tested with chi-squared tests for categorical variables and Mann-Whitney tests for continuous variables (i.e., age, number of years of education completed, pre-hospital GCS score, ISS, GCS score at discharge). Mann-Whitney tests were used for continuous variables because the data were not normally distributed.

Logistic regression analyses were conducted to assess the association between potential predictors (independent variables) and access to rehabilitation in the year following injury (dependent variable). Because of the large number of potential predictors, independent variables included in the regression models were selected using a two-stage procedure. During the first stage, variables were preselected in the 80 imputed datasets separately using a Least Absolute Shrinkage and Selection Operator (LASSO) regression. Briefly, the LASSO regression is a method that shrinks unstable estimates towards zero and thus excludes irrelevant variables.[28] LASSO regression has been found to outperform other common variable selection methods (e.g., stepwise selection, best subset selection).[29] During the second stage, the number of preselections per variable was calculated, and variables that were preselected more than 60 times were considered as potential predictors. Given that the literature on the combination of the LASSO regression with multiple imputations is scarce, the previous cut-off was arbitrarily chosen to allow the selection of variables that were preselected in more than 75% of the imputed datasets, and to indirectly allow a relatively large number of potential predictors to be included in the regression analysis. Ten variables were finally included in the regression model: sex, number of years of education completed, pre-injury employment, region, pre-hospital GCS score, ISS, stratum, intracranial surgery, extracranial surgery, and extracranial complication. Among them, seven variables were preselected in all 80 imputed datasets. All variables were included in the models as categorical variables with the exception of number of years of education completed, pre-hospital GCS score and ISS, which were included as continuous variables. Sensitivity analyses were further conducted in different age groups (i.e., <18 years, 18-65 years, >65 years) and strata (i.e., admission to ICU, admission to hospital ward, direct discharge from emergency room) to study the replicability of the study findings in these subgroups. Adjusted regression models were conducted in each of the imputed datasets and results were subsequently pooled. Pooled results from the logistic regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

The statistical analysis was performed with R 3.6.2 (The R Foundation).[30] P-values were corrected using the Benjamini-Hochberg adjustment method, and p-values <0.05 were considered statistically significant.

Results

There were 4,498 patients included in this study. After multiple imputations, 67.0% were men and the median [interquartile range (IQR)] age was 50.0 (30.0-66.0) years (**Table 1**). The prevalence of rehabilitation within the year following TBI was 31.4% (inpatient rehabilitation: 17.8%; outpatient rehabilitation: 20.8%; both inpatient and outpatient rehabilitation: 7.2%), and was significantly different between the three strata (i.e., admitted to ICU: 48.3%; admitted to hospital ward: 19.2%; directly discharged from ER: 10.7%; p-value<0.001). Pre-injury employment, living in Northern or Southern Europe, no pre-injury use of beta-blockers, no pre-injury use of anticoagulants or platelet aggregation inhibitors, rural area of injury, undetermined injury intention (i.e., neither unintentional nor intentional), admission to ICU, intracranial surgery, extracranial surgery, intracranial complication, and extracranial complication were more frequent in patients who had than in those who did not have access to rehabilitation, while age, pre-hospital GCS score and GCS score at discharge were lower, and number of years of education completed and ISS higher in the group with rehabilitation than in the group without rehabilitation. The two most frequent inpatient rehabilitation facilities were units specialized in TBI rehabilitation (59.6%) and general rehabilitation units (43.2%; **Figure 1**), while the five most frequent types of outpatient rehabilitation were physical therapy (80.9%), occupational therapy (27.2%), psychological services (22.5%), cognitive remediation (20.9%), and speech therapy (20.9%; **Figure 2**). The results of the adjusted regression analysis including the 10 variables that were preselected using the LASSO procedure are displayed in **Figure 3**. Access to rehabilitation was positively and significantly predicted by female sex (OR=1.50), increased number of years of education completed [OR=1.05 (per one-unit increase in years)], living in Northern (OR=1.62; reference: Western Europe) or Southern Europe (OR=1.74), pre-hospital GCS score [OR=1.03 (per one-unit decrease in the total GCS score)], Injury Severity Score [OR=1.01 (per one-unit increase in the total ISS)], intracranial surgery (OR=1.33), extracranial surgery (OR=1.99), and extracranial complication (OR=1.75). On contrast, significant negative predictors were lack of pre-injury employment (OR=0.80), living in Central and Eastern Europe (OR=0.42), and admission to hospital ward (OR=0.47; reference: admission to intensive care unit) or discharge from emergency room (OR=0.24). Similar findings were overall obtained in patients aged 18-65 years (i.e., the working age population) and in those admitted in ICU (**Supplementary Table 2**).

Discussion

Main findings

The prevalence of rehabilitation in the year following injury was around 31% in this European study. Significant predictors of access to rehabilitation were sex, number of years of education completed, pre-injury employment, region, prehospital GCS score, ISS, stratum, intracranial surgery, extracranial surgery, and extracranial complication. To the best of our knowledge, this is the first international longitudinal observational study investigating predictors of access to rehabilitation in the year following TBI.

Interpretation of the findings

It was observed that access to rehabilitation in the year following TBI was relatively low, even for individuals with severe TBI. This is in line with recent single-country studies conducted in different settings.[10,11,13] In terms of the type of rehabilitation, the study results also concur with results from another secondary analysis of the PariS-TBI cohort,[14] and both studies identified physical therapy, occupational therapy, psychological services, cognitive remediation, and speech therapy as frequent types of rehabilitation after TBI. It remains however surprising that, although cognitive impairments and behavioural changes are major causes of disability after TBI,[31] access was lower for psychological services and cognitive remediation than for physical therapy in patients with TBI, and this raises concerns about the adequacy of available resources for the patients' needs. That being said, the reasons for the lack of rehabilitation were not documented in the present study, and factors other than adequacy of available resources (e.g., lack of referral to occupational and speech therapists, healthcare professionals' assumptions about the benefits of rehabilitation for a given individual, patient reluctance to undergo rehabilitation) may be important.

There was a significant association between several sociodemographic factors and the odds of rehabilitation in the year following injury. Female sex was positively associated with access to rehabilitation in patients with TBI. Given that previous research has yielded opposite results,[15,16] this finding must be interpreted with caution. However, previous studies included patients with severe TBI only, while statistical analyses were not adjusted for several confounding factors such as education and complications, and this may explain the discrepancy between this work and the literature. One hypothesis to explain the association between sex and access to rehabilitation is that men are less adherent to rehabilitation programs after TBI than women, and further studies are needed to test this hypothesis. This study further showed for the first time that educational attainment was positively associated with access to rehabilitation. As educational attainment also predicts functional recovery after moderate-to-severe TBI,[32] the present study suggests that the burden of TBI may be particularly high in people with a lower educational level. Moreover, having no pre-injury employment was a risk factor for not undergoing rehabilitation compared with having a pre-injury employment. This finding is in line with the literature,[13,15] and underlines potential inequalities by income levels and type of health insurance in the access to rehabilitation after TBI. In addition, given that unemployment is a risk factor for lack of social support,[33] it is possible that marginalization also plays a significant role in the relationship between pre-injury employment and the access to rehabilitation following TBI. The odds of rehabilitation were also higher in patients living in Southern or Northern Europe, and lower in those living in Central and Eastern Europe, rather than in those living in Western Europe. This may be explained by differences in the numbers of rehabilitation professionals and by differences in healthcare funding between European countries. Indeed, recent statistics indicate that the number of physiotherapists per 100,000 inhabitants is much lower in Central and Eastern European countries than in Western and Northern European countries,[34] while the most common payment systems for occupational therapy in primary care vary widely between these countries.[35] Another important finding of this study is that age was not included in the regression model after applying the two-stage variable selection procedure, and therefore was deemed not to be a potential predictor of access to rehabilitation in the year following TBI. This finding must be interpreted with caution as previous research has obtained opposite results.[12,15–17] However, previous research failed to adjust for pathways of care,[15] and it is reasonable to think that older adults are at a higher risk of not being admitted to ICU and thus at a higher risk of not having access to rehabilitation than younger adults.

One additional major predictor of rehabilitation in the year following TBI that was identified in this study was stratum (i.e., admission to ICU, admission to hospital ward, direct discharge from ER), which is an indirect measure of TBI severity. The present findings corroborate the results of a cohort study of a smaller sample size identifying transfer through a non-specialized medical ward before discharge as a risk factor for non-referral to rehabilitation (OR=0.08).[13] Another study of retrospective cohort design (N=10,443 patients with TBI) further showed that variables positively associated with the risk for being directly discharged home were young age, low Charlson Comorbidity Index, short length of stay in acute care, no special care day (i.e., no day spent in ICU), cause of injury other than motor vehicle collision, and rural location.[11] Finally, a retrospective study of 343 patients with moderate-to-severe TBI from the Netherlands found that one third of the sample was directly discharged home and that approximatively 26% of individuals returning home displayed unfavourable outcomes (i.e., cognitive, behavioural, physical).[36] Taking together, these findings suggest that pathways of care after TBI have a significant impact on the odds of undergoing rehabilitation in the months following injury, and that patients discharged home may be at a higher risk for no rehabilitation than those admitted to ICU and later discharged to rehabilitation units.

