Delirium during Inpatient Rehabilitation: Detection, Risk Factors, Clinical Implications, and Risk Assessment

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“Chi mi toglie il regio scettro? Qual m’incalza orrendo spettro! Chi pe’l crine, ohimè, m’afferra? Chi mi stringe? Chi m’atterra? […] Ah fantasmi ho sol presenti... hanno acciar di fiamme ardenti! E di sangue il ciel vermiglio sul mio capo si versò! Ah! Perché, perché sul ciglio una lagrima spuntò?” [1]

“Who is it that takes my royal sceptre from me? What horrid spectre is pursuing me? Who seizes me, alack, by the hair? Who is crushing me?... Who lays me low? […] I am surrounded by phantoms…they are having flaming swords of fire! And the blood-red sky has fallen upon my head! Why, oh why did a tear start from my eye?”

“Nabucco” by Giuseppe Verdi (1813 – 1901), part II “L’empio”, 8th scene.

Perhaps one of the first cases of delirium described in the literature.

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Abbreviations

ACB	Anticholinergic Cognitive Burden
ACRM	American Congress of Rehabilitation Medicine
AIC	Akaike Information Criterion
AOR	Adjusted Odds Ratio
APA	American Psychiatric Association
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CAM	Confusion Assessment Method
CI	Confidence Interval
CIRS	Cumulative Illness Rating Scale
CPM	Clinical Prediction Model
CRP	C-Reactive Protein
DP	Probability of Developing Delirium
DRG	Diagnosis Related Groups
DSM	Diagnostic and Statistical Manual of Mental Disorders
EHR	Electronic Health Record
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drugs Administration
FIM	Functional Independence Measure
FN	False Negative
FP	False Positive
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
ICU	Intensive Care Unit
IQR	Interquartile range

ML	Machine Learning
NLP	Natural Language Processing
NPV	Negative Predictive Value
OR	Odds Ratio
PPV	Positive Predictive Value
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristics
RWD	Real World Data
RWE	Real World Evidence
SD	Standard Deviation
TN	True Negative
TP	True Positive
WBC	White Blood Cells
WHO	World Health Organization

Summary

One of the main goals of epidemiology is to identify factors that increase the risk of a single individual or a population developing a certain disease to reduce its morbidity or mortality. For this purpose, observational analytical studies, such as cohort studies or case-control studies, are often appropriate, as these kinds of studies are generally cheaper, more generalizable, and can be conducted on a larger scale than experimental studies.

Rehabilitation is a fundamental process in modern medicine that aims, through an interdisciplinary approach, to restore and maintain optimal physical, sensory, intellectual, psychological, and social functioning in patients with acute or chronic disabilities.

Delirium is known as a brain syndrome that dramatically impairs consciousness, attention, perception, thought, memory, psychomotor behavior, emotions, and the sleep-wake cycle of affected inpatients. In both acute and rehabilitation settings, delirium has been associated with prolonged length of stay and increased mortality. Furthermore, as patients suffering from delirium are unable to fulfill the rehabilitation therapy schedule, they often achieve poor rehabilitation outcomes, such as reduced autonomy after discharge. Delirium consequences cause annually additional costs for rehabilitation facilities and the entire healthcare system.
Preventing delirium and thus minimizing its clinical implications is possible, non-pharmacological interventions, such as cognitive stimulation or patient mobilization have been proven to be effective. However, to implement targeted interventions, it is essential to identify patients potentially at risk of developing delirium during inpatient rehabilitation.

This thesis aimed to identify a set of risk factors for the development of incident delirium during inpatient rehabilitation, to assess the impact of delirium on functional rehabilitation outcomes and length of rehabilitation, and to develop a clinical prediction model based on parameters available on admission able to quantify the individual's

risk of developing delirium during inpatient rehabilitation. For this purpose, the thesis was structured on three projects based on data from a collective of approximately 10’000 patients who underwent inpatient rehabilitation at ZURZACH Care, Rehaklinik Bad Zurzach, an inpatient rehabilitation clinic in Switzerland.

We first developed and validated a chart-based method to detect incident delirium episodes within our study population. The developed method, based on delirium predictive key words identified within medical notes, was able to detect incident delirium episodes with low to moderate accuracy. However, supplemented with experts’ review, this method was able to identify a validated population of 125 incident delirium episodes.

Based on the validated delirium episodes and routinely collected clinical data, we conducted a retrospective matched case-control study in the subsequent project. The results identified older age, neurological rehabilitation, reduced Functional Independence Measure (FIM), and high disease (CIRS) or anticholinergic burden (ACB) at admission as factors associated with a considerably increased risk of incident delirium during rehabilitation. Patients with infectious diseases, disorders of fluid, electrolyte and acid-base balance, and Parkinson’s disease at admission, and patients treated with laxatives, heparins, antidepressants, dopaminergic agents, and antipsychotics during rehabilitation, were at an increased risk of developing delirium compared to patients without these conditions or patients not receiving these drug classes. Furthermore, we observed that patients who became delirious during rehabilitation had a longer mean stay and a poorer functional rehabilitation outcome than patients without delirium.

In the last project, we developed a clinical prediction model based on parameters available at rehabilitation admission. We observed that age, FIM, disorders of fluid, electrolyte and acid-base balance, use of other analgesic and antipyretics or anti-Parkinson drugs on admission, and an ACB ≥3 were selected as predictor parameters. Upon validation, this model would allow an individual’s risk calculation of developing incident delirium during inpatient rehabilitation.

General Introduction

Epidemiology

Definition

"Epidemiology is the study of how a disease is distributed in populations and the factors that influence or determine this distribution. Why does a disease develop in some people and not in others?" With this definition and question, Leon Gordis introduces the basic premise of epidemiology, namely that diseases are not distributed randomly within a population, but that single individuals have genetic or environmental characteristics able to predispose or protect them against certain diseases.[2] Usually the development of a disease is related to an interaction between several genetic and environmental factors. One of the main objectives of epidemiology is to reduce the morbidity or mortality of a certain disease by identifying and addressing the factors that increase a person's or population's risk for that disease. For instance, by developing a prevention program for a disease based on its assessed risk factors.[2]

In the context of risk factors, it is important to differentiate between modifiable characteristics such as obesity, diet, and other lifestyle factors, which may be improved to minimize the risk of disease, and not modifiable characteristics such as age, sex, and race, which cannot be altered, but need to be known to identify high-risk subgroups of a population and, for instance, implement targeted preventive strategies.[2]

Other objectives of epidemiology are to characterize the distribution of diseases in the community, to study the natural history and prognosis of diseases (e.g., morbidity or mortality rates), and to evaluate existing and newly developed preventive and therapeutic procedures in health care systems. Furthermore, epidemiology provides the scientific evidence to develop public policy related to environmental problems, genetic issues, and other applications regarding disease prevention and health promotion. Prevention programs may be population-based, where a preventive measure is widely applied to an entire population and is generally noninvasive and not expensive (e.g., dietary advice for preventing coronary disease), or high-risk group based, where preventive measure is directed to a population subgroup with an

expected high risk for a certain disease (e.g., mammography for the prevention of breast cancer).[2]

