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A systematic review of comorbidity measurement methods for patients with non-traumatic brain injury in inpatient rehabilitation settings

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Abstract

This review summarizes comorbidity measurements used on patients with non-traumatic brain injury (nTBI) in inpatient rehabilitation and describes findings on measurement validation and comorbidity profiles. MEDLINE and MEDLINE In-Process, EMBASE, PsycINFO, the Cochrane Database of Systematic Reviews, Health and Psychosocial Measurement Instruments were searched. Two reviewers screened results according to pre-defined inclusion and exclusion criteria. Population, statistical methods, comorbidity measurement, justification of its use, and results involving comorbidity were extracted using a standard table. Of 9476 articles retrieved, 16 were included. Comorbidity has been measured using various methods including: number and type within various classification systems, such as the International Disease Classification system, the Charlson Comorbidity Index, Centers for Medicare and Medicaid Services Comorbidity Tiers, Patient Comorbidity and Complexity Level values, and subsets of diagnoses within non-administrative data studies. No studies have assessed the predictive ability of the comorbidity measurements for inpatient rehabilitation outcomes in this population. As comorbidities are common among the nTBI population, the predictive validity of comorbidity measurements should be assessed to determine the most appropriate measure to predict or risk adjust rehabilitation outcomes, which has implications for the development of clinical guidelines and to inform health service research, planning, and delivery.

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Keywords

brain injuries; rehabilitation; comorbidity; review

Acquired non-traumatic brain injury (nTBI) is defined as an insult to the brain that affects its structure or function, resulting in impairments of cognition, communication, physical function, or psychosocial behavior, which is caused by tumors, infectious diseases, hypoxic injuries, metabolic disorders, and toxic exposure – excluding conditions that are congenital, degenerative, or induced by birth trauma¹. NTBI is at least as common as traumatic brain injury (TBI)². Yet, the cost of treatment for patients with nTBI are three times higher than the cost of treatment for patients with TBI, with the costs of inpatient rehabilitation amounting to approximately one third of the total costs for the 10% of patients with nTBI that are discharged to inpatient rehabilitation³.

Given the significant costs of inpatient rehabilitation, it is important to understand the factors associated with inpatient rehabilitation outcomes for these patients. Assessment of comorbidity – a distinct clinical condition that exists or may occur during a patient's clinical course⁴ – is particularly important because the presence of comorbid health conditions can affect health care outcomes^{5–9} and the prevalence of individuals with comorbid medical conditions is increasing¹⁰. Evidence regarding the prevalence of comorbidity and their effect on health care outcomes depends on the comorbidity measurement and statistical methods employed¹¹. However, comorbidity measurement is complicated by various definitions and tools¹². For example, comorbidity data extracted from administrative databases or medical records^{13–15} are often coded using standardized systems such as the International Classification of Diseases (ICD), which can be further aggregated using indices such as the Charlson Comorbidity Index (CCI)¹⁶. In addition, comorbidity classification systems have been developed to predict the cost of inpatient rehabilitation care, such as the United States Center for Medicare and Medicaid (CMS) Comorbidity Tier system or Patient Comorbidity and Complexity Level (PCCL) values. Finally, patient classification systems have been developed that incorporate comorbidity information, such as Diagnosis Related Groups (DRGs)¹⁷ and the US Inpatient Rehabilitation Facilities Case Mix Groups (CMGs).

Many comorbidity measurement methods have been developed for specific outcomes, namely cost or mortality, and in specific patient populations and settings. For example, the CCI included 19 conditions that were significantly associated with 1-year mortality in a sample of patients admitted to a medical center in New York in 1984. It was later validated in breast cancer patients¹⁶, updated for use with administrative databases in Medicare lumbar spinal surgery patients and hospitalized patients^{18,19}, and recently updated with reassigned weights in a more contemporary setting²⁰. PCCLs, calculated based on complication and comorbidity levels using a proprietary system developed by the Independent Hospital Pricing Authority, are used within various DRG systems, such as the Australian-refined and German DRGs¹⁷. The CMS Comorbidity Tiers system was developed across all inpatient rehabilitation patients according to cost of treatment based on specific comorbidities hypothesized to increase costs, which were grouped into three tiers based on the association between comorbidities and cost across Rehabilitation Impairment

Categories^{21,22}. While the Comorbidity Tier system has been developed for the inpatient rehabilitation setting, it has not been validated specifically for patients with nTBI across a variety of patient oriented rehabilitation outcomes, such as functional outcome.

Although the predictive validity of certain comorbidity indices have been synthesized for certain patient populations (e.g. mortality in patients with cancer²³ and cardiovascular disease²⁴), it has not been conducted for inpatient rehabilitation outcomes (such as length of stay or functional independence) in patients with nTBI. As such, it is not clear whether these comorbidity measures appropriately capture the effect of comorbidity on inpatient rehabilitation outcomes or how comorbidities can affect rehabilitation outcomes for patients with nTBI. Therefore, the primary objective of this systematic review is to address this research gap by surveying the literature on methods to measure comorbidity for patients with nTBI in inpatient rehabilitation. The secondary objective is to determine whether the studies assessed the predictive ability of the comorbidity measures for inpatient rehabilitation outcomes in patients with nTBI. The final objective is to summarize the profile of comorbidities and their effect on inpatient rehabilitation outcomes for patients with nTBI. The study of comorbidity, and its measurement and association with outcomes, can be used by clinicians to understand the profile of comorbidities in patients with nTBI in inpatient rehabilitation settings, the effect of comorbidity on rehabilitation outcomes, and may thus be used for health service delivery and planning.