Another interesting result of this study is that prehospital GCS score, ISS, intracranial surgery, extracranial surgery, and extracranial complication positively predicted the odds of rehabilitation, suggesting that initial severity of clinical impairments, injury severity, polytrauma, and complications may have a long-term impact on the access to rehabilitation. Although recovery of consciousness following TBI may be a slow process,[37] previous research has indicated that a substantial proportion of patients with impaired consciousness who undergo rehabilitation are able to achieve functional independence in several domains (e.g., self-care, mobility, cognition) within the decade following TBI.[38] Rehabilitation interventions for patients in a minimally conscious state may focus on sensory stimulation, postural changes and the prevention of joint contractures.[39] In terms of injury severity and polytrauma, patients with TBI frequently have other lesions such as facial trauma and limb fracture.[40] TBI survivors with polytrauma are more likely to have access to rehabilitation compared to their counterparts with TBI only because other lesions may be responsible of additional functional limitations (e.g., dysphagia associated with facial trauma, limb fracture-related pain). Finally, the positive relationship of intracranial and extracranial surgery with rehabilitation may be explained by the severity of the initial injury itself, but also by the fact that these surgical procedures often require extended bed rest, and this can potentially have multiple deleterious effects on the body (e.g., undernutrition, sarcopenia, cardiorespiratory deconditioning).[41] Unfortunately, our current analysis was unable to define whether the rehabilitation delivered was because of TBI itself, intracranial/extracranial injuries, complications, or all of them.

Finally, the sensitivity analyses overall corroborated the study findings in people aged 18-65 years and in those admitted to ICU after brain injury. This suggests that these results may be extrapolated to the working age population and to patients with severe TBI. The fact that numerous associations were not significant anymore in other subgroups (i.e., patients admitted to hospital ward, those directly from emergency room, those aged <18 years, those aged >65 years) may be explained by the fact that the sample size of these subgroups was relatively small and the analyses might thus have lacked statistical power.

Implications and directions for future research

Given that rehabilitation is associated with several positive outcomes in TBI (e.g., increased attention,[42] return to independent functional status,[43] improved societal participation[44]), while TBI is a major cause of disability,[7] implementing strategies favouring rehabilitation after TBI at both national and international level is essential. One key initiative is to give patients with TBI the opportunity to undergo rehabilitation even if they are discharged home after acute care, and rehabilitation programs may be conducted in day hospital or home settings.[45] Some of these programs may incorporate tele-rehabilitation, which has recently been developed in both paediatric and adult TBI populations,[46,47] and this may help overcome the problem of access to specialized rehabilitation services. As neurobehavioral changes are frequent after TBI, and as patients may show poor self-awareness,[48] initiating early multidisciplinary rehabilitation may help patients better understand their needs and the potential interest of physical or occupational therapy. Furthermore, identifying patients who would benefit the most from rehabilitation is crucial, particularly in settings where the provision of rehabilitation services is limited. Health professionals should also bear in mind that male TBI patients and those with a low educational level or without pre-injury employment are at an increased risk for lack of rehabilitation, and thus sex, educational attainment and employment should be factors to take into account when identifying the most appropriate pathway of care for these patients. Finally, at the European level, measures should be taken to harmonize the management of patients with TBI across countries, while the education of rehabilitation professionals has to be extended and rehabilitation facilities to be implemented in regions with severely unmet needs (e.g., Central and Eastern Europe).[49] In terms of future research, further international studies are warranted to corroborate the presents findings, and to better understand the reasons for the lack of rehabilitation in a high proportion of patients with TBI (e.g., poor geographic access, financial barriers, lack of patient adherence, fragmented pathways of care). Moreover, since there are important differences between European neurotrauma centers in terms of structural and process characteristics of in-hospital acute rehabilitation and referral to post-acute rehabilitation facilities,[50,51] more studies are needed to better understand these differences and their potential impact on rehabilitation outcomes. Recent evidence suggests that rehabilitation following TBI should be early and intensive, while it should be undergone in specialized units.[52] Finally, new modalities of rehabilitation have recently emerged (e.g., exercise therapy), and it is important to shed light on the potential role played by these therapies in the overall management of TBI survivors.[53]

Strengths and limitations

The major strengths of this study are the use of data from 17 European countries and the large sample size. Nonetheless, this study has also some limitations. Given that there is no standardized definition for access to rehabilitation, it was arbitrary defined in the present study as access to inpatient and/or outpatient rehabilitation. Furthermore, there was a lack of data on the duration of rehabilitation, and more detailed data on rehabilitation would have also allowed better understanding of the reasons for the lack of rehabilitation. Besides, several potential predictors of interest (e.g., ethnicity, income, type of health insurance, early functional deficit or disability) were not included in the statistical analyses, while some of the data on rehabilitation relied on self-reports, and thus these data might have been subject to recall bias. In addition, this study only included patients presenting to study hospitals, which were all centers interested in neurotrauma, and thus it is possible that the access to rehabilitation is even worse elsewhere. Moreover, the stratum of those who were discharged from the ED was underrepresented in this sample and patients from this stratum were followed for six months only. It was also hypothesized that missing data was missing at random (MAR) and not missing not at random (MNAR), and this hypothesis may have impacted the multiple imputation of missing data and indirectly the present findings. Finally, to the best of the knowledge of the authors, there is no clear statistical guidance on how to select independent variables using LASSO regression in multiple imputed datasets, and the cut-off of 60 pre-selections was arbitrarily chosen.

Conclusions

About one-third of patients had access to rehabilitation in the year following TBI in the participating European countries, and in addition to expected factors, sex, number of years of education completed, pre-injury employment, and region of living were significantly associated with the odds of rehabilitation. Based on these results, there is an urgent need to implement national and international guidelines and strategies for access to rehabilitation after TBI. Further studies of prospective design are warranted to corroborate these findings in other settings.

Disclosures

Acknowledgments

Nothing to declare.

Funding

Data used in preparation of this manuscript were obtained in the context of CENTER-TBI, a large collaborative project with the support of the European Union 7th Framework program (EC grant 602150). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA) and from Integra LifeSciences Corporation (USA). Data for the CENTER-TBI study were collected through the Quesgen e-CRF (Quesgen Systems Inc, USA), hosted on the INCF platform and extracted via the INCF Neurobot tool (INCF, Sweden). The funder had no role in the study design, collection, analysis, and interpretation of the data; writing of the report; and the decision to submit the article for publication.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Contributors

Louis Jacob contributed to the design of the study, managed the literature searches, undertook the statistical analysis, wrote the first draft of the manuscript, and contributed to the correction of the manuscript. Mélanie Cogné, Olli Tenovuo, Cecilie Røe, Nada Andelic, Marek Majdan, Jukka Ranta, Peter Ylen, and Helen Dawes contributed to the design of the study and the correction of the manuscript. Philippe Azouvi contributed to the design of the study, managed the literature searches and contributed to the correction of the manuscript. All authors contributed to and have approved the final manuscript.

References

1. Frost RB, Farrer TJ, Primosch M, Hedges DW. Prevalence of traumatic brain injury in the general adult population: a meta-analysis. *Neuroepidemiology*. 2013;40:154–159.

2. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir. (Wien)*. 2015;157:1683–1696.

3. Martins ET, Linhares MN, Sousa DS, et al. Mortality in severe traumatic brain injury: a multivariated analysis of 748 Brazilian patients from Florianópolis City. *J. Trauma*. 2009;67:85–90.

4. Song SY, Lee SK, Eom KS. Analysis of Mortality and Epidemiology in 2617 Cases of Traumatic Brain Injury : Korean Neuro-Trauma Data Bank System 2010–2014. *J. Korean Neurosurg. Soc.* 2016;59:485–491.

5. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. *Morb. Mortal. Wkly. Rep. Surveill. Summ. Wash. DC 2002*. 2017;66:1–16.

6. Andelic N, Sigurdardottir S, Schanke A-K, Sandvik L, Sveen U, Roe C. Disability, physical health and mental health 1 year after traumatic brain injury. *Disabil. Rehabil.* 2010;32:1122–1131.

7. Ilie G, Adlaf EM, Mann RE, et al. Associations between self-reported lifetime history of traumatic brain injuries and current disability assessment in a population sample of Canadian adults. *PLoS ONE*. 2018;13. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5755742/. Accessed November 9, 2019.

8. Gimigliano F, Negrini S. The World Health Organization "Rehabilitation 2030: a call for action." *Eur. J. Phys. Rehabil. Med.* 2017;53:155–168.

9. Turner-Stokes L, Disler PB, Nair A, Wade DT. Multi-disciplinary rehabilitation for

acquired brain injury in adults of working age. *Cochrane Database Syst. Rev.* 2005:CD004170.

10. Andriessen TMJC, Horn J, Franschman G, et al. Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. *J. Neurotrauma*. 2011;28:2019–2031.

11. Chen AY, Zagorski B, Parsons D, Vander Laan R, Chan V, Colantonio A. Factors associated with discharge destination from acute care after acquired brain injury in Ontario, Canada. *BMC Neurol.* 2012;12:16.