Study Designs in Epidemiology

Observational Studies vs. Experimental Studies

In epidemiological research there are two main groups of study designs, experimental and observational, the latter are further subdivided into descriptive and analytical. Experimental studies differ from observational studies in that an investigator allocates (or does not allocate) an intervention to participants, rather than just observes exposure in populations. The aim of experimental studies is generally to test a hypothesis (e.g., randomized controlled trials [RCTs]).[3] The choice of the most suitable study design primarily depends on the study question and the availability of data. Although experimental studies can test causal associations between exposures and outcomes and provide a higher level of scientific evidence than observational studies, they are not suitable in some cases. In such cases, e.g. if the intervention is unethical because the exposure is already known to be harmful, if the outcome is rare or time-delayed and could therefore not be captured in an experimental study with limited study populations or observational periods, or if an experimental study is too expensive, observational studies can be more appropriate.[4]

Descriptive Observational Studies

Descriptive observational studies characterize exposure and outcome without investigating their association. They include case reports, case series, ecologic studies, and some cross-sectional studies. The main difference to analytical observational studies is the lack of a comparison group. For this reason, descriptive studies are not able to assess an association between outcome and exposure.[5]

Analytical Observational Studies

Analytical observational studies investigate associations between exposures and outcomes. The main types of analytical observational studies are cohort studies, case-control studies, case-crossover, and some cross-sectional studies (with a comparison group).[5]

Cohort Studies

In a cohort study, a group of exposed individuals and a group (or more) of nonexposed (or differently exposed) individuals are selected and followed up to compare the incidence of a disease (outcome) in both groups. If the incidence of the disease differs among the exposed and the unexposed group, there may exist an association between the exposure and the outcome. This association "may exist" because, since in a cohort study, study participants are not randomized to an intervention (the exposure), there might be factors that led people to be exposed, that are also associated with the outcome. The lack of randomization is the main difference between a cohort study and an RCT, in which individuals are randomly assigned to the intervention (exposed) or control (unexposed) group. An association between an exposure and an outcome can be positive if the incidence of the outcome is higher in the exposed group than in the unexposed group or negative (or protective) if the incidence of the disease is lower in the exposed group than in the unexposed group. Cohort studies can be performed prospectively (also called concurrent cohort studies) or retrospectively (also called nonconcurrent or historical cohort study), if data on exposure and outcomes (e.g., from a patient or disease registry) are available at the time of the study conduction (Figure 1).[6]

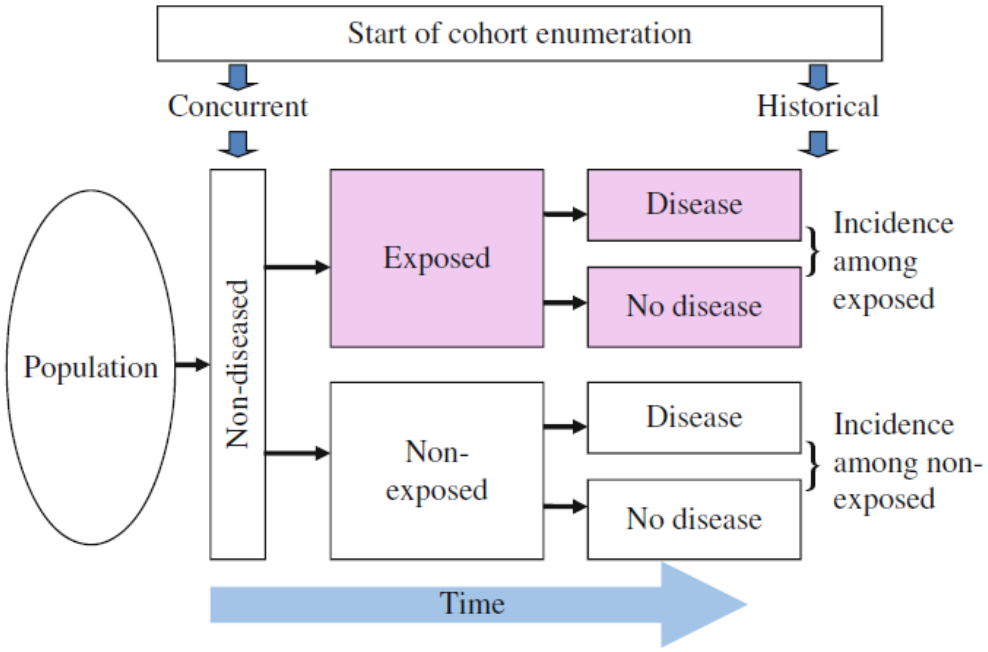

Figure 1: Design of a prospective (concurrent) or a retrospective (historical) cohort study. (Miller et al.[7])

Case-Control Studies

In a case-control study, to examine the association between one or more exposures to an outcome, a group of individuals with the outcome (cases) is compared with a selected group of individuals without (controls). If the prevalence of an exposure differs among diseased and non-diseased groups, there may exist an association between the exposure and the outcome (Figure 2). Because of the study design, case-control studies may be affected by two common systematic errors (or biases). The first one is related to the validity of retrospectively collected exposure information, which may differ between people with the outcome and people without the outcome (recall bias). This kind of bias is typical for data collected through interviews, whereas it is less common for data collected from standardized databases such as health care registers. The second common systematic error is related to the selection of controls, as other factors than the exposure of interest, such as age or sex, may be associated with the outcome (selection bias). To minimize this kind of bias, one should select the controls from the same source population as the cases (e.g., from the same hospital ward). Furthermore, as in case-control studies, the proportion between cases and controls is determined by the investigator and does not reflect the real proportion among the source population, it is not possible to estimate the incidence or prevalence of the outcome.[8,9]

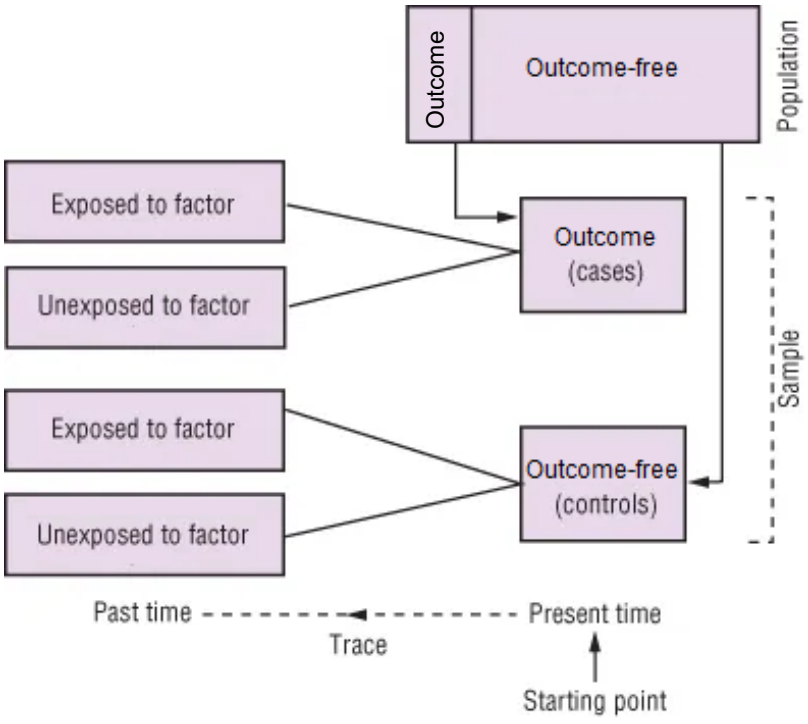

Figure 2: Design of a case-control study. (adapted from «Basicmedical Key»[10])