Methods

This systematic review was conducted based on a previously developed and published protocol²⁵. The presentation of results was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist²⁶ (See Supplementary Checklist).

Search Strategy

The following databases were searched for relevant articles:

1. MEDLINE (1946 to 3 July 2014) and MEDLINE In-Process (3 July 2014)
2. Embase (1946 to 3 July 2014)
3. Cochrane Database of Systematic Reviews (2005 to 3 July 2014)
4. PsycINFO (1806 to 3 July 2014)
5. HAPI (1985 to 3 July 2014)

Grey literature was searched using 'Grey Matters: A Practical Search Tool for Evidence Based Medicine'²⁷. Resources from national rehabilitation research groups, such as The US CMS and Canadian Institute for Health Information (CIHI), were used to survey available information from health service providers. Finally, the reference lists of included articles were searched.

The search strategy combined the concepts 'nTBI', 'comorbidity', and 'rehabilitation'. Broad terms were purposely used to define nTBI to increase sensitivity and more narrow

terms were used to define specific nTBI conditions. The terms for comorbidity included risk adjustment concepts related to health services research, such as ‘diagnosis related groups’, ‘case-mix’, and ‘resource intensity weighting’, as they may incorporate comorbidity information. All database results were limited to English language. A limit to human only studies was applied in MEDLINE and limits to exclude conference material (abstracts, paper, proceeding, reviews), and editorials, letters, or notes were applied in Embase (see supplementary file for search strategy from Khuu et al., 2015²⁵).

Study Selection

Two reviewers independently assessed all titles and abstracts for inclusion using predetermined eligibility criteria in two rounds of screening. In the first round, record titles and abstracts were screened for reports that included an nTBI population in inpatient rehabilitation. When both the title and abstract lacked the required information to make a decision, possibly relevant records were included for the full-text screen. In the second round, full-text articles were reviewed to confirm measurement of comorbidity in patients with any type of nTBI within an inpatient rehabilitation setting.

Eligible study designs included cohort studies, case-control studies, randomized controlled trials, or systematic reviews. Qualitative studies, case-reports, abstracts, conference material, and editorials or commentaries were excluded because these sources of information are unlikely to present the level of detail and information required for the purposes of this systematic review. Ecological studies were excluded because they do not provide sufficient evidence for individual level effects of comorbidity on rehabilitation outcomes. Stroke was excluded from this review to reflect current research and clinical practice in rehabilitation where stroke is treated separately from other acquired non-traumatic brain injuries²⁵.

Data extraction

Data were extracted using a standard table. Author, publication year, purpose of study, year(s) of study, study design, location and setting, data source or type, number of patients with nTBI, and subtype(s) of nTBI, were extracted to characterize the studies. To address the primary research objective, the comorbidity measurement method and statistical method used to quantify comorbidities were extracted. To address the secondary research objective, validation studies cited or validation statistics, if reported, were extracted. To address the tertiary objective, any statistics related to comorbidity were extracted, including descriptive or analytic statistics.

Quality Assessment

Critical Appraisal Skills Programme (CASP) checklists²⁸ were used to guide the assessment of validity and reliability. Methodological quality – such as the use of appropriate statistical tests, accounting for confounding, and the study population selection method – was of particular importance as it can affect the interpretation and generalizability of results.

Analyses

Due to the heterogeneity of articles retrieved, the results are presented in a narrative synthesis²⁹. The results were grouped into clusters by the region of study because health

services research techniques are regionally specific and the type of data used because some measures have been developed for administrative data whereas others have not.

Results

The search results are presented in Figure 1. The search yielded a total of 11575 records, from which 9476 records remained after duplicates were removed. Of the 9476 records, 83 met the criteria for a full text screen, from which 16 were included for review. Data extraction results are summarized in Table 1. The majority of articles (13/16) used a retrospective cohort design. Of these 13 studies, 11 used administrative data sources and 2 used medical file reviews. Of the 11 studies that used national administrative data, 5 were conducted in Canada and used the National Rehabilitation Reporting System (NRS) as the data source, 3 were conducted in the USA using the Uniform Data System for Medical Rehabilitation (UDSMR) and CMS data, one was conducted in Italy using an electronic registry for severe acquired brain injury, one was conducted in Germany using administrative data from a single neurological rehabilitation hospital, and one was conducted in the USA using an institutional database. The remaining 3/16 studies used a retrospective case-series, a prospective cross-sectional, and a prospective matched-case-case design. The overall quality of the articles was good according to the CASP checklists. However, justification for the use various comorbidity measurements as they pertain to rehabilitation outcomes in patients with nTBI were rarely provided.