12. Cuthbert JP, Corrigan JD, Harrison-Felix C, et al. Factors that predict acute hospitalization discharge disposition for adults with moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 2011;92:721-730.e3.

13. Jourdan C, Bayen E, Bosserelle V, et al. Referral to rehabilitation after severe traumatic brain injury: results from the PariS-TBI Study. *Neurorehabil. Neural Repair*. 2013;27:35–44.

14. Jourdan C, Bayen E, Darnoux E, et al. Patterns of post-acute health care utilization after a severe traumatic brain injury: Results from the PariS-TBI cohort. *Brain Inj.* 2015;29:701–708.

15. Odgaard L, Poulsen I, Kammersgaard LP, Johnsen SP, Nielsen JF. Surviving severe traumatic brain injury in Denmark: incidence and predictors of highly specialized rehabilitation. *Clin. Epidemiol.* 2015;7:225–234.

16. Schumacher R, Walder B, Delhumeau C, Müri RM. Predictors of inpatient (neuro)rehabilitation after acute care of severe traumatic brain injury: An epidemiological study. *Brain Inj.* 2016;30:1186–1193.

17. Vadlamani A, Perry JA, McCunn M, Stein DM, Albrecht JS. Racial Differences in Discharge Location After a Traumatic Brain Injury Among Older Adults. *Arch. Phys. Med. Rehabil.* 2019;100:1622–1628.

18. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma

Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery*. 2015;76:67–80.

19. James SL, Theadom A, Ellenbogen RG, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18:56–87.

20. Steyerberg EW, Wiegers E, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol.* 2019;18:923–934.

21. Zeiler FA, Ercole A, Cabeleira M, et al. Univariate comparison of performance of different cerebrovascular reactivity indices for outcome association in adult TBI: a CENTER-TBI study. *Acta Neurochir. (Wien)*. 2019;161:1217–1227.

22. Publications Office - European Union. EuroVoc thesaurus. 2019. Available at: https://op.europa.eu/fr/web/eu-vocabularies/th-dataset/-/resource/dataset/eurovoc.

23. Daabiss M. American Society of Anaesthesiologists physical status classification. *Indian J. Anaesth.* 2011;55:111–115.

24. Baker SP, O'Neill B, Haddon W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J. Trauma*. 1974;14:187–196.

25. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple Imputation by Chained Equations: What is it and how does it work? *Int. J. Methods Psychiatr. Res.* 2011;20:40–49.

26. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat. Med.* 2011;30:377–399.

27. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol. Methods*. 2002;7:147–177.

28. Walter S, Tiemeier H. Variable selection: current practice in epidemiological studies. *Eur.*

J. Epidemiol. 2009;24:733–736.

29. Strohmeier H, Scholte WF, Ager A. Factors associated with common mental health problems of humanitarian workers in South Sudan. *PLoS ONE*. 2018;13. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6209176/. Accessed November 11, 2019.

30. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019. Available at: https://www.R-project.org/.

31. Stenberg M, Godbolt AK, Nygren De Boussard C, Levi R, Stålnacke B-M. Cognitive Impairment after Severe Traumatic Brain Injury, Clinical Course and Impact on Outcome: A Swedish-Icelandic Study. *Behav. Neurol.* 2015;2015:680308.

32. Schneider EB, Sur S, Raymont V, et al. Functional recovery after moderate/severe traumatic brain injury: a role for cognitive reserve? *Neurology*. 2014;82:1636–1642.

33. Kong F, Perrucci CC, Perrucci R. The impact of unemployment and economic stress on social support. *Community Ment. Health J.* 1993;29:205–221.

34. Eurostat. Healthcare personnel statistics - dentists, pharmacists and physiotherapists. 2019. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php/Healthcare_personnel_statistics_-_dentists,_pharmacists_and_physiotherapists#Healthcare_personnel.

35. Bolt M, Ikking T, Baaijen R, Saenger S. Occupational therapy and primary care. *Prim. Health Care Res. Dev.* 2019;20. Available at: https://europepmc.org/articles/PMC6476805/. Accessed November 12, 2019.

36. de Koning ME, Spikman JM, Coers A, Schönherr MC, van der Naalt J. Pathways of care the first year after moderate and severe traumatic brain injury-discharge destinations and outpatient follow-up. *Brain Inj.* 2015;29:423–429.

37. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends*

Neurosci. 2010;33:1–9.

38. Hammond FM, Giacino JT, Nakase Richardson R, et al. Disorders of Consciousness due to Traumatic Brain Injury: Functional Status Ten Years Post-Injury. *J. Neurotrauma*. 2019;36:1136–1146.

39. Elliott L, Walker L. Rehabilitation interventions for vegetative and minimally conscious patients. *Neuropsychol. Rehabil.* 2005;15:480–493.

40. Groswasser Z, Cohen M, Blankstein E. Polytrauma associated with traumatic brain injury: incidence, nature and impact on rehabilitation outcome. *Brain Inj.* 1990;4:161–166.

41. Dittmer DK, Teasell R. Complications of immobilization and bed rest. Part 1: Musculoskeletal and cardiovascular complications. *Can. Fam. Physician*. 1993;39:1428–1437.

42. Couillet J, Soury S, Lebornec G, et al. Rehabilitation of divided attention after severe traumatic brain injury: a randomised trial. *Neuropsychol. Rehabil.* 2010;20:321–339.

43. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet Lond. Engl.* 2009;373:1874–1882.

44. Malec JF. Impact of comprehensive day treatment on societal participation for persons with acquired brain injury. *Arch. Phys. Med. Rehabil.* 2001;82:885–895.

45. Doig E, Fleming J, Kuipers P, Cornwell P, Khan A. Goal-directed outpatient rehabilitation following TBI: a pilot study of programme effectiveness and comparison of outcomes in home and day hospital settings. *Brain Inj.* 2011;25:1114–1125.

46. Ownsworth T, Arnautovska U, Beadle E, Shum DHK, Moyle W. Efficacy of Telerehabilitation for Adults With Traumatic Brain Injury: A Systematic Review. *J. Head Trauma Rehabil.* 2018;33:E33–E46.

47. Corti C, Oldrati V, Oprandi MC, et al. Remote Technology-Based Training Programs for

Children with Acquired Brain Injury: A Systematic Review and a Meta-Analytic Exploration. *Behav. Neurol.* 2019;2019:1346987.

48. Arnould A, Dromer E, Rochat L, Van der Linden M, Azouvi P. Neurobehavioral and self-awareness changes after traumatic brain injury: Towards new multidimensional approaches. *Ann. Phys. Rehabil. Med.* 2016;59:18–22.

49. Eldar R, Kullmann L, Marincek C, Sekelj-Kauzlarić K, Svestkova O, Palat M. Rehabilitation medicine in countries of Central/Eastern Europe. *Disabil. Rehabil.* 2008;30:134–141.

50. Cnossen MC, Lingsma HF, Tenovuo O, et al. Rehabilitation after traumatic brain injury: A survey in 70 European neurotrauma centres participating in the CENTER-TBI study. *J. Rehabil. Med.* 2017;49:395–401.

51. Tverdal CB, Howe EI, Røe C, et al. Traumatic brain injury: Patient experience and satisfaction with discharge from trauma hospital. *J. Rehabil. Med.* 2018;50:505–513.

52. Oberholzer M, Müri RM. Neurorehabilitation of Traumatic Brain Injury (TBI): A Clinical Review. *Med. Sci. Basel Switz.* 2019;7.

53. Morris T, Gomes Osman J, Tormos Muñoz JM, Costa Miserachs D, Pascual Leone A. The role of physical exercise in cognitive recovery after traumatic brain injury: A systematic review. *Restor. Neurol. Neurosci.* 2016;34:977–988.