Case-Crossover and Cross-Sectional Studies

In case-crossover studies, the exposure of interest is assessed on the same subject and compared during two distinct time periods, the first period immediately before the outcome (exposed), and the second period generally further away from the outcome (unexposed). Because of this study design, all cases serve as their own controls, with the advantage that cases and controls are comparable in most of their characteristics, except for the exposure of interest. This design is restricted to testing transient exposures with a short latency between exposure and outcome, for example, to assess if an intense physical exercise could trigger a myocardial infarction. In addition to this restriction, a major limitation of this study design is the potential risk of recall bias, as exposure information is often derived from subject interviews and persons generally recall better an episode that occurred shortly before a critical event, such as an intense physical exercise minutes before a myocardial infarction, than a similar episode that occurred months earlier in the absence of any critical event.[8]

In contrast, in cross-sectional studies, both exposure and outcome are assessed simultaneously for each subject at a certain point in time. The association between exposure and outcome can be assessed by comparing the prevalence of the outcome within exposed and unexposed subjects or by comparing the prevalence of the exposure within people with the outcome and people without. Although cross-sectional studies can be very useful to explore possible risk factors for an outcome, their main limitation is the inability to establish a temporal relationship between exposure and outcome.[8]

Because of their simplicity and relatively low resource requirements, case-crossover and cross-sectional studies represent an effective method for generating hypotheses on possible associations between exposures and outcomes. However, given the limitations mentioned, to establish etiologic relationships, it is often necessary to rely on case-control or cohort studies.[8]

Quality and Validity of Diagnostic or Screening Tests

In epidemiology, to characterize the distribution of diseases or assess possible risk factors associated with a disease, it is fundamental to distinguish between diseased and undiseased individuals within a population. For this purpose, clinical tests or screening methods are used in modern medicine praxis. The quality of these screening or diagnostic tests is relevant for single patients who want to know whether they are suffering from a certain disease but is also crucial for epidemiological studies, which should base on solid and reliable data on who is diseased and who is not. Two questions need to be answered to assess the quality of a clinical test: “How good is the test at identifying people with the disease and how good is the test at identifying people without the disease?” To do this, it is necessary to compare the test results (positive / negative) with an unequivocal diagnosis or an already validated diagnostic method (diseased / undiseased) for the respective disease, namely a gold standard. From this comparison, one can distinguish between four different groups: Individuals who have the disease and have tested positive (true positive [TP]), individuals who do not have the disease and have tested negative (true negative [TN]), individuals who do not have the disease but have tested positive (false positive [FP]), and individuals who have the disease but have tested negative (false negative [FN]). The ability of the test to correctly identify those who have the disease (first question), is defined as “sensitivity” and is calculated as the proportion of diseased people (TP + FN) who were correctly identified as positive by the test (TP). Otherwise, the ability of a test to correctly identify those who do not have the disease (second question), is defined as “specificity” and is calculated as the proportion of undiseased people (TN + FP) who are correctly identified as negative by the test (TN) (Figure 3).[11]

	TRUE CHARACTERISTICS IN THE POPULATION	
Test Results	**With Disease**	**Without Disease**
Positive	True positive (TP) = Have disease and have positive test	False positive (FP) = No disease, but have positive test
Negative	False negative (FN) = Have disease, but have negative test	True negative (TN) = No disease and have negative test
	$\text{Sensitivity} = \frac{TP}{TP + FN}$	$\text{Specificity} = \frac{TN}{TN + FP}$

Figure 3: Comparison between the test result and the true characteristics. (Gordis L.[11])

However, in clinical settings, a different kind of question may be much more relevant: “If a test result is positive, what is the probability that the positively tested patient has the disease?” or “If a test result is negative, what is the probability that the negatively tested patient does not have the disease?” The proportion of patients who tested positive and actually have the disease is defined as the positive predictive value (PPV) and is calculated by dividing the number of true positives (TP) by the total number who tested positive (TP + FP). In the same way, the proportion of patients who tested negative and actually do not have the disease is defined as the negative predictive value (NPV) and is calculated by dividing the number of true negatives (TN) by the total number who tested negative (TN + FN).[11]

Since the PPV and the NPV are influenced by the prevalence of a disease, they are less reliable for assessing the intrinsic quality of a diagnostic test, especially for diseases with low prevalence. However, the PPV has the advantage of being calculated even in the absence of data on the discernment between true and false negatives and is therefore preferred in some validation studies.[12]

Pharmacoepidemiology

By applying methods used in epidemiology to the content area of clinical pharmacology (the study of the effects of drugs in single human individuals), one can answer inquiries of pharmacoepidemiology, an applied discipline that aims to study the use and the effects of drugs in large populations.[9] Pharmacoepidemiology has become increasingly important in recent decades due to the growing need for regulatory authorities to monitor adverse drug reactions after approval. Post-marketing surveillance (phase IV) comprises pharmacovigilance and pharmacoepidemiology studies and aims to identify adverse drug reactions that were not identified in phase I-III clinical trials. Pharmacovigilance studies are based on the collection of spontaneous reports of adverse drug reactions. Pharmacovigilance is suitable to collect information and formulate hypotheses about unknown and rare drug adverse reactions but is inappropriate for the formal quantification of adverse drug reactions. For this purpose, pharmacoepidemiology studies are required. Compared to phase I-III clinical trials, post-marketing pharmacoepidemiological studies are generally performed in larger population-based databases, which allow even the detection of very rare adverse events. In addition, these databases enable the detection of adverse events that may occur after a long latency period, by comprising sufficient exposure time. Above all, they include the real target population of a certain drug, including people who are usually excluded from clinical trials for ethical reasons (e.g., children or pregnant women).[13] Pharmacoepidemiological research is thus able to describe patterns of drug use under “real-life” conditions and to quantitatively investigate not only adverse reactions but also previously undetected positive effects of drugs.[9]

Rehabilitation

Definition and Goals

The rehabilitation process traditionally aimed to facilitate the normalization of human functions after injury, disease, or congenital disabilities.[14] According to the World Health Organization (WHO), rehabilitation "is a process aimed at enabling disabled persons to reach and maintain their optimal physical, sensory, intellectual, psychological, and social functional levels". Rehabilitation provides disabled people with the tools they need to attain independence and self-determination".[15] Literally, rehabilitation means "redressing" (Latin habitat – dress) and can therefore be interpreted as "to redress" the original independence and self-determination in the existing environment.[14] In Switzerland, rehabilitation is based on the model of the International Classification of Functioning, Disability, and Health (ICF) (Figure 4).[16,17] This model describes the health situation not only from the perspective of the disease but also from a modern and global functional perspective including the personal situation in everyday life, work, and society. This is also the key principle to identifying problems and needs, and setting rehabilitation goals at the beginning of the rehabilitation process.[16]