Comorbidity Measurement

Comorbidity in patients with nTBI have been measured using various methods, including number and type based on ICD-10 or pre-2008 diagnostic health codes in the NRS, CCI based on the DAD, number or type of comorbidity based on ICD-9 codes, or Comorbidity Tier based on the USDMR, and PCCL to classify comorbidity. Of the 16 studies that assessed a nTBI population, 7 studies stratified analyses and results by nTBI either as a whole, or by subtype of nTBI. Given the purpose of this systematic review, only comorbidity results from the studies that stratified by nTBI are described here whereas the other studies³⁵⁻⁴¹ are summarized in Table 1. Of the studies that stratified by nTBI, four were retrospective studies based on Canadian administrative health data, one was an Italian study of severe acquired brain injury, one was a retrospective chart review study from Australia, and one was a prospective matched case-case study conducted in Turkey. None of the studies compared the relative ability of various comorbidity measures to predict inpatient rehabilitation outcomes for patients with nTBI. However, one study assessed the predictive ability of one comorbidity measure for one outcome: Chen et al. (2014) assessed the association of the CCI with living setting at discharge from inpatient rehabilitation and found the association was not significant ($p>0.1$).

Comorbidity Profiles

Comorbidities are common among the nTBI population, with mental health and addictions mentioned in two of the studies that looked at types of comorbidity. Three of the four Canadian administrative health data studies used the NRS for inpatient rehabilitation data and stratified by TBI vs. nTBI^{3,30,31}. The CCI, calculated from acute hospitalization data,

was used as a descriptive measure, in which similar results were found across the three studies: approximately 57% of nTBIs had a low CCI score (0–1), 30% had a moderate CCI score (2–3), and 12% had a high CCI score of (4+) ³⁰. Colantonio et al. (2011) measured the number and type of comorbidity using pre-admit comorbidity fields in the NRS ². Patients with nTBI had an average of 3.9 (SD=3.0) comorbidities, which included circulatory system (51.3%), nervous system (44.2%), mental health (32.6%), endocrine, nutritional, metabolic, and immune system (27.3%), musculoskeletal (22.8%), and genitourinary disorders (21.1%). Depressive disorders were the most common mental health condition and occurred in 34% of nTBI patients. Avesani et al. (2013) stratified patients with nTBI by anoxia, and other conditions (which included infections and tumors) using an Italian national registry of severe acquired brain injury ³². Paraosteoarthropathies (POA) and pressure sores at admission and discharge were reported. Anoxic patients had the highest rate of POA on discharge (9.03%) whereas patients in the other category had the highest rate of pressure sores on admission and discharge (45.28% and 20.75%, respectively). O'Brien and Todd (2009) retrospectively studied 10 patients with hypoxic brain injury due to heroin overdose ³³, in which prior drug use and psychiatric history were reported. In this sample, 50% were daily heroin users, 10% were regular heroin users, 20% were occasional users, and 50% had prior psychiatric histories, including suicide attempts (20%) and treatment for depression (30%). Geler-Kulcu et al. (2009) performed a matched case-case study using patients with brain tumor ³⁴. The presence of diabetes mellitus and coronary heart disease were noted within 24 hours of admission to the inpatient rehabilitation program. A small proportion of these patients had diabetes mellitus (10%) and coronary heart disease (24%) comorbidities.

Discussion

The objectives of this study were to determine 1) the methods used to measure comorbidity in patients with nTBI within an inpatient rehabilitation setting; 2) the predictive ability of the comorbidity measurement methods for rehabilitation outcomes; and 3) the profile of comorbidity in patients with nTBI in inpatient rehabilitation settings. The 16 studies that met inclusion criteria for this systematic review showed a large degree of heterogeneity in the method used to measure comorbidity and how the comorbidity information was used and presented.

The comorbidity measurements used across the studies were associated with the type and location of study. A common source of data was administrative health databases, which holds the potential to capture comorbidities systematically. Specifically, it has the ability to capture a large range of health conditions present at admission and/or discharge from various healthcare settings. The coding of these health conditions are also conducted using standardized classification systems (e.g., ICD), which provides a common language across regions and studies. Given the strengths of administrative data for capturing comorbid health conditions, the validity of comorbidity coding in these databases should be assessed and/or improved. For example, coding using the comorbidity diagnosis fields in the DAD in Canada has been rated as 'poor', depending on the healthcare condition ³⁵, and, the validity of comorbidity information in the NRS is not known ³⁶. It has also been suggested that administrative data likely underestimates comorbidity compared to medical record reviews ³⁷. As such, comorbidity coding in administrative data could be improved or

supplemented, for example, by incorporating information from medical records, which may be possible through various electronic medical record initiatives³⁸. Finally, administrative data systems used in Rollnik and Janosch (2010), Avesani et al. (2013), and Alam et al. (2008) were not further described and the remaining studies used medical records and tracked unique and diverse sets of comorbid conditions, for which reliability and data quality are not known. Thus, it is recommended that a description of the data source be included in all research articles to enable further reading and research into the data source for various purposes, including systematic reviews.

This systematic review highlighted the lack of information on the predictive ability of comorbidity measurements currently used in nTBI research on inpatient rehabilitation outcomes. This is particularly important because these measures can influence study outcomes and interpretation. Thus, when using comorbidity indexes, authors should be cautious when choosing a comorbidity measure that is suited for their outcome of interest, and when possible, either validate the measure for their outcome of interest in their population of interest, provide a clear clinical rationale for choosing the measure, or both. These practices would help improve the validity of comorbidity measurement.