The CENTER-TBI participants and investigators:

Cecilia Åkerlund[1], Krisztina Amrein[2], Lasse Andreassen[3], Audny Anke[4], Anna Antoni[5], Gérard Audibert[6], Maria Luisa Azzolini[7], Ronald Bartels[8], Pál Barzó[9], Romuald Beauvais[10], Ronny Beer[11], Bo-Michael Bellander[12], Antonio Belli[13], Habib Benali[14], Maurizio Berardino[15], Luigi Beretta[7], Morten Blaabjerg[16], Peter Bragge[17], Alexandra Brazinova[18], Vibeke Brinck[19], Joanne Brooker[20], Camilla Brorsson[21], Andras Buki[22], Monika Bullinger[23], Manuel Cabeleira[24], Alessio Caccioppola[25], Emiliana Calappi[25], Maria Rosa Calvi[7], Peter Cameron[26], Guillermo Carbayo Lozano[27], Marco Carbonara[25], Simona Cavallo[15], Giorgio Chevallard[28], Arturo Chieregato[28], Giuseppe Citerio[29,30], Iris Ceyisakar[31], Hans Clusmann[32], Mark Coburn[33], Jonathan Coles[34], Jamie D. Cooper[35], Marta Correia[36], Amra Čović [37], Nicola Curry[38], Endre Czeiter[22], Marek Czosnyka[24], Claire Dahyot-Fizelier[39], Paul Dark[40], Véronique De Keyser[41], Vincent Degos[14], Francesco Della Corte[42], Hugo den Boogert[8], Bart Depreitere[43], Đula Đilvesi [44], Abhishek Dixit[45], Emma Donoghue[20], Jens Dreier[46], Guy-Loup Dulière[47], Ari Ercole[45], Patrick Esser[40], Erzsébet Ezer[48], Martin Fabricius[49], Valery L. Feigin[50], Kelly Foks[51], Shirin Frisvold[52], Alex Furmanov[53], Pablo Gagliardo[54], Damien Galanaud[14], Dashiell Gantner[26], Guoyi Gao[55], Pradeep George[56], Alexandre Ghuysen[57], Lelde Giga[58], Ben Glocker[59], Jagoš Golubovic[44], Pedro A. Gomez [60], Johannes Gratz[61], Benjamin Gravesteijn[31], Francesca Grossi[42], Russell L. Gruen[62], Deepak Gupta[63], Juanita A. Haagsma[31], Iain Haitsma[64], Raimund Helbok[11], Eirik Helseth[65], Lindsay Horton [66], Jilske Huijben[31], Peter J. Hutchinson[67], Bram Jacobs[68], Stefan Jankowski[69], Mike Jarrett[19], Ji-yao Jiang[55], Faye Johnson[70], Kelly Jones[50], Mladen Karan[44], Angelos G. Kolias[67], Erwin Kompanje[71], Daniel Kondziella[49], Evgenios Koraropoulos[45], Lars-Owe Koskinen[72], Noémi Kovács[73], Ana Kowark[33], Alfonso Lagares[60], Linda Lanyon[56], Steven Laureys[74], Fiona Lecky[75,76], Didier Ledoux[74], Rolf Lefering[77], Valerie Legrand[78], Aurelie Lejeune[79], Leon

Levi[80], Roger Lightfoot[81], Hester Lingsma[31], Andrew I.R. Maas[41], Ana M. Castaño-León[60], Marc Maegele[82], Alex Manara[83], Geoffrey Manley[84], Costanza Martino[85], Hugues Maréchal[47], Julia Mattern[86], Catherine McMahon[87], Béla Melegh[88], David Menon[45], Tomas Menovsky[41], Ana Mikolic[31], Benoit Misset[74], Visakh Muraleedharan[56], Lynnette Murray[26], Ancuta Negru[89], David Nelson[1], Virginia Newcombe[45], Daan Nieboer[31], József Nyirádi[2], Otesile Olubukola[75], Matej Oresic[90], Fabrizio Ortolano[25], Aarno Palotie[91, 92, 93], Paul M. Parizel[94], Jean-François Payen[95], Natascha Perera[10], Vincent Perlbarg[14], Paolo Persona[96], Wilco Peul[97], Anna Piippo-Karjalainen[98], Matti Pirinen[91], Horia Ples[89], Suzanne Polinder[31], Inigo Pomposo[27], Jussi P. Posti[99], Louis Puybasset[100], Andreea Radoi[101], Arminas Ragauskas[102], Rahul Raj[98], Malinka Rambadagalla[103], Jonathan Rhodes[104], Sylvia Richardson[105], Sophie Richter[45], Samuli Ripatti[91], Saulius Rocka[102], Olav Roise[106,107], Jonathan Rosand[108], Jeffrey V. Rosenfeld[109], Christina Rosenlund[110], Guy Rosenthal[53], Rolf Rossaint[33], Sandra Rossi[96], Daniel Rueckert[59], Martin Rusnák[111], Juan Sahuquillo[101], Oliver Sakowitz[86,112], Renan Sanchez-Porras[112], Janos Sandor[113], Nadine Schäfer[77], Silke Schmidt[114], Herbert Schoechl[115], Guus Schoonman[116], Rico Frederik Schou[117], Elisabeth Schwendenwein[5], Charlie Sewalt[31], Toril Skandsen[118,119], Peter Smielewski[24], Abayomi Sorinola[120], Emmanuel Stamatakis[45], Simon Stanworth[38], Robert Stevens[121], William Stewart[122], Ewout W. Steyerberg[31,123], Nino Stocchetti[124], Nina Sundström[125], Anneliese Synnot[20,126], Riikka Takala[127], Viktória Tamás[120], Tomas Tamosuitis[128], Mark Steven Taylor[18], Braden Te Ao[50], Alice Theadom[50], Matt Thomas[83], Dick Tibboel[129], Marjolein Timmers[71], Christos Tolias[130], Tony Trapani[26], Cristina Maria Tudora[89], Peter Vajkoczy [131], Shirley Vallance[26], Egils Valeinis[58], Zoltán Vámos[48], Mathieu van der Jagt[132], Gregory Van der Steen[41], Joukje van der Naalt[68], Jeroen T.J.M. van Dijck[97], Thomas A. van Essen[97], Wim Van Hecke[133], Caroline van Heugten[134], Dominique Van Praag[135], Thijs Vande Vyvere[133], Roel P. J. van Wijk[97], Alessia Vargiolu[30], Emmanuel Vega[79], Kimberley Velt[31], Jan Verheyden[133], Paul M. Vespa[136], Anne Vik[117,137], Rimantas Vilcinis[128], Victor Volovici[64], Nicole von Steinbüchel[37], Daphne Voormolen[31], Petar Vulekovic[44], Kevin K.W. Wang[138], Eveline Wiegers[31], Guy Williams[45], Lindsay Wilson[66], Stefan Winzeck[45], Stefan Wolf[139], Zhihui Yang[138], Alexander Younsi[86], Frederick A. Zeiler[45,140], Veronika Zelinkova[18], Agate Ziverte[58], Tommaso Zoerle[25]

[1] Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden

[2] János Szentágothai Research Centre, University of Pécs, Pécs, Hungary

[3] Department of Neurosurgery, University Hospital Northern Norway, Tromso, Norway

[4] Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway, Tromso, Norway

[5] Trauma Surgery, Medical University Vienna, Vienna, Austria

[6] Department of Anesthesiology & Intensive Care, University Hospital Nancy, Nancy, France

[7] Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy

[8] Department of Neurosurgery, Radboud University Medical Center, Nijmegen, The Netherlands

[9] Department of Neurosurgery, University of Szeged, Szeged, Hungary

[10] International Projects Management, ARTTIC, Munchen, Germany

[11] Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria

[12] Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska University Hospital, Stockholm, Sweden

[13] NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK

[14] Anesthesie-Réanimation, Assistance Publique – Hopitaux de Paris, Paris, France

[15] Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino - Orthopedic and Trauma Center, Torino, Italy

[16] Department of Neurology, Odense University Hospital, Odense, Denmark

[17] BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Victoria, Australia

[18] Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia

[19] Quesgen Systems Inc., Burlingame, California, USA

[20] Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

[21] Department of Surgery and Perioperative Science, Umeå University, Umeå, Sweden

[22] Department of Neurosurgery, Medical School, University of Pécs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Hungary

[23] Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

[24] Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

[25] Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[26] ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia

[27] Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain

[28] NeuroIntensive Care, Niguarda Hospital, Milan, Italy

[29] School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy

[30] NeuroIntensive Care, ASST di Monza, Monza, Italy

[31] Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands

[32] Department of Neurosurgery, Medical Faculty RWTH Aachen University, Aachen, Germany

[33] Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany

[34] Department of Anesthesia & Neurointensive Care, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK

[35] School of Public Health & PM, Monash University and The Alfred Hospital, Melbourne, Victoria, Australia

[36] Radiology/MRI department, MRC Cognition and Brain Sciences Unit, Cambridge, UK

[37] Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany

[38] Oxford University Hospitals NHS Trust, Oxford, UK

[39] Intensive Care Unit, CHU Poitiers, Potiers, France

[40] University of Manchester NIHR Biomedical Research Centre, Critical Care Directorate, Salford Royal Hospital NHS Foundation Trust, Salford, UK

[41] Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium

[42] Department of Anesthesia & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy

[43] Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium

[44] Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

[45] Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

[46] Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[47] Intensive Care Unit, CHR Citadelle, Liège, Belgium

[48] Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary

[49] Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark

[50] National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand

[51] Department of Neurology, Erasmus MC, Rotterdam, the Netherlands

[52] Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromso, Norway

[53] Department of Neurosurgery, Hadassah-hebrew University Medical center, Jerusalem, Israel

[54] Fundación Instituto Valenciano de Neurorrehabilitación (FIVAN), Valencia, Spain

[55] Department of Neurosurgery, Shanghai Renji hospital, Shanghai Jiaotong University/school of medicine, Shanghai, China

[56] Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden

[57] Emergency Department, CHU, Liège, Belgium

[58] Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia

[59] Department of Computing, Imperial College London, London, UK

[60] Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain

[61] Department of Anesthesia, Critical Care and Pain Medicine, Medical University of Vienna, Austria

[62] College of Health and Medicine, Australian National University, Canberra, Australia

[63] Department of Neurosurgery, Neurosciences Centre & JPN Apex trauma centre, All India Institute of Medical Sciences, New Delhi-110029, India