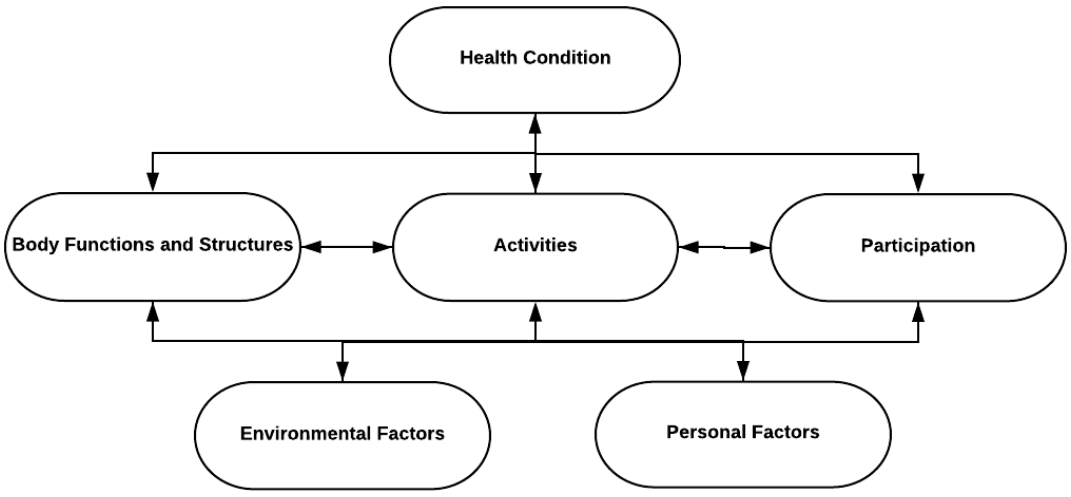

Figure 4: The ICF rehabilitation model. (adapted from WHO[17])

The rehabilitation process begins with the assessment of the individual's disability, by classifying health-related problems into the following three areas:[14]

- *Impairments:* problems in body function or structure, such as aphasia or motor deficits.
- *Activity limitations:* difficulties a person may experience in performing activities.
- *Participation limitations:* problems a person may encounter in participating in everyday life situations.

Rehabilitation goals are then set to address health-related problems of each specific area:[16,17]

1. Treating impairments in body function or structure by using specific therapies.
2. Resolution of activity limitation through the training or the development of functional compensation capacities.
3. Reduction of activity or participation limitations by adapting the environment to the patient's situation, e.g., by using assistive devices.
4. Planning the therapy based on individual requirements and considering contextual factors such as psychosocial and environmental factors.
5. Teaching preventive strategies (secondary prevention).

In this sense, rehabilitation is also indicated in chronic diseases and palliative situations to maintain the health condition and prevent excessive functional decline.[17]

To achieve the above-mentioned goals, modern rehabilitation relies on the one hand on an interdisciplinary team which includes physicians, nurses, psychologists, physiotherapists, occupational therapists, speech therapists, and recreational therapists, but on the other hand on the disabled person, which is involved in both planning and decision making.[16]

Functional Independence Measure and Cumulative Illness Rating Scale

In the 1980s, the need for a standardized functional assessment measure in rehabilitation medicine to assess the degree of dysfunction, disability, or handicap of patients, and the effect of rehabilitation, has grown steadily. This need was also justified because the Diagnosis Related Groups classification system (DRG) for diseases, developed at that time, did not take into account the severity of the diseases and consequently the functional impairment degree of patients. The idea focused on the development of a systematic score system based on the evaluation of patients' capacity, or need of assistance from other people, to perform basic daily activities, such as eating or taking care of personal hygiene.[18]

For this purpose, in the United States a task force created by the American Congress of Rehabilitation Medicine (ACRM), after reviewing numerous publications of functional assessment instruments, selected and defined 18 functional assessment items (13 motoric and 5 cognitive) and a seven-point rating scale to assess the degree of independency for every single item (Figure 5). This instrument was named Functional Independence Measure (FIM) and it has been subsequently validated in several studies.[18] At present, the FIM is systematically and widely used in the rehabilitation field to measure patients' rehabilitation progress and also to determine reimbursement rates.[19]

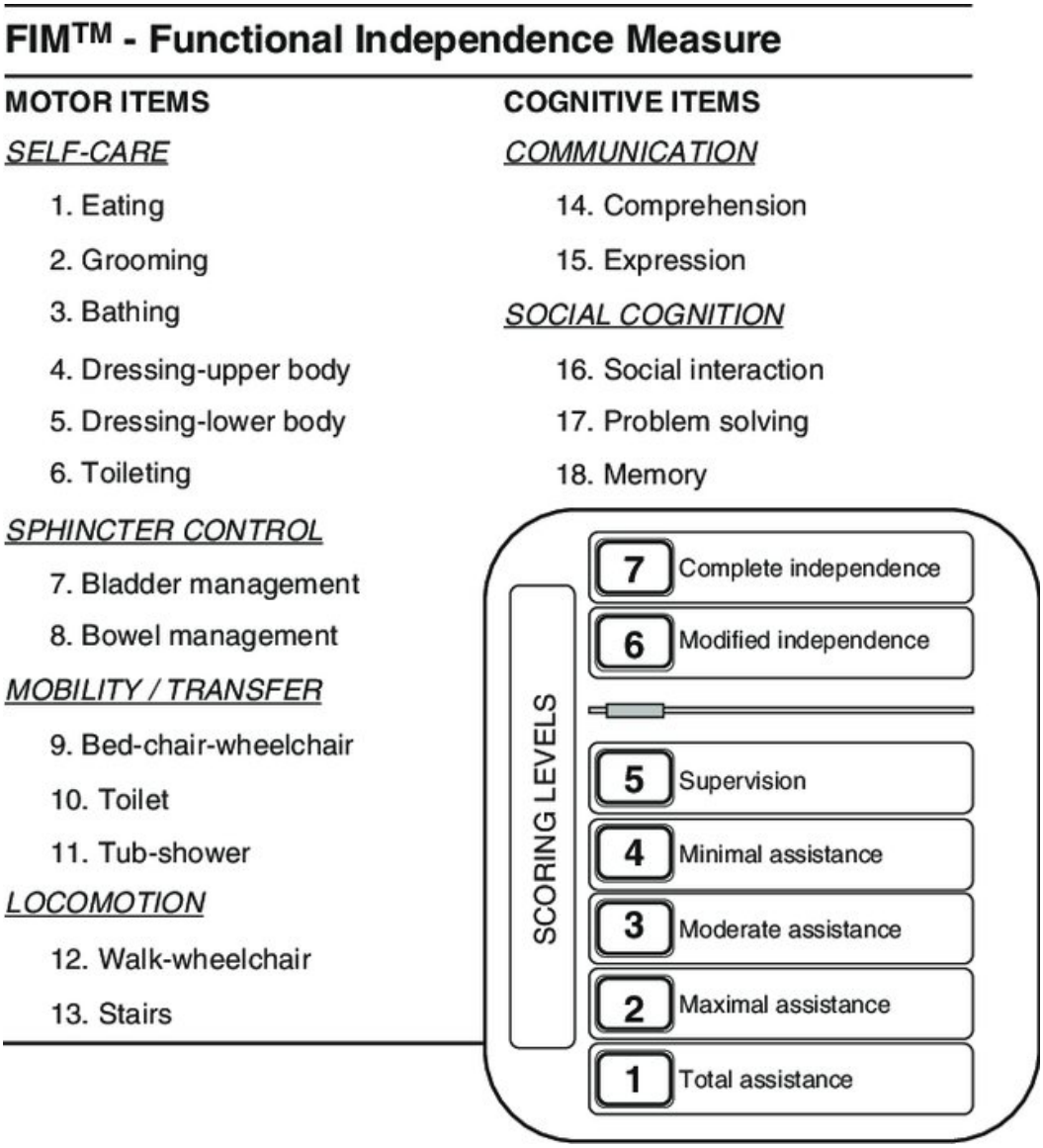

Figure 5: The FIM scale rates the degree of independency in 18 activities of daily living (1: total assistance; 7: complete independence): 13 motoric items (total score 13–91) and 5 cognitive items (total score 5–35). (Tesio L.[20])