In addition to variability in data sources and methods used to measure comorbidity, there was also variability in the types of nTBI conditions included and subgroup stratification for analyses across the studies. For instance, five studies collapsed analyses and presented results across all patient groups, which were diverse and included all cancer patients in rehabilitation³⁹, all inpatient rehabilitation⁴⁰, all neurologic rehabilitation patients⁴¹, all patients in states of severely altered consciousness⁴², and all patients with disorders of consciousness⁴³. Furthermore, two studies included nTBI patients in a 'brain dysfunction' group^{44,45}, which also included TBI. The generalization of comorbidity profiles from studies that collapsed nTBI patients into a larger group may not be valid. Thus caution should be exercised when generalizing the prevalence of comorbidity and their effect on functional outcome and length of stay following inpatient rehabilitation. Consequently, the following discussion focuses on the studies that have provided estimates for nTBI as a whole or subtypes of nTBI.

Of the 7 studies that reported comorbidity statistics for patients with nTBI specifically, only one of these studies used comorbidity (CCI) in a multivariable regression and it did not meet model selection criteria³¹. Profiles of comorbidity were presented in 7 studies. Four studies by Colantonio et al. that stratified analyses by nTBI as a whole^{2,3,30,31}. Based on these studies, most nTBI patients in inpatient rehabilitation settings are expected to have a low CCI score and a small proportion are expected to have high CCI scores. Moreover, patients with nTBI frequently experience a diversity of comorbid conditions, including mental, circulatory, nervous system, endocrine, nutritional, metabolic, immune, musculoskeletal, genitourinary conditions. Within mental health diagnoses, with depressive disorders were the most common being the most common, followed by confusion, and then other conditions. However, it is unclear whether these results are confounded by etiology. For example, it is possible that patients with primary or secondary metastatic brain cancer may skew the CCI results of the nTBI population as a whole.

Three studies presented results for specific nTBI populations, including one study on brain tumor³⁴, one study presented results for anoxia and other nTBI, which included brain infections and neoplasms⁴⁶, and one study presented patients with hypoxic brain damage due to heroin overdose³². These studies show that differences by etiology may be expected given that there was a high rate of POA in anoxic patients compared to a high rate of pressure sores in patients with brain tumor or infection, prevalent drug use and psychiatric history in patients with hypoxic brain injured patients due to heroin overdose, and the presence of diabetes and coronary heart disease in patients with brain tumor. However, in these studies only specific medical conditions were investigated. A more comprehensive assessment of the distribution of other comorbidities would be helpful in providing a better description of comorbidity profiles in patients with specific nTBI conditions.

The results of this systematic review are in accordance with other systematic reviews on comorbidity measurements for different populations. Similar to studies of comorbidity measurements for cancer patients²³ and patients with cardiovascular diagnoses²⁴, it appears that no standard exists for comorbidity measurement for patients with nTBI. However, comorbidities can affect rehabilitation outcomes. For example, based on a systematic review of comorbidities on outcomes of COPD rehabilitation, comorbidities can influence pulmonary rehabilitation outcomes⁷. Comorbidity has also been shown to be an independent predictor of rehabilitation efficiency in geriatric and hip arthroplasty rehabilitation patients⁴⁷. Furthermore, the choice of comorbidity measurement affects the results studies on rehabilitation outcomes. For example, at least one study on stroke rehabilitation outcomes showed that comorbidities are important predictors of stroke rehabilitation outcomes, and how they are classified impacts the results of statistical models used in assessing quality of care⁹. Accordingly, it has been suggested that comparisons of the predictive ability of comorbidity measurements should be specific to subsets of patients populations¹⁴. The study of the comparative predictive ability of various comorbidity measurements on rehabilitation outcomes within nTBI patients is important given the similarity in prevalence and cost of rehabilitation of these patients compared to patients with traumatic brain injury³. Therefore, this review shows a substantial research gap that needs to be addressed.

Study Limitations

The strength of this systematic review is the sensitivity of the search strategy as a result of including proxy terms for each of the concepts. However, it is possible that relevant articles were not captured due to imperfect indexing systems of the databases searched. For example, the search strategy may have excluded articles that captured comorbidity and reported it in full text but were not mentioned in the title or abstract or indexed with keywords or controlled language. In addition, the definition of comorbidity was limited to medical conditions, and as such, related phenomena that may affect rehabilitation outcome, such as procedures or functional ability, were not investigated. Finally, due to the relatively small number of papers that were included in this review, caution should be exercised when interpreting the results because they may not be externally generalizable. We hope that more research will be conducted in this area in order to increase the generalizability of results.

Conclusion

To the best of the authors' knowledge, this is the first systematic review of methods that have been used to measure comorbidity in patients with nTBI in inpatient rehabilitation settings. The results of this systematic review demonstrate a variety of comorbidity measurements are used to describe comorbidity in this population with no information on the predictive ability of the various comorbidity measurements for inpatient rehabilitation outcomes such as functional outcome and length of stay for the nTBI population. This may affect the results and interpretation of studies that describe comorbidities or their impact on rehabilitation outcomes. Moreover, there is a lack of evidence to suggest that subgroups of nTBI patients experience similar comorbidities and that any given method of comorbidity measurement will best predict inpatient rehabilitation outcomes, which may be related to the limited number of articles that investigate nTBI or specific nTBI conditions and present comorbidity information for these conditions. Therefore it would be informative to investigate each type of nTBI specifically and to determine comorbidity measurements that are predictive of given rehabilitation outcome for that type of nTBI.