[64] Department of Neurosurgery, Erasmus MC, Rotterdam, the Netherlands

[65] Department of Neurosurgery, Oslo University Hospital, Oslo, Norway

[66] Division of Psychology, University of Stirling, Stirling, UK

[67] Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital & University of Cambridge, Cambridge, UK

[68] Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

[69] Neurointensive Care , Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[70] Salford Royal Hospital NHS Foundation Trust Acute Research Delivery Team, Salford, UK

[71] Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

[72] Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden

[73] Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-II/8, University of Pécs, Pécs, Hungary

[74] Cyclotron Research Center , University of Liège, Liège, Belgium

[75] Centre for Urgent and Emergency Care Research (CURE), Health Services Research Section, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

[76] Emergency Department, Salford Royal Hospital, Salford UK

[77] Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany

[78] VP Global Project Management CNS, ICON, Paris, France

[79] Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France

[80] Department of Neurosurgery, Rambam Medical Center, Haifa, Israel

[81] Department of Anesthesiology & Intensive Care, University Hospitals Southhampton NHS Trust, Southhampton, UK

[82] Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany

[83] Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK

[84] Department of Neurological Surgery, University of California, San Francisco, California, USA

[85] Department of Anesthesia & Intensive Care,M. Bufalini Hospital, Cesena, Italy

[86] Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany

[87] Department of Neurosurgery, The Walton centre NHS Foundation Trust, Liverpool, UK

[88] Department of Medical Genetics, University of Pécs, Pécs, Hungary

[89] Department of Neurosurgery, Emergency County Hospital Timisoara , Timisoara, Romania

[90] School of Medical Sciences, Örebro University, Örebro, Sweden

[91] Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland

[92] Analytic and Translational Genetics Unit, Department of Medicine; Psychiatric & Neurodevelopmental Genetics Unit, Department of Psychiatry; Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

[93] Program in Medical and Population Genetics; The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, MA, USA

[94] Department of Radiology, University of Antwerp, Edegem, Belgium

[95] Department of Anesthesiology & Intensive Care, University Hospital of Grenoble, Grenoble, France

[96] Department of Anesthesia & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy

[97] Dept. of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Dept. of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands

[98] Department of Neurosurgery, Helsinki University Central Hospital

[99] Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland

[100] Department of Anesthesiology and Critical Care, Pitié -Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France

[101] Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute, Barcelona, Spain

[102] Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania

[103] Department of Neurosurgery, Rezekne Hospital, Latvia

[104] Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburg, Edinburgh, UK

[105] Director, MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK

[106] Division of Orthopedics, Oslo University Hospital, Oslo, Norway

[107] Institue of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

[108] Broad Institute, Cambridge MA Harvard Medical School, Boston MA, Massachusetts General Hospital, Boston MA, USA

[109] National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia

[110] Department of Neurosurgery, Odense University Hospital, Odense, Denmark

[111] International Neurotrauma Research Organisation, Vienna, Austria

[112] Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany

[113] Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary

[114] Department Health and Prevention, University Greifswald, Greifswald, Germany

[115] Department of Anaesthesiology and Intensive Care, AUVA Trauma Hospital, Salzburg, Austria

[116] Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands

[117] Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark

[118] Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway

[119] Department of Physical Medicine and Rehabilitation, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[120] Department of Neurosurgery, University of Pécs, Pécs, Hungary

[121] Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, USA

[122] Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK

[123] Dept. of Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

[124] Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy

[125] Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden

[126] Cochrane Consumers and Communication Review Group, Centre for Health Communication and Participation, School of Psychology and Public Health, La Trobe University, Melbourne, Australia

[127] Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland

[128] Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania

[129] Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands

[130] Department of Neurosurgery, Kings college London, London, UK

[131] Neurologie, Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany

[132] Department of Intensive Care Adults, Erasmus MC– University Medical Center Rotterdam, Rotterdam, the Netherlands

[133] icoMetrix NV, Leuven, Belgium

[134] Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK

[135] Psychology Department, Antwerp University Hospital, Edegem, Belgium

[136] Director of Neurocritical Care, University of California, Los Angeles, USA

[137] Department of Neurosurgery, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[138] Department of Emergency Medicine, University of Florida, Gainesville, Florida, USA

[139] Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[140] Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

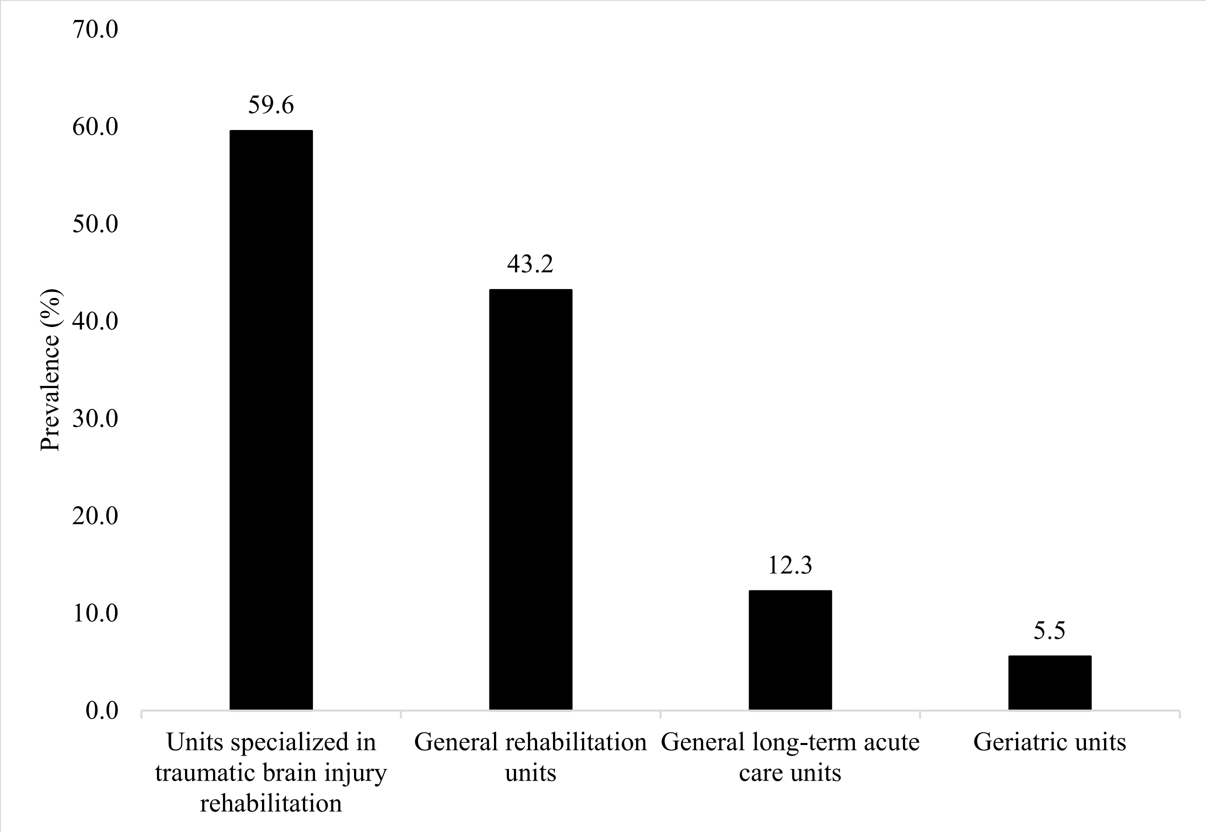


Figure 1. Types of medical units involved in the inpatient rehabilitation of patients with traumatic brain injury

Access to rehabilitation was assessed in the year following traumatic brain injury.
This analysis was restricted to individuals who had access to inpatient rehabilitation (N=685).
There was no missing value in the variables of interest and therefore no multiple imputations were needed.
Since participants may have undergone inpatient rehabilitation in several healthcare units (e.g., units specialized in traumatic brain injury rehabilitation, general rehabilitation units), total sum overreaches 100%.