Another instrument routinely used in rehabilitation to measure physical impairment is the Cumulative Illness Rating Scale (CIRS). Unlike the FIM, which focuses on the patient's functional capacity regardless of the diagnosed diseases, the CIRS aims to measure the impairment degree due to comorbidities. The CIRS rates 13 independent organ areas with a four-point rating scale to describe the degree of impairment due to a disease (0: none - no impairment to that organ/system; 1: mild - impairment does not interfere with normal activity; 2: moderate - impairment interferes with normal activity; 3: severe - impairment is disabling; 4: extremely severe - impairment is life-threatening) (Figure 6).[21] The CIRS has been validated in different settings and has proven to be a valid indicator of health status among geriatric inpatients.[22–24]

CUMULATIVE ILLNESS RATING SCALE
(Linn, Linn, Gurel)

Each system should be rated as follows:

0—None
1—Mild
2—Moderate
3—Severe
4—Extremely Severe

CARDIOVASCULAR-RESPIRATORY SYSTEM

1. :__: CARDIAC (heart only)
2. :__: VASCULAR (blood, blood vessels and cells, marrow, spleen, lymphatics)
3. :__: RESPIRATORY (lungs, bronchi, trachea below the larynx)
4. :__: EENT (eye, ear, nose, throat, larynx)

GASTROINTESTINAL SYSTEM

5. :__: UPPER GI (esophagus, stomach, duodenum, biliary and pancreatic trees)
6. :__: LOWER GI (intestines, hernias)
7. :__: HEPATIC (liver only)

GENITOURINARY SYSTEM

8. :__: RENAL (kidneys only)
9. :__: OTHER GU (ureters, bladder, urethra, prostate, genitals)

MUSCULO-SKELETAL-INTEGUMENTARY SYSTEM

10. :__: MSI (muscles, bone, skin)

NEUROPSYCHIATRIC SYSTEM

11. :__: NEUROLOGIC (brain, spinal cord, nerves)
12. :__: PSYCHIATRIC (mental)

GENERAL SYSTEM

13. :__: ENDOCRINE-METABOLIC (includes diffuse infections, poisonings)

Figure 6: The CIRS rates the impairment degree due to comorbidities based on 13 independent organ areas (total score 0–52). (Linn et al.[21])

Delirium

Definition and Manifestation

Delirium is known as an etiologically non-specific organic brain syndrome characterized by concomitant disturbances of consciousness, attention, perception, thinking, memory, psychomotor behaviors, emotions, and the sleep-wake cycle.[25,26] Delirium may occur with or without pre-existing neurocognitive disorders and may vary in duration from several hours to several days and in severity from mild to severe.[25,26]

Diagnostic criteria for delirium are defined according to the following classification systems:

- The International Classification of Disease, 10th revision (ICD-10) of the WHO.[25]
- The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) of the American Psychiatric Association (APA).[26]

The ICD-10 distinguishes between the Clinical Diagnostic Guidelines for Clinical Practice and the much stricter Diagnostic Criteria for Research and Practice. In contrast to the DSM-V, the ICD-10 assigns delirium to two different chapters according to the etiology: organic mental disorders and disorders caused by psychotropic substances. Both classification systems agree on the three main diagnostic criteria: disturbance of attention, cognitive impairment, and acute onset and fluctuating course. Disturbance of attention refers to an inability to focus, maintain or shift attention. The cognitive impairment includes, in particular, short-term memory impairment, disorientation (especially temporal), and perceptual disorders such as illusory misperceptions and hallucinations (especially visual). The acute onset is usually defined within hours or days, while the fluctuation of symptoms over a single day.[27] Furthermore, the ICD-10 requires the additional presence of the following symptoms for a definitive diagnosis: psychomotor disorder, sleep-wake cycle disorder, and affective disorder, such as depression, anxiety or fear, irritability, euphoria, apathy, and perplexity.[27] The ICD-10 classification is therefore stricter, and fewer patients are diagnosed with delirium than with the DSM-V criteria.[28] The specific criteria for each delirium classification system are summarized in Table 1.

Table 1: Diagnostic criteria for delirium. (adapted and translated from Savaskan et al.[27])

Feature	DSM-V	ICD-10 DIAGNOSTIC CRITERIA FOR RESEARCH AND PRACTICE	ICD-10 DIAGNOSTIC GUIDELINES FOR CLINICAL PRACTICE
Disturbance of consciousness or attention	Reduced ability to direct, focus, sustain and shift attention and reduced environmental awareness.	Disturbance of consciousness, i.e., reduced awareness of surroundings with reduced ability to focus, maintain, and shift attention.	Disturbance of consciousness (somnolence to coma), attention disorder (reduced ability to focus, maintain, and shift attention).
Cognitive impairment	Cognitive impairment such as memory impairment, disorientation, speech disorder, visual-spatial disorder or perceptual disorder.	1. Impaired short-term memory (immediate recall) with relatively intact long-term memory, and 2. Disorientation to time, place, or person	Global disorders of cognition, perceptual disorders such as optical hallucinations, disturbed perception, incoherence, short-term memory disorder, temporal disorientation, in severe cases also in terms of location and person
Psychomotor disorder	Not specified	At least one of the following characteristics: 1. Rapid, unpredictable change between hypo- and hyperactivity. 2. Prolonged reaction time 3. Increased or decreased fluency of speech 4. Increased shock response	Hypo- or hyperactivity and unpredictable change between the two; prolonged reaction time; increased or decreased fluency; increased shock response.
Disturbance of the sleep-wake rhythm	Not specified	At least one of the following characteristics: 1. sleep disturbance, in severe cases complete insomnia, with or without daytime sleepiness or reversal of the sleep-wake rhythm. 2. Nocturnal worsening of the symptoms 3. Nightmares that may persist after awakening as hallucinations or illusions.	Sleep disturbances, in severe cases complete insomnia or reversal of the sleep-wake rhythm; sleepiness during the day; worsening at night. Symptomatology: nightmares that may persist after awakening as hallucinations or illusions.
Affective disorder	Not specified	Not specified	Depression, anxiety, irritability, euphoria, apathy, or helplessness
Course	Acute onset (usually within hours or a few days) and fluctuation throughout the day	Sudden onset and change of symptom expression during the day	Acute onset, changing in the course of the day, total duration less than six months

Etiology	Evidence (from history, physical examination, or laboratory findings) of a physical illness causative for the disorder or of substance induction (psychotropic substances, medication).	Objective evidence (based on history, physical, neurological and laboratory examinations) of an underlying cerebral or systemic disease (other than psychotropic substances).	Not specified
Comment	The disorder cannot be better explained by a pre-existing neurocognitive disorder or a vigilance disorder, such as a coma.	Affective disorders, such as depression, anxiety or fear, irritability, euphoria, apathy or wondering perplexity, and perceptual disorders (illusions or hallucinations) are typical but not specific to the diagnosis.	Not specified

Subtypes

Delirium is classified into hyperactive, hypoactive, and mixed (Table 2).[29] In the case of hyperactive delirium, symptoms such as agitation and hallucinations, sometimes with aggressive behavior as well as vegetative disorders, are more pronounced. Patients can be verbally and physically threatening.[30] In hypoactive delirium, however, patients are often apathetic, and the symptoms are easily confused with depression. In clinical practice, careful and expert observation skills are required to detect its subtle feature. Therefore, the hypoactive form of delirium tends to be misdiagnosed and patients often fail to receive the necessary interventions.[31,32] But even if recognized, the hypoactive form has a worse prognosis in terms of mortality than the hyperactive form.[32]