The results of this review (and similar reviews in other patient populations, cited in this review) show that there are no standards for measuring comorbidity. Next steps would depend on the purpose of measuring and reporting comorbidity. If the purpose is to describe the distribution of comorbid medical conditions that are present during an inpatient rehabilitation episode, future research could aim to validate currently available methods for measuring comorbidity. For example, a chart abstraction study of the sensitivity and specificity of diagnosis fields in the NRS would be informative. In addition, leveraging electronic medical records for a more comprehensive picture of comorbidity, generally, would be helpful. If the purpose is to determine the association of comorbidity with inpatient rehabilitation outcomes, then future research should aim to validate specific measures or indexes of comorbidity for the nTBI population.

The ability to generalize and apply the measures of comorbidity, particularly for risk adjustment in health service research, is limited by heterogeneity in comorbidity measurement method, differences in population stratification, and differences in the statistical techniques used to relate comorbidity to rehabilitation outcomes. Estimates of comorbidity profiles by nTBI subtype, and their effect of comorbidity on rehabilitation outcomes including LOS, functional outcome, and readmissions would be more informative and useful for the development of clinical training guidelines. Moreover, this information could be used to provide more accurate evidence for the various factors associated with rehabilitation outcomes, which can be used for effective and efficient planning and delivery of inpatient rehabilitation services. Therefore, future studies should explore the face and predictive validity of comorbidity measurement in relation to known or potentially important confounders, such as age and sex, and provide estimates of the prevalence of comorbidities by patient types in order to increase the generalizability of research outputs to specific populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

CASP	Critical Appraisal Skills Programme
CCI	Charlson Comorbidity Index
CMG	Case Mix Group
CMS	Centers for Medicare and Medicaid
CIHI	Canadian Institute for Health Information
DAD	Discharge Abstract Database
DRG	Diagnosis-related group
FIM	Functional Independence Measure
FRG	Function-related group
ICD	International Classification of Diseases
LOS	Length of Stay
NRS	National Rehabilitation Reporting System
nTBI	non-traumatic brain injury
PCCL	Patient Clinical Complexity Level
PE/DVT	Pulmonary embolism/Deep vein thrombosis
POA	Paraosteoarthritis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UDSMR	Uniform Data System for Medical Rehabilitation

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Figure 1. PRISMA flow diagram showing the flow of information through the different phases of the systematic review, including records identified, included and excluded, and reasons for exclusions. CDSR=Cochrane Database of Systematic Reviews; nTBI=non-traumatic brain injury.

Summary of study characteristics and comorbidity results

Table 1

Authors, date	Purpose	Study Design, Years, Setting	Data type: Data source	Population and stratification	Comorbidity Measurement, Rationale, Quantification Method, Outcome, Covariates	Comorbidity Results
Studies that stratified by nTBI						
Chen et al., 2014 ³¹	Examine factors associated with living setting at discharge from inpatient rehabilitation for TBI and nTBI patients using the Andersen Behavioral Model	Retrospective cohort; 2003–2006; Inpatient rehabilitation; Ontario, Canada	Population based, administrative: DAD, NRS	nTBI (N=1848) defined in the DAD, linked to NRS within 365 days, using ICD-10 codes for brain infections, encephalopathy, toxic effects, anoxia, vascular insults, and brain neoplasms	Comorbidity: CCI based on DAD Rationale: Charlson et al., 1987 Methods: Descriptive (frequency), two step bivariate logistic regression Outcome: Discharge living setting Covariates: LOS, Functional Independence Measure, living setting and arrangement at admission, residence, level of informal support, age, sex	% with CCI, Total: 0–1: 58.5 2–3: 30.0 4+=11.5 % with CCI, Discharged home/other: 0–1: 58.9 2–3: 29.5 4+: 11.5 % with CCI, Discharged residential care: 0–1: 56.7 2–3: 32.1 4+: 11.2 CCI did not meet MV model selection criteria
Chan et al., 2013 ³⁰	Examine a population-based profile of older adults with acquired brain injury, and their functional outcomes in in-patient rehabilitation	Retrospective cohort; 2003–2010; Acute care and inpatient rehabilitation; Ontario, Canada	Population based, administrative: DAD, NRS	nTBI (N=1530) identified in the DAD, ICD-10 codes for anoxia, brain tumors, encephalitis, meningitis, metabolic encephalopathy, other brain disorders and infections, toxic effects of substances, chiefly non-medical as to source, and vascular insults not captured in other national studies of stroke	Comorbidity: CCI based on DAD Rationale: Charlson et al. 1987 Method: Descriptive (frequency), Chi-squared test Outcome: LOS	% of nTBI with CCI: 0–1: 57.1 2–3: 30.6 4+: 12.3 CCI 2+: nTBI > TBI (p<0.0001)
Chen et al., 2012 ³	Provide accurate and comprehensive estimates of direct medical costs from initial hospitalization up to 2 years post injury among individuals with ABI	Retrospective cohort; 2004–2007; Health care continuum; Ontario, Canada	Population based, administrative: DAD, NRS, Home Care Reporting System, Continuing Care Reporting System, OHIP	nTBI (N=31501) identified in the DAD using ICD-10 Codes for toxicity, complications of medical care, anoxia, vascular insults, brain tumors, encephalitis, metabolic encephalopathy, meningitis	Comorbidity: CCI based on DAD Rationale: N/A Method: Descriptive (frequency) Outcomes: LOS, cost	% of nTBI with CCI in those discharged to rehab: 0–1: 52 2–3: 32 4+: 16
Colantonio et al., 2011 ¹²	Profiling the demographic and clinical characteristics of persons with an ABI, receiving inpatient rehabilitation services in Canada, from a	Retrospective cohort; 2001–2006; Inpatient rehabilitation; Ontario, Canada	Population based, administrative: NRS	nTBI (N=2759) based on non-traumatic brain dysfunction Rehabilitation Client Group, including, e.g., anoxia, ruptured intracranial aneurysms, neoplasm, encephalitis, metabolic toxicity	Comorbidity: Number and type of pre-2008 diagnostic health codes in the NRS Rationale: N/A Methods: Descriptive (mean, frequency), t-test, Chi-squared test Outcomes: Functional Independence Measure, LOS	Mean= 3.9 diagnoses; Significantly more than TBI (p<0.0001) Higher % of mental health diagnoses compared to TBI (p=0.0008) % of nTBI with: Depressive disorder: 34.1 Confusion: 30.7 Others:23.7