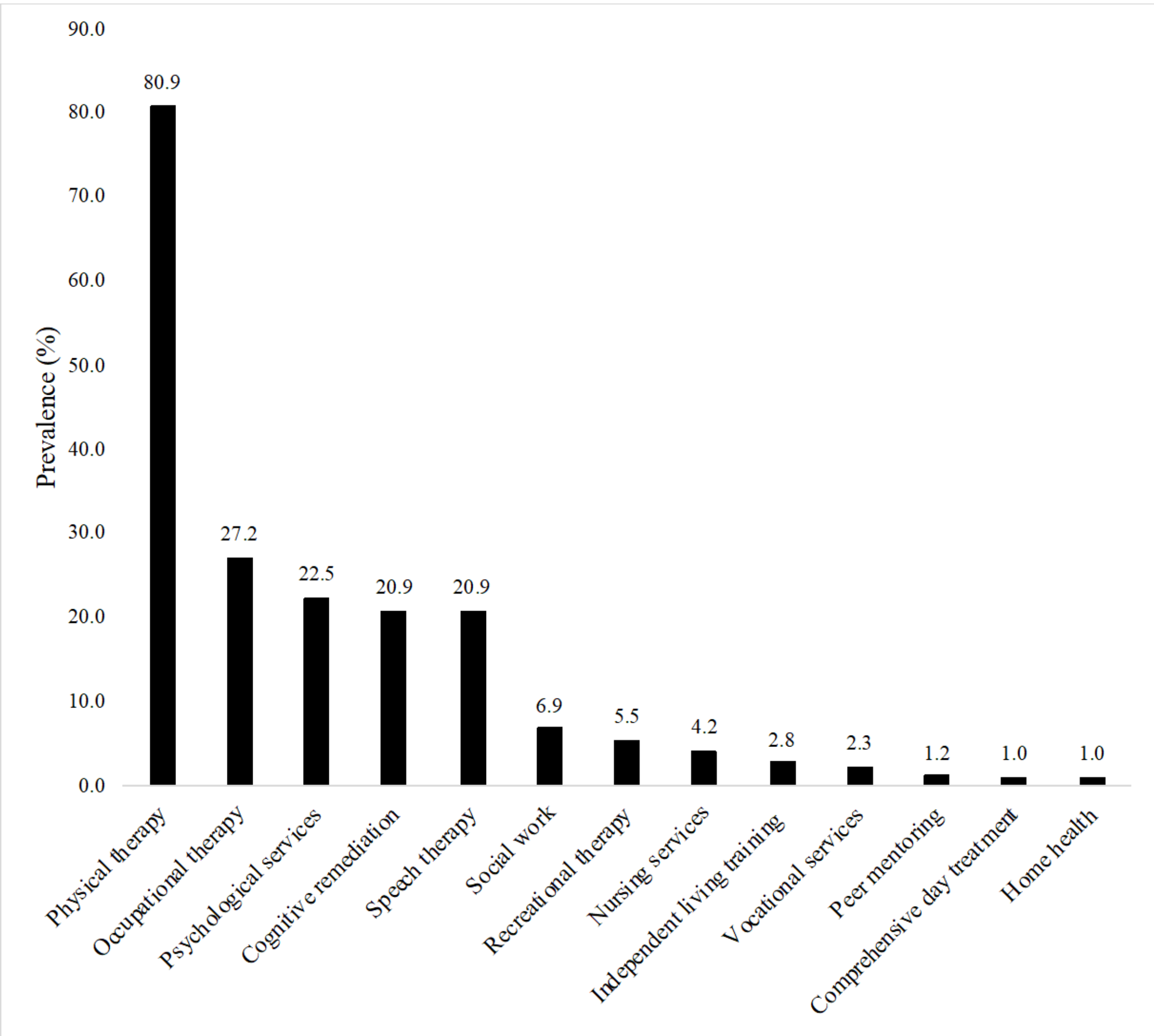


Figure 2. Types of outpatient rehabilitation in patients with traumatic brain injury

Access to rehabilitation was assessed in the year following traumatic brain injury.
This analysis was restricted to individuals who had access to outpatient rehabilitation (N=810).
Seventy datasets were imputed by chained equations. The number of imputed datasets was estimated using the proportion of individuals with at least one missing value (70%).
Since participants may have undergone different types of outpatient rehabilitation, total sum overreaches 100%.

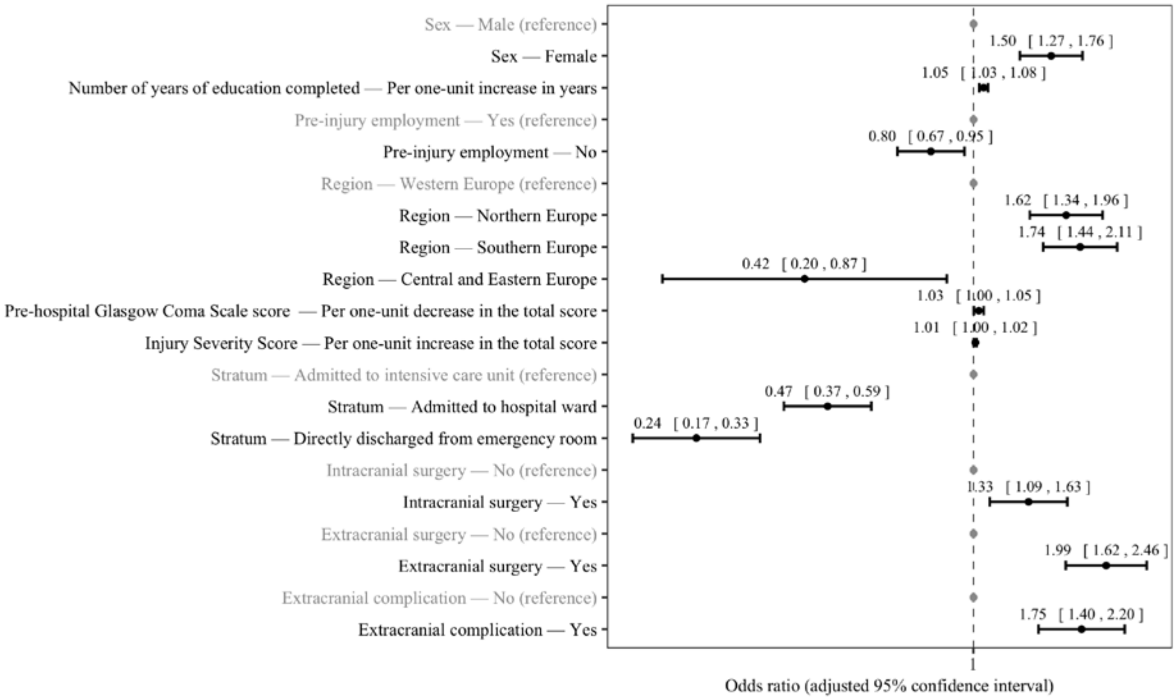


Figure 3. Predictors of rehabilitation in the year following the injury in patients with traumatic brain injury (LASSO penalized logistic regression)

Abbreviation: LASSO Least Absolute Shrinkage and Selection Operator.
Rehabilitation was assessed in the year following traumatic brain injury.
Eighty datasets were imputed by chained equations. The number of imputed datasets was estimated using the proportion of individuals with at least one missing value (77%).
The selection of independent variables included in the regression model relied on a two-stage method. During the first stage, variables were preselected in the 80 imputed datasets separately using a LASSO procedure. During the second stage, the number of preselections per variable was calculated, and variables with more than 60 preselections were arbitrarily considered as potential predictors. Ten variables were included in regression models.
The multivariate regression model was conducted in each of the imputed datasets and results were subsequently pooled.
Confidence intervals were corrected using the Benjamini-Yekutieli adjustment method.

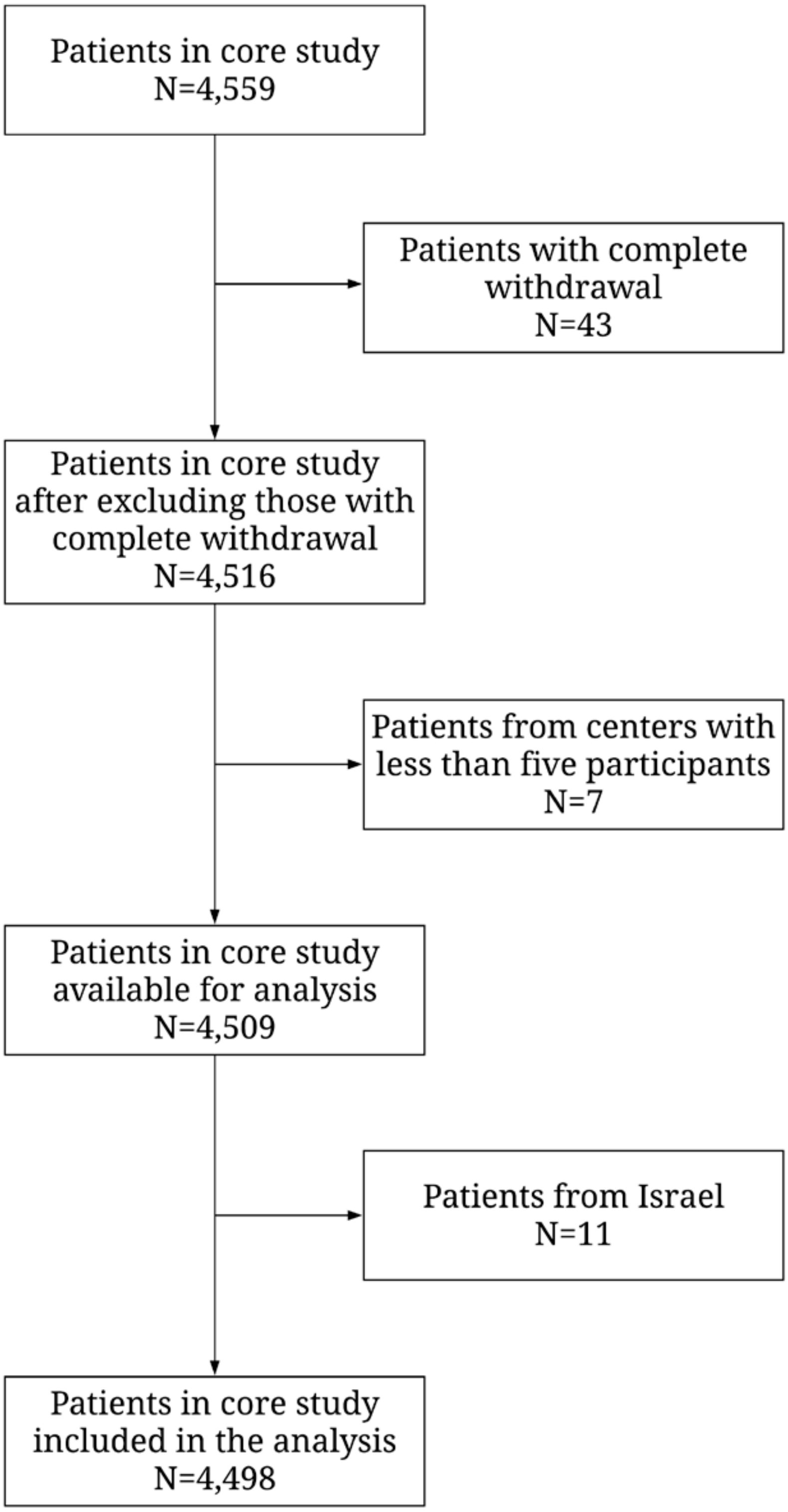
Table 1. Sample characteristics before and after multiple imputations (overall and by rehabilitation status)