Table 2: Delirium subtypes and symptoms. (adapted and translated from Savaskan et al.[27])

HYPERACTIVE DELIRIUM	HYPOACTIVE DELIRIUM	MIXED DELIRIUM
Increased motor activity Restlessness Wandering Agitation, impatience, aggressiveness Mood swings Psychotic symptoms Vegetative impairment	Reduced motor function Slowing down Passivity Apathy Maybe psychotic symptoms	Alternation of hyperactive and hypoactive symptoms

Prevalence, Incidence, and Epidemiology

Criteria of the DSM-V are generally used to diagnose delirium in clinical practice and are exclusively based on subjective clinical observations and not on specific tests or laboratory analyses.[26] For this reason, the diagnosis of delirium remains challenging, and due to the fluctuating nature of various cognitive, behavioral, and psychological symptoms, it can often be missed or confused with different psychiatric disorders. Among the best-known differential diagnoses of delirium are dementia, depression, and status epilepticus.[33] This causes great variability in the reported prevalence and incidence of delirium within inpatient settings. Depending on the clinical setting and the average age of the investigated populations, reported delirium prevalence at hospital admission varies between 11% and 25% among patients over 65 years. Reported cumulative delirium incidence among non-intensive care inpatients varies between 3% and 51%, with a range from 11% to 14% in general medical wards, 20% to 29% in the geriatric unit, and 20% to 22% in post-acute care.[34–36] The large variation in the reported prevalence and incidence of delirium among inpatients highlights the heterogeneity in the methodology used to assess delirium. Although delirium is not an exclusively nosocomial disease, there are limited data on its prevalence and incidence in the outpatient setting. A review among the older general population reported a delirium prevalence of 1-2% in persons over 65 years and 10% in persons over 85 years.[37]

Assessment and Monitoring

Several assessment or screening tools have been developed and validated over time to diagnose delirium or to measure its intensity. Most of these tools are based on clinical or trained medical staff observations according to the DSM criteria and only a few to the ICD-10 criteria.[38] Besides the observation criteria, screening tools differ in terms of setting (general medical wards, geriatrics, intentional care, oncology, palliative care, neurology, psychiatry, and rehabilitation), assessment method (structured questions or simple observation of daily activities), aim (screening, diagnosis or assessment of severity) and qualification of raters (physician, nurse or lay person).[27] For this reason, there is no ideal delirium assessment instrument suitable for every situation; instead, the choice should be made according to the specific needs and criteria mentioned above. The most common delirium assessment tools are summarized in Table 3.

Table 3: Most commonly used delirium assessment tools, their restrictions, and aims.[38–43]

DELIRIUM INSTRUMENT, YEAR OF PUBLICATION	REQUIRED QUALIFICATIONS OF RATERS	VALIDITY OF SETTING	REFERENCE CRITERIA	AIM
Confusion Assessment Method (CAM), 1990	Trained lay or clinical staff	Various medical settings (incl. rehabilitation)	DSM-III-R	Diagnostic
Delirium Observation Scale (DOSS), 2003	Nurses without specialized training	General wards, palliative care, cardiac surgery	DSM-IV	Screening
Delirium Rating Scale-Revised-98 (DRS-R-98), 2001	Psychiatrically trained clinicians	Various medical settings (incl. rehabilitation)	DSM-IV	Assessment of severity
Memorial Delirium Assessment Scale (MDAS), 1997	Trained clinicians	Surgical, Oncology, Palliative care	DSM-III-R or DSM-V	Assessment of severity

Pathophysiology and Risk Factors

The pathogenesis of delirium is usually multifactorial. It can be explained by the model of complex interactions between pre-existing, predisposing factors on the one hand and acute or sub-acute precipitating factors on the other.[44–46] While predisposing factors determine the individual vulnerability and thus the underlying risk of a patient developing delirium, precipitating factors are the triggers of delirium (Figure 7). In order to prevent or treat delirium, it is important to recognize both: the predisposing factors to determine the individual risk profile and thus implement appropriate preventive measures and the precipitating factors to address them directly and thus treat delirium causally.[27]

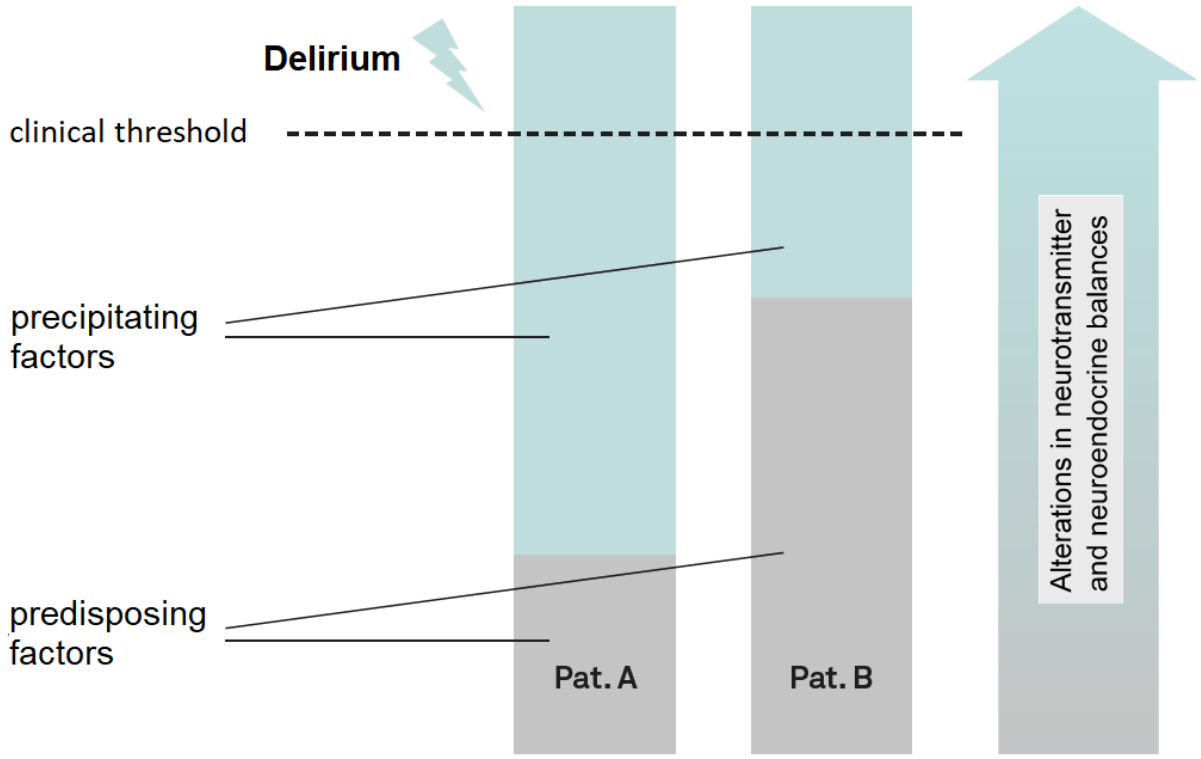

Figure 7: Multifactorial model of the pathogenesis of delirium: the cumulative effect of individual predisposing and precipitating factors. Patient A: Low vulnerability (grey base), only a severe acute or subacute disturbance (light blue column) triggers delirium. Patient B: High vulnerability, even a relatively mild physical or psychological stress factor can trigger delirium.
(adapted and translated from Savaskan et al.[27])