Authors, date	Purpose	Study Design, Years, Setting	Data type: Data source	Population and stratification	Comorbidity Measurement, Rationale, Quantification Method, Outcome, Covariates	Comorbidity Results
Avesani et al., 2013 ³²	population-based perspective					Alcohol dependence: 12.6 Affective psychoses: 11.3 Dementia: 8.5 Drug dependence: 7.3 Personality disorders: 4.9
	Collect epidemiological and clinical data and evaluate functional outcome of patients with severe traumatic and non-traumatic ABI admitted to rehabilitation facilities, and to compare data of patients with ABI of different etiologies	Retrospective cohort; 2008–2011; 29 rehabilitation facilities; Italy	Electronic database, administrative: Electronic Italian National Registry for severe acquired brain injury	Anoxic brain damage (N=177) Other (brain infections and neoplasms; N=53)	Comorbidity: Paraosteothropathies and pressure sores, at admission and discharge Rationale: N/A Method: Descriptive (frequency) Outcomes: Number of days elapsed between onset and rehab admission, rehab LOS, discharge destination, death and vegetative status, Disability Rating Scale	% of patients with anoxic brain injury with: Paraosteothropathies: Admission: 5.08 Discharge: 9.03 Pressure sore: Admission: 38.41 Discharge: 19.77 % of patients with brain infections/neoplasms with: Paraosteothropathies: Admission: 35.84 Discharge: 3.77 Pressure sore: Admission: 45.28 Discharge: 20.75 Across all patient groups, pressure score associated longer LOS, Disability Rating Scale score, and lower rate of discharge home
Ortlen and Todd, 2009 ³³	Document the disability experienced by 10 people with hypoxic brain injuries following heroin overdose	Retrospective cohort; 1997–1999; Brain injury rehabilitation facility; Melbourne, Australia	Medical records: Royal Talbot Rehabilitation Center	Hypoxic brain injury due to heroin overdose (N=10)	Comorbidity: Medical histories, drug use (main substance and frequency); Psychiatric history (yes/no) Rationale: Evidence from their effects in TBI and extrapolate to heroin-related hypoxia Method: Descriptive (frequency) Outcome: FIM, community integration questionnaire	% with heroin use: Daily: 50 Regular: 10 Occasional: 20 % with psychiatric history: Any: 50 Suicide attempts: 20 Treatment for depression: 30
Geler-Kulcu et al., 2009	Compare the locomotor functional recovery of patients with brain tumor and patients with stroke	Prospective matched case-control; case (years unknown); Inpatient rehabilitation; Istanbul, Turkey	Data collected within 24 hours of admission to inpatient rehab	Brain tumor (N=21)	Comorbidity: Presence of diabetes mellitus or coronary heart disease Rationale: N/A Method: Descriptive (frequency) Outcome: Motor assessment scale, Postural Assessment scale, Berg Balance Scale, Functional Independence Measure	% of brain tumor patients with: Diabetes mellitus: 10 Coronary heart disease: 24
Studies that did not stratify by nTBI						
Ortenbacher et al., 2014 ⁴¹	Determine 30-day readmission rates and factors related to readmission for	Retrospective cohort; 2006–2011; Inpatient	Population based, administrative: 4 Centers for Medicare and	Brain dysfunction (N=62974)	Comorbidity: CMS Tier comorbidity Rationale: Carter and Totten, 2005	% of brain dysfunction patients in each tier: Tier 1 : 2.7 Tier 2: 14.9