Characteristics	Category	Prior to multiple imputations				After multiple imputations				Missing values
			Rehabilitation				Rehabilitation			
		Overall	No	Yes	P-value	Overall	No	Yes	P-value	
Sociodemographic factors										
Sex	Male	67.0	67.5	66.9	0.744	67.0	67.2	66.7	0.744	0.0
	Female	33.0	32.5	33.1		33.0	32.8	33.3		
Age (years)	**Median (interquartile range)**	**50.0 (30.0-66.0)**	**49.0 (29.0-66.0)**	**47.0 (29.0-61.0)**	**0.013**	**50.0 (30.0-66.0)**	**51.0 (30.0-67.1)**	**48.9 (29.5-64.0)**	**0.032**	**0.0**
Marital status	Not married/separated/divorced/widowed/other	49.3	50.4	48.9	0.525	49.1	49.6	48.0	0.469	9.6
	Married/living together	50.7	49.6	51.1		50.9	50.4	52.0		
Number of years of education completed	**Median (interquartile range)**	**13.0 (10.0-16.0)**	**12.0 (10.0-16.0)**	**13.0 (11.0-16.0)**	**<0.001**	**12.2 (10.0-16.0)**	**12.0 (10.0-15.5)**	**13.0 (10.9-16.0)**	**<0.001**	**28.8**
Pre-injury employment	**No**	**50.4**	**51.7**	**42.4**	**<0.001**	**50.5**	**52.9**	**45.3**	**<0.001**	**11.8**
	Yes	**49.6**	**48.3**	**57.6**		**49.5**	**47.1**	**54.7**		
Region	**Western Europe**	**51.3**	**53.1**	**44.3**	**<0.001**	**51.3**	**53.7**	**46.0**	**<0.001**	**0.0**
	Northern Europe	**24.2**	**23.7**	**25.2**		**24.2**	**23.7**	**25.3**		
	Southern Europe	**21.6**	**19.6**	**30.1**		**21.6**	**18.9**	**27.7**		
	Central and Eastern Europe	**2.8**	**3.6**	**0.3**		**2.8**	**3.7**	**0.9**		
Psychoactive substances (current use)										
Tobacco	No	69.8	70.5	68.7	0.403	69.0	69.7	67.4	0.295	19.5
	Yes	30.2	29.5	31.3		31.0	30.3	32.6		
Alcohol	No	63.2	62.9	65.6	0.242	63.0	62.3	64.7	0.292	19.5
	Yes	36.8	37.1	34.4		37.0	37.7	35.3		
Sedative drugs	No	92.5	93.2	92.2	0.451	91.9	92.3	91.1	0.391	21.2
	Yes	7.5	6.8	7.8		8.1	7.7	8.9		
Cannabis	No	95.3	95.7	94.0	0.069	94.7	95.2	93.6	0.111	20.8
	Yes	4.7	4.3	6.0		5.3	4.8	6.4		
Other illicit drugs	No	98.0	98.1	97.8	0.655	97.4	97.6	96.9	0.445	20.9
	Yes	2.0	1.9	2.2		2.6	2.4	3.1		

Pre-injury medical history										
ASA score	I	57.2	58.6	60.4	0.542	57.4	56.9	58.4	0.725	3.0
	II	32.2	31.8	31.0		32.1	32.4	31.5		
	III	9.9	8.9	8.3		9.8	9.9	9.5		
	IV	0.7	0.7	0.3		0.7	0.8	0.6		
Neurological condition	No	87.9	88.2	88.8	0.655	87.9	87.8	88.3	0.665	3.0
	Yes	12.1	11.8	11.2		12.1	12.2	11.7		
Other somatic condition	No	44.0	44.6	45.7	0.655	44.0	43.7	44.7	0.655	0.7
	Yes	56.0	55.4	54.3		56.0	56.3	55.3		
Psychiatric condition	No	86.2	86.4	87.1	0.659	86.1	85.9	86.4	0.677	3.5
	Yes	13.8	13.6	12.9		13.9	14.1	13.6		
Previous traumatic brain injury	No	90.3	89.7	90.9	0.391	90.2	89.8	91.0	0.391	7.8
	Yes	9.7	10.3	9.1		9.8	10.2	9.0		
Use of beta-blockers	**No**	**89.9**	**89.9**	**93.1**	**0.005**	**89.6**	**88.7**	**91.3**	**0.043**	**4.7**
	Yes	**10.1**	**10.1**	**6.9**		**10.4**	**11.3**	**8.7**		
Use of anticoagulants or platelet aggregation inhibitors	**No**	**82.9**	**83.2**	**87.6**	**0.002**	**82.8**	**81.7**	**85.2**	**0.017**	**3.6**
	Yes	**17.1**	**16.8**	**12.4**		**17.2**	**18.3**	**14.8**		
Injury-related factors										
Geographical area of injury	**Urban**	**80.3**	**81.4**	**76.6**	**0.002**	**80.1**	**81.5**	**77.2**	**0.003**	**4.3**
	Rural	**19.7**	**18.6**	**23.4**		**19.9**	**18.5**	**22.8**		
Injury intention	**Unintentional**	**89.4**	**89.8**	**90.3**	**<0.001**	**89.4**	**89.4**	**89.5**	**0.001**	**0.5**
	Intentional	**6.3**	**6.9**	**4.4**		**6.3**	**7.0**	**4.8**		
	Undetermined	**4.3**	**3.3**	**5.4**		**4.3**	**3.6**	**5.7**		
Pre-hospital Glasgow Coma Scale score	**Median (interquartile range)**	**14.0 (7.0-15.0)**	**14.0 (12.0-15.0)**	**10.0 (6.0-14.0)**	**<0.001**	**14.0 (9.0-15.0)**	**14.1 (12.1-15.0)**	**11.2 (6.0-15.0)**	**<0.001**	**40.3**
Injury Severity Score	**Median (interquartile range)**	**16.0 (9.0-29.0)**	**13.0 (6.0-22.0)**	**26.0 (16.0-41.0)**	**<0.001**	**16.0 (9.0-29.0)**	**13.0 (8.0-25.0)**	**25.3 (16.0-41.0)**	**<0.001**	**1.2**
Medical care, complications and discharge										
Stratum	**Admitted to intensive care unit**	**47.5**	**32.8**	**74.6**	**<0.001**	**47.5**	**35.8**	**73.0**	**<0.001**	**0.0**
	Admitted to hospital ward	**33.7**	**41.7**	**20.3**		**33.7**	**39.7**	**20.6**		
	Directly discharged from emergency room	**18.8**	**25.5**	**5.1**		**18.8**	**24.4**	**6.4**		

Intracranial surgery	**No**	**76.0**	**83.7**	**66.1**	**<0.001**	**79.4**	**84.9**	**67.5**	**<0.001**	**18.2**
	Yes	**24.0**	**16.3**	**33.9**		**20.6**	**15.1**	**32.5**		
Extracranial surgery	**No**	**80.0**	**87.7**	**64.6**	**<0.001**	**82.8**	**89.5**	**68.4**	**<0.001**	**18.2**
	Yes	**20.0**	**12.3**	**35.4**		**17.2**	**10.5**	**31.6**		
Intracranial complication	**No**	**85.7**	**91.0**	**77.8**	**<0.001**	**85.2**	**89.1**	**76.9**	**<0.001**	**33.0**
	Yes	**14.3**	**9.0**	**22.2**		**14.8**	**10.9**	**23.1**		
Extracranial complication	**No**	**79.6**	**88.3**	**65.3**	**<0.001**	**79.6**	**86.4**	**64.9**	**<0.001**	**33.0**
	Yes	**20.4**	**11.7**	**34.7**		**20.4**	**13.6**	**35.1**		
Glasgow Coma Scale score at discharge	**Median (interquartile range)**	**15.0 (15.0-15.0)**	**15.0 (15.0-15.0)**	**15.0 (14.0-15.0)**	**<0.001**	**15.0 (15.0-15.0)**	**15.0 (15.0-15.0)**	**15.0 (14.0-15.0)**	**<0.001**	**38.5**

Abbreviation: ASA American Society of Anesthesiologists.
Data are per cent unless otherwise specified.
Variables for which the difference between the group with and the group without rehabilitation is significant after multiple imputations are displayed in bold.
Rehabilitation was assessed in the year following traumatic brain injury.
Eighty datasets were imputed by chained equations. The number of imputed datasets was estimated using the proportion of individuals with at least one missing value (77%).
P-values were based on chi-squared tests for categorical variables and on Mann-Whitney U tests for continuous variables. P-values were corrected using the Benjamini and Hochberg adjustment method.