Based on several studies (clinical observations in animal models, drug side effects, or biomarker studies), it can be assumed that relatively unspecific pathophysiological changes in the neurotransmitter and neuroendocrine balances are associated with the pathogenesis of delirium.[46–49] The cerebral neurotransmitter changes include above all a decrease in acetylcholine and an increase in dopamine. Other pathogenetic mechanisms, such as neuroinflammatory processes, disruption of the hypothalamic-pituitary-adrenocortical axis, cerebral hypoperfusion, oxidative stress, and mitochondrial dysfunction, also appear to be involved in the promotion of neurotransmitter imbalance and neuronal network dysfunction.[47,50–52] Similarly, a decrease in melatonin secretion, an increase in cortisol, and altered concentrations of various inflammatory mediators have been observed in patients with delirium.[49]
Depending on predisposing factors, pathophysiological changes may be pre-existing at a low, clinically irrelevant level and cumulatively contribute to the risk of delirium (Figure 7), or they may also amplify the physiological response to an acute trigger. For example, the combination of chronic elevated low-level inflammatory activity associated with older age, depression, neurodegenerative or vascular disease, and an acute, relatively mild inflammatory stimulus, such as in the case of systemic inflammation in urinary tract infections, may be sufficient to affect neurotransmitter changes and neuroendocrine alterations and trigger delirium.[47,51–53]

A large number of risk factors for delirium have been identified within the literature, but to date, no study has compared a wide range of risk factors simultaneously. Therefore, it is not possible to systematically classify the risk factors according to their weights in relation to the others. Existing classifications of delirium risk factors are very heterogeneous and depend both on the authors and on the international recommendations on which they are based.[27] However, most national scientific societies agree with the classification of predisposing and precipitating factors proposed by Inouye et al. and summarized in Table 4.[35]

Table 4: Predisposing and precipitating factors for delirium according to Inouye et al.[35].

PREDISPOSING FACTORS	PRECIPITATING FACTORS
Demographic characteristics	Cumulative use of medication
Cognitive and physical condition	Primary neurological disease (i.e., Stroke, meningitis, cerebral hemorrhage)
Sensory disturbances	Infectious and metabolic disease
Decreased fluid intake	Severity of illness
Polypharmacy	Surgical procedures (i.e., Orthopedic, cardiac or other interventions)
Use of psychotropic drugs	Pain
Alcohol abuse	Emotional stress
Comorbidity	

Prevention and Treatment

Both prevention and treatment of delirium are based on pharmacological interventions, such as drug treatment, and non-pharmacological interventions, such as cognitive stimulation or time orientation.

Current scientific evidence does not support the use of medication to prevent delirium.[54,55] Some studies have shown a positive effect of haloperidol on the incidence and duration of delirium in hospitalized patients.[56,57] However, the numerous side effects of haloperidol, such as extrapyramidal symptoms or QT-prolongation, preclude safe preventive use in patients at risk of delirium.[58] Several studies, including a RCT, have shown possible efficacy in preventing delirium for melatonin or the melatonin receptor agonist ramelteon.[59–62] Melatonin is an endogenous hormone involved in circadian rhythms and the sleep-wake cycle. Abnormal melatonin secretion found in elderly patients with postoperative delirium may suggest an implication in the pathophysiology of delirium and support the protective effect of melatonin supplementation.[63] However, this effect seems confined to surgical and ICU patients, and the dosage, as well as the duration of the melatonin supplementation, remains unclear.[64,65] For these reasons, and despite its favorable side effects profile, the prophylactic use of melatonin in high-risk delirium patients remains a pragmatic and individual decision of the clinical staff.

Non-pharmacological interventions to prevent delirium are generally based on identifying and reversing potential precipitating delirium factors and mitigating environmental triggers. A recent Cochrane review identified 22 randomized controlled trials (RCTs) that compared multi-component non-pharmacological interventions, such as daily observation, early mobilization, cognitive stimulation, reorientation, or prevention of hypoxemia, dehydration, malnutrition, and constipation, to standard care. The authors concluded that non-pharmacologic approaches reduced the incidence of delirium by around 43% across all hospital settings (excluded ICU), while no difference was found in mortality.[66]

The treatment of delirium is divided into causal therapy and symptomatic therapy. Causal therapy consists of attempting to remove a delirium precipitating factor, such as treating an infection or adjusting an electrolyte imbalance, whereas symptomatic therapy aims to combat the symptoms of delirium and is almost limited to the treatment

of psychosis associated with hyperactive delirium. Although causal therapy is preferable to symptomatic therapy, it is often not possible to identify the trigger factor of delirium or there is a need to quickly interrupt the patient's psychosis due to the risk of self-harm, in which case symptomatic therapy plays a primary role.

While several drug classes have been studied, the scientific evidence for the symptomatic treatment of delirium remains limited and controversial. Antipsychotics, whose effects are mediated, depending on generation, by blockade of brain dopamine and serotonin receptor pathways, are the preferred drug class for the symptomatic treatment of delirium in many international guidelines.[27,67–69] First-generation antipsychotics (e.g., haloperidol, chlorpromazine) are mainly used against psychosis, hallucinations, and agitation, while second-generation antipsychotics, which act mainly on serotonin receptors, are preferred to treat emotional and social withdrawal.[70] However, these effects have mainly been observed in subjects with schizophrenia. Evidence on the therapeutic efficacy of antipsychotics in delirious patients is still limited. Two recent systematic reviews including several RCTs found no differences for antipsychotics, compared to placebo, in the length of stay at the hospital, delirium duration and mortality, and insufficient or no evidence regarding the effect on cognitive function and delirium severity.[54,70] Moreover, the use of antipsychotics is associated with potentially serious side effects such as cardiac arrhythmias or extrapyramidal symptoms, and above all increased all-cause mortality in elderly patients.[71,72] For these reasons, an increasingly careful approach to the use of antipsychotics, with low dosages and time-limited duration of therapy, is suggested in more recent guidelines.[73,74] At present, the substance with the most evidence, clinical experience, and even an official indication for the acute treatment of delirium by the Swiss authority for the authorization and supervision of therapeutic products (Swissmedic) is haloperidol.[74,75] Atypical antipsychotics such as quetiapine, with a more favorable side effect profile, are recommended only in case of contraindications for the use of haloperidol such as Parkinson's disease.[74]

Benzodiazepines are used as the first-line therapy in the treatment of withdrawal delirium among patients with addiction disorders. Since they can cause delirium themselves, or worsen existing symptoms, the use of these drugs to treat delirium outside the indication of addiction disorders is not recommended.[67,76,77]

As acetylcholine is considered to play a role in the pathogenesis of delirium,[78] some studies have investigated the efficacy of cholinesterase inhibitors in the treatment of

delirium, especially in patients with dementia.[79–82] Although some results suggested a long-term preventive effect of cholinesterase inhibitors on delirium among patients with dementia, the use of this drug class is no longer recommended for the treatment of delirium due to the increased mortality observed in patients treated with rivastigmine in a RCT.[81]

Delirium During Inpatient Rehabilitation

During inpatient rehabilitation, certain patients are at high risk for delirium due to the combination of predisposing and precipitating factors, such as age, immobilization, multiple medications, and postoperative or post-intensive care status.[35] Delirium is present in approximately one-third of stroke patients admitted to an inpatient rehabilitation unit, and is associated with increased mortality and functional decline.[83,84] Because delirious patients are unable to fulfill the intensive and interdisciplinary therapy schedule, they often experience prolonged rehabilitation stays and unfavorable rehabilitation outcomes, such as reduced autonomy or further institutionalization after discharge.[83,85–87] These clinical consequences cause exorbitant additional costs to inpatient rehabilitation facilities and the whole healthcare system each year.[84] Furthermore, patients affected by delirium suffer from a sudden change in reality, accompanied by feelings of intense fear, panic, loneliness, helplessness, and anger.[88] Up to 85% of patients affected remember their delirium experience with unpleasant feelings and sometimes shame about their behavior, and some can also develop post-traumatic stress disorder.[89,90] Delirium can therefore be a dramatic and stressful situation not only for the affected patients but also for their families.