Authors, date	Purpose	Study Design, Years, Setting	Data type: Data source	Population and stratification	Comorbidity Measurement, Rationale, Quantification Method, Outcome, Covariates	Comorbidity Results
	patients receiving post acute inpatient rehabilitation	rehabilitation facilities; USA	Medicaid Services files: 1. Medical Provider Analysis and Review; 2. Inpatient Rehabilitation Facility-Patient Assessment Instrument; 3. Beneficiary summary file; 4. Inpatient Rehabilitation Facility Rate settings		Method: Descriptive (frequency) Outcome: 30-day hospital readmission	Tier 3: 25.9 No Tier: 56.5 % of 30 day readmission in each tier: Tier 1: 24.6 Tier 2: 18.4 Tier 3: 18.6 No Tier: 14.5
Otenbacher et al., 2004 ⁴⁰	Examine changes in LOS, functional status, living setting, and mortality in patients completing inpatient rehabilitation	Retrospective cohort: 1994–2001; Inpatient rehabilitation facilities; USA	Population based, administrative: Uniform Data System for Medical Rehabilitation	Brain dysfunction (N=13275) Non-traumatic brain dysfunction (N=4859) Comorbidity results collapsed across all impairment groups (N=162819)	Comorbidity: 1. CMS Tier comorbidity 2. Other diseases based on ICD9CM 3. Total number of comorbidities (0, 1–3, or 3+) Rationale: N/A Methods: Descriptive (frequency), Quasi likelihood analysis Outcomes: LOS, effectiveness, efficiency, living setting, mortality Covariates: age, marital status, sex, race/ethnicity, living situation, payment source	% of all inpatients with # comorbidity, 2001: 0: 35 1–3: 45 >3: 20 Across all brain dysfunction, comorbidities and age were statistically significant covariates in the quasi-likelihood models with effectiveness efficiency, follow-up, living setting, and mortality as outcomes Independent result of comorbidity not presented
Stineman et al., 1998 ³⁶	Determine if diagnostic information (ICD9CM codes) improves rehabilitation length of stay prediction when used with Functional Independence Measure FRGs classification system	Retrospective cohort: 1992; 252 inpatient rehabilitation facilities; USA	Population based, administrative: Uniform Data System for Medical Rehabilitation	All inpatient rehabilitation (N=82646) nTBI=1.13%	Comorbidity: 1. Unique ICD-9-CM codes 2. Number and type of Major Diagnostic Category 3. Number and type of chapter headings from ICD-9-CM Rationale: Physician concern regarding lack of comorbidity info. in Functional Independence Measure-Function Related Groups (FIM-FRGs) Method: Descriptive (frequency), linear regression Outcome: LOS Covariates: age, FIM-FRGs	% with ICD-9-CM codes associated with longest median LOS in non-traumatic brain dysfunction patients: 1. Cerebral artery occlusion: 2.6 2. Artificial opening status: 2.5 3. Other venous thrombosis: 1.9 Addition of diagnostic information increases explained variance by 1.9% from 31.5% to 33.4% (using ICD9CM codes); Chapter headings performed less well (numbers not reported)
McEwen et al., 2012 ³⁵	Describe patients admitted to ORP-SJRH and to analyze the relationships	Retrospective cohort: 2008–2010; Single center	Population based, administrative: NRS	All patients discharged from oncology rehabilitation (N=153) Brain cancer: 5.22%	Comorbidity: Number of pre-admit comorbid health conditions based on ICD-10-CA in the NRS Rationale: N/A	Simple linear regression was conducted with the following explanatory variables: age, sex, living alone, length of stay, number

Authors, date	Purpose	Study Design, Years, Setting	Data type: Data source	Population and stratification	Comorbidity Measurement, Rationale, Quantification Method, Outcome, Covariates	Comorbidity Results
	between patient characteristics and key rehabilitation outcomes in order to provide planning data for future prospective studies	rehabilitation facility; St. John's Rehab Hospital, Canada			Method: General linear models Outcome: Functional Independence Measure Covariates: age, sex, living alone, type of cancer, LOS	of comorbidities, and type of cancer, and results were used to assist with building a general linear model. Variable selection criteria were not reported, and comorbidity was not included in final models, therefore it was likely not significant.
Rollnik and Janosch, 2010 ³⁷	Investigate developments in length of stay in neurological early rehabilitation units in recent years as well as the parameters that influence patients' length of stay	Retrospective cohort; 2005–2008; Neurological rehabilitation hospital; Germany	Single center, administrative: BDH-Klinik Hessisch Oldendorf	Results presented across all neurological rehab inpatients (N=2060) Hypoxic damage: 3.2% Neoplasias: 2.7%	Method: Patient Clinical Complexity Level (PCCL); German Diagnosis Related Groups; Number of subdiagnoses Rationale: N/A Method: Frequency (frequency), ANOVA, LSD, Pearson correlation Outcome: LOS, early rehab Barthel index Covariates: Type of discharge	% of all patients with PCCL 0–4: 0: 2 1: 0.7 2: 4.3 3: 25.5 4: 67.4 Higher PCCL (4 vs. others): longer LOS (F:40.4, p<0.001) Number of subdiagnoses correlated with LOS (r:0.33, p<0.0001)
Alam et al., 2008 ⁴⁸	Determine whether patients with diagnoses of neoplasm undergoing acute rehabilitation differ from other patients in frequency of acute care transfer and type of medical complications	Retrospective cohort; 2001–2005; Acute rehabilitation hospital within an academic medical center; USA	Institutional database: MetroHealth Medical Center	Results presented across all patients with neoplasm, and non-neoplasm cases requiring transfer back to acute care (N=188) Meningioma of brain: 11.7%	Comorbidity: Selected major comorbid conditions (heart disease, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, deep vein thrombosis, pulmonary embolus, urinary tract infection, pneumonia), tier status Rationale: Various published literature cited in the introduction Method: Descriptive (frequency) Outcome: Frequency of unplanned transfer and reasons for the transfer	% of all patients with neoplasm with: Heart disease: 66 Stroke: 36 UTI: 33 Diabetes mellitus: 19 Chronic obstructive pulmonary disease: 12 % of all patients with neoplasm with: Tier 0: 65.1 Tier 1: 5.8 Tier 2: 13.8 Tier 3: 15.3
Nakase-Richardson et al., 2013 ⁴⁶	Report the injury and demographic characteristics, medical course, and rehabilitation outcome for a consecutive series of veterans and activity duty military personnel	Retrospective cohort; 2004–2009; 4 VHA PRCs with inpatient rehabilitation; California, Minnesota, Virginia, Florida, USA;	Abstracted electronic medical record: Veterans Health Administration's Polytrauma Rehabilitation Center / Emerging Consciousness Program	Nontrauma including stroke, anoxia, encephalopathy (N=16)	Comorbidity: Conditions requiring intervention: spasticity, dysautonomia, seizure, intracranial infection, heterotopic ossification, pulmonary embolism/deep vein thrombosis (PE/DVT), rehabilitation admission ventilator dependent Rationale: N/A Method: Descriptive (frequency) Outcome: Glasgow Coma Scale, Functional Independence Measure, Coma Recovery Scale-R, Rancho Levels of Cognitive Functioning Scale, Galveston Orientation and Amnesia Test, Orientation Log	% within non-trauma: Spasticity: 88 PE/DVT-anticoagulation: 75 PE/DVT-filter replacement: 6 PE/DVT-prophylaxis: 6 Dysautonomia: 38 Seizure: 19 Heterotopic ossification: 13 Hydrocephalus with shunt replacement: 12 Rehab admission ventilator-dependent: 6