Supplementary Figure 1. Flow chart of the patients included in this European study

The initial flow chart of the CENTER-TBI study is available in the study of Steyerberg and colleagues (Figure 1).[20]

Supplementary Table 1. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number	Section
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 3	Title and Abstract (Objective)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	Abstract (Methods and Results)
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 and 6	Introduction (paragraph 2)
Objectives	3	State specific objectives, including any prespecified hypotheses	6	Introduction (paragraph 3)
Methods				
Study design	4	Present key elements of study design early in the paper	6 and 7	Methods (Study participants)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 and 7	Methods (Study participants and Data collection, handling and storage)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6 and 7	Methods (Study participants)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10	Methods [Access to rehabilitation (dependent variable) and Predictors of access to rehabilitation (independent variables)]
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10	Methods [Access to rehabilitation (dependent variable) and Predictors of access to rehabilitation (independent variables)]

Bias	9	Describe any efforts to address potential sources of bias	6, 7, and 10-12	Methods [Study participants, Data collection, handling and storage, and Statistical analyses (paragraph 1)]
Study size	10	Explain how the study size was arrived at	7	Methods (Study participants) and Supplementary Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11 and 12	Methods [Statistical analyses (paragraphs 2 and 3)]
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-12	Methods (Statistical analyses)
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable	
		(*c*) Explain how missing data were addressed	10 and 11	Methods [Statistical analyses (paragraph 1)]
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable	
		(*e*) Describe any sensitivity analyses	12	Methods [Statistical analyses (paragraph 3)]
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplementary Figure 1	
		(b) Give reasons for non-participation at each stage	Supplementary Figure 1	
		(c) Consider use of a flow diagram	Supplementary Figure 1	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12 and 13	Results
		(b) Indicate number of participants with missing data for each variable of interest	Table 1	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12 and 13	Results

		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable	
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 and 13	Results, Table 1 and Figure 3
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13	Results and Supplementary Table 2
Discussion				
Key results	18	Summarise key results with reference to study objectives	13 and 14	Discussion (Main findings)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19	Discussion (Strengths and limitations)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17	Discussion (Interpretation of the findings)
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-19	Discussion (Implications and directions for future research, and Strengths and limitations)
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20	Disclosures (Funding)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplementary Table 2. Predictors of rehabilitation in the year following the injury in patients with traumatic brain injury by age and by stratum (LASSO penalized logistic regression)

		Age <18 years (N=255)		Age 18-65 years (N=3,050)		Age >65 years (N=1,193)		Admission to intensive care unit (N=2,137)		Admission to hospital ward (N=1,517)		Direct discharge from emergency room (N=844)	
Characteristics	Category	Odds ratio (adjusted 95% confidence interval)	P-value	Odds ratio (adjusted 95% confidence interval)	P-value	Odds ratio (adjusted 95% confidence interval)	P-value	Odds ratio (adjusted 95% confidence interval)	P-value	Odds ratio (adjusted 95% confidence interval)	P-value	Odds ratio (adjusted 95% confidence interval)	P-value
Sex	Male	Reference											
	Female	**2.89 [1.06, 7.86]**	**0.036**	**1.42 [1.14, 1.76]**	**0.001**	**1.51 [1.03, 2.19]**	**0.027**	**1.46 [1.16, 1.84]**	**0.001**	**1.68 [1.19, 2.38]**	**0.002**	1.24 [0, Inf]	0.788
Number of years of education completed	Per one-unit increase in years	1.02 [0.88, 1.19]	0.994	**1.06 [1.02, 1.09]**	**0.001**	**1.05 [1.01, 1.10]**	**0.024**	**1.06 [1.02-1.09]**	**0.001**	**1.06 [1.01, 1.11]**	**0.005**	1.02 [0, Inf]	0.788
Pre-injury employment	Yes	Reference											
	No	2.03 [0.23, 18.01]	0.748	**0.78 [0.61, 0.98]**	**0.034**	1.11 [0.58, 2.12]	0.710	**0.74 [0.59,0.93]**	**0.010**	0.94 [0.64, 1.37]	0.818	0.67 [0, Inf]	0.539
Region	Western Europe	Reference											

	Northern Europe	1.15 [0.38, 3.45]	0.994	**1.79 [1.41, 2.27]**	**<0.001**	1.47 [0.91, 2.35]	0.115	**2.06 [1.56, 2.71]**	**<0.001**	1.28 [0.86, 1.90]	0.205	1.17 [0, Inf]	0.842
	Southern Europe	1.07 [0.28, 4.06]	0.994	**1.76 [1.38, 2.25]**	**<0.001**	**1.72 [1.12, 2.64]**	**0.020**	**1.83 [1.43, 2.36]**	**<0.001**	1.44 [0.90, 2.31]	0.119	1.85 [0, Inf]	0.357
	Central and Eastern Europe	0.00 [0.00, Inf]	0.994	0.40 [0.15, 1.04]	0.056	0.55 [0.10, 3.06]	0.457	0.60 [0.22, 1.66]	0.305	0.08 [0.00, Inf]	0.985	0.00 [0, Inf]	0.997
Pre-hospital Glasgow Coma Scale score	Per one-unit decrease in the total score	1.07 [0.80, 1.25]	0.547	1.02 [0.95, 1.06]	0.110	1.02 [0.96, 1.09]	0.457	**1.04 [1.01-1.07]**	**0.010**	0.99 [0.89, 1.09]	0.818	0.92 [0, Inf]	0.818
Injury Severity Score	Per one-unit increase in the total score	1.00 [0.95, 1.04]	0.994	**1.01 [1.00, 1.02]**	**0.031**	1.01 [0.99, 1.02]	0.386	1.00 [1.00, 1.01]	0.251	**1.03 [1.01, 1.05]**	**0.006**	1.03 [0, Inf]	0.539
Stratum	Admitted to intensive care unit	Reference						Not applicable					
	Admitted to hospital ward	**0.19 [0.04, 0.83]**	**0.036**	**0.38 [0.28, 0.51]**	**<0.001**	0.80 [0.49, 1.32]	0.406						

	Directly discharged from emergency room	0.01 [0.00, Inf]	0.994	**0.20 [0.14, 0.31]**	**<0.001**	**0.36 [0.16, 0.79]**	**0.020**						
Intracranial surgery	No	Reference											
	Yes	**4.61 [1.33, 16.05]**	**0.036**	1.21 [0.93, 1.56]	0.131	1.42 [0.87, 2.29]	0.158	**1.34 [1.08, 1.67]**	**0.009**	1.25 [0.55, 2.81]	0.692	0.35 [0, Inf]	0.997
Extracranial surgery	No	Reference											
	Yes	**3.97 [1.12, 14.13]**	**0.036**	**1.88 [1.44, 2.46]**	**<0.001**	**1.83 [1.07, 3.13]**	**0.024**	**2.13 [1.66, 2.72]**	**<0.001**	1.55 [0.90, 2.68]	0.115	2.40 [0, Inf]	0.704
Extracranial complication	No	Reference											
	Yes	2.98 [0.69, 12.76]	0.192	**1.80 [1.35, 2.40]**	**<0.001**	**1.68 [1.08, 2.60]**	**0.024**	**1.67 [1.29, 2.15]**	**<0.001**	**2.54 [1.42, 4.53]**	**0.001**	0.50 [0, Inf]	0.997

Abbreviation: LASSO Least Absolute Shrinkage and Selection Operator.

Rehabilitation was assessed in the year following traumatic brain injury.

Eighty datasets were imputed by chained equations. The number of imputed datasets was estimated using the proportion of individuals with at least one missing value (77%).

The selection of independent variables included in the regression model relied on a two-stage method. During the first stage, variables were preselected in the 80 imputed datasets separately using a LASSO procedure. During the second stage, the number of preselections per variable was calculated, and variables with more than 60 preselections were arbitrarily considered as potential predictors. Ten variables were included in regression models.

The multivariate regression model was conducted in each of the imputed datasets and results were subsequently pooled, while analyses were stratified by age and stratum.

Confidence intervals and p-values were corrected using the Benjamini-Yekutieli and the Benjamini-Hochberg adjustment method, respectively.

Independent variables significantly associated with access to rehabilitation are displayed in bold.