Authors, date	Purpose	Study Design, Years, Setting	Data type: Data source	Population and stratification	Comorbidity Measurement, Rationale, Quantification Method, Outcome, Covariates	Comorbidity Results
Ng and Chua, 2005 ³⁸	Identify and characterize demographics, injury variables, complications, and functional outcomes in Asian patients presenting with States of Severely Altered Consciousness	Retrospective case series; 1998–2002; Inpatient neurological rehabilitation center; Singapore	Medical Records: Systematic chart review of all patients with states of severely altered consciousness	Patients with states of severely altered consciousness (N=30) Anoxic=16.6%	Comorbidity: All medical complications (new or exacerbated): Pneumonia = fever > 38 degrees Celsius and chest infiltrates consistent with consolidation. UTI = fever > 38 with pyuria Rationale: N/A Method: Descriptive, Two-tailed t-test or Mann-Whitney U test Outcome: Disability Rating Scale, Ranchos Amigos Scale, Modified Barthel Index	% of all patients with: More than 1 episode of hospital acquired infection requiring treatment: 73 UTI: 53 Pneumonia: 30 Central fever: 63 Spasticity: 93 Seizure: 36.7 Sepsis: 13 Status epilepticus: 10 Neurological deterioration: 7 Patients with central fever more functionally disabled (p:0.045)
Ganesh et al., 2013 ³⁹	To identify, for patients in states of seriously impaired consciousness, comorbid conditions present during inpatient rehabilitation and their association with function at one year	Prospective cross-sectional; 1996–2007; 4 inpatient rehabilitation facilities; USA	Emergency department, intensive care, acute care, and rehabilitation records, family/surrogate interview; Larger study database (n=157) for observational study on neurobehavioral recovery, inpatient rehabilitation, and functional outcome	Including both TBI and nTBI (vascular injuries and anoxia) N=68 Anoxia: 11.8%	Comorbidity: 1. Medical complications: UTI, hydrocephalus with or without shunt replacement, hypertension, seizures, pneumonia, renal failure, hypertonicty 2. Number of comorbidities 3. High No. of complication = 3+ Rationale: Included based on discussion of effects of comorbidities on health outcomes in introduction Method: Descriptive (frequency), Spearman correlations, linear regression Outcome: Cognitive, motor, and total Functional Independence Measure	% of all patients with: Active seizures: 45.6 Spasticity: 56.7 UTIs: 47.1 Preinjury hypotension: 3.0 Preinjury hypertension: 14.9 Injury onset hypertension: 42.6 Hydrocephalus: 38.2 Hydrocephalus requiring shunt: 30.9 Pneumonia: 61.7 Preinjury Alcohol abuse: 12.5 Presence of hydrocephalus, active seizures, spasticity, and UTIs are associated with lower functioning 1 year after injury No. of medical complications correlated with FIM total (r: -0.451, p<0.001), cognitive (r: -0.383, p<0.001), and motor (r: -4.93, p<0.001) High number of complications, controlling for etiology, significantly related to FIM motor (b: -21.6) and total 1 year FIM scores (b: -26.23)

DAD: Discharge Abstract Database
NRS: National Rehabilitation Reporting System
TBI: Traumatic brain injury
nTBI: Non-traumatic brain injury
N/A: Not applicable
CCI: Charlson Comorbidity Index
OHIP: Ontario Health Insurance Plan
UTI: Urinary Tract Infection