Despite the high prevalence of delirium and its negative impact on patient outcomes and costs within inpatient rehabilitation settings, the implementation of appropriate screening and management of delirium remains rare.[91] Delirium often remains undiagnosed and delirious patients are therefore unable to receive specific measures, such as non-pharmacological interventions that have been demonstrated to be effective.[35,67] Oh-Park et al. identified six specific causes for the lack of delirium awareness in inpatient rehabilitation settings: 1) a subjective difficulty in using delirium screening instruments, 2) the assumption that mental confusion is normal in the elderly, 3) limited resources and frequent staff turnover among the medical staff, 4) suboptimal management of priorities by the multidisciplinary leadership, 5) an ineffective communication between staff members of different disciplines, and 6) an inadequate documentation system that fails to assess the positive impact of delirium-specific interventions.[91]

Aims of the Thesis

Delirium represents a common problem for patients and caregivers during inpatient rehabilitation. In this setting, delirium has been often associated with longer rehabilitation periods, increased costs, and reduced functional rehabilitation outcomes.[83,85,86,92–94] However, the knowledge about specific risk factors that might facilitate the identification of patients who are susceptible to delirium during inpatient rehabilitation remains limited.

The primary aim of this thesis was to identify risk factors for incident delirium during inpatient rehabilitation. Furthermore, this thesis aimed to describe the impact of delirium on functional rehabilitation outcomes and length of rehabilitation stay. Also, it aimed to develop a clinical prediction model based on parameters available on admission to inpatient rehabilitation that can quantify the risk of a specific patient of developing incident delirium during rehabilitation. For this purpose, this thesis was structured into three projects, with data based on a collective of approximately 10'000 patients who underwent inpatient rehabilitation at ZURZACH Care, Rehaklinik Bad Zurzach, an inpatient rehabilitation clinic in Switzerland. Patients' characteristics such as age, sex, rehabilitation discipline, and length of stay, as well as clinical data such as diagnoses, administered drugs, and functional scores, had already been systematically recorded in electronic health records (EHRs). However, incident delirium episodes had not been documented within these EHRs.

The first project of the thesis aimed to i) develop a chart-based method to detect incident delirium episodes within the EHRs, based on the approach of identifying delirium predictive key words (common terms used to describe delirious patients) in medical notes, ii) validate this method by conducting an expert review of the detected patients' charts as a gold standard, and iii) identify a population of validated incident delirium episodes within the EHRs of ZURZACH Care for further research purposes.

The second project of the thesis aimed to investigate the association between incident delirium during inpatient rehabilitation and a wide range of possible risk factors such as sex, age, rehabilitation discipline, functional scores, prevalent diseases or conditions, and administered drugs. Furthermore, this project aimed to describe the clinical implications of patients who developed delirium and of patients who did not. For these purposes, an exploratory case-control study was conducted, based on the EHRs of ZURZACH Care and considering the population of incident delirium episodes that were validated in the first part of the thesis as cases.

The third project of the thesis aimed to develop a clinical prediction model able to estimate the risk of developing incident delirium of a specific patient during inpatient rehabilitation, based on predictors available at admission, such as sex, age, rehabilitation discipline, functional scores, prevalent diseases or conditions, and medication history. Parameters included in the development of the model were selected according to the risk factors identified in the case-control study (second project), further evidence from the literature, and clinical expertise.

First Project

Detecting Incident Delirium within Routinely Collected Inpatient Rehabilitation Data: Validation of a Chart-Based Method

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Abstract

Background

Delirium is a brain condition associated with poor outcomes in rehabilitation. It is therefore important to assess delirium incidence in rehabilitation.

Purpose

To develop and validate a chart-based method to identify incident delirium episodes within the electronic database of a Swiss rehabilitation clinic, and to identify a study population of validated incident delirium episodes for further research purposes.

Design

Retrospective validation study.

Settings

Routinely collected inpatient clinical data from ZURZACH Care.

Participants

All patients undergoing rehabilitation at ZURZACH Care, Rehaklinik Bad Zurzach between 2015 and 2018 were included.

Methods

Within the study population, we identified all rehabilitation stays for which ≥2 delirium-predictive key words (common terms used to describe delirious patients) were recorded in the medical charts. We excluded all prevalent delirium episodes and defined the remaining episodes to be potentially incident. At least two physicians independently confirmed or refuted each potential incident delirium episode by reviewing the patient charts. We calculated the positive predictive value (PPV) with 95% confidence interval (95% CI) for all potential incident delirium episodes and for specific subgroups.

Results

Within 10,515 rehabilitation stays we identified 554 potential incident delirium episodes. Overall, 125 potential incident delirium episodes were confirmed by expert review. The PPV of the chart-based method varied from 0.23 (95% CI 0.19–0.26) overall to 0.69 (95% CI 0.56–0.79) in specific subgroups.

Conclusions

Our chart-based method was able to capture incident delirium episodes with low to moderate accuracy. By conducting an additional expert review of the medical charts, we identified a study population of validated incident delirium episodes. Our chart-based method contributes towards an automated detection of potential incident delirium episodes that, supplemented with expert review, efficiently yields a validated population of incident delirium episodes for research purposes.

Introduction

Delirium is an etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness, attention, perception, thinking, memory, psychomotor behavior, emotion, and the sleep-wake cycle.[26,96] Delirium can occur with or without pre-existing neurocognitive disorders and can vary in duration and severity.[96]

Despite the fact that delirium has been associated with increased mortality in the rehabilitation setting as well as an increased risk for post-surgery and post-hospital, long-term consequences, to date, only few studies have assessed incidence and prevalence of delirium and associated risk factors in this setting.[92,93,97–102] This may primarily be explained by the lack of validated methods to identify delirium during rehabilitation. Consequently, the prevalence of delirium in electronic real-world databases, including rehabilitation databases which could be used to conduct observational studies, was reported to be severely underestimated.[35,103]

Due to its highly fluctuating nature and several differential diagnoses with similar key symptoms, diagnosing delirium in inpatients is challenging.[104] Validated screening tools, such as the Confusion Assessment Method (CAM), have been developed to detect delirium in several inpatient settings.[38,40,105] However, as these tools are insufficiently validated in the rehabilitation setting, require specialized training and are time-consuming, standardized delirium screening in rehabilitation has remained rare.[91] Inouye et al.[106] proposed a different approach to identify potential delirium episodes based on systematic screening of inpatients' medical charts, which was validated on a general medicine ward and subsequently used in several studies.[97,107,108] Another study compared the chart-based approach with the prospective interview-based screening instrument CAM and suggested that the chart-based method was more likely to detect delirium episodes occurring outside the screening-times of interview-based methods, but less likely to detect hypoactive forms of delirium.[109] However, the key advantage of the chart-based method is its retrospective character, which allows the detection of potential delirium episodes by screening pre-existing clinical data.

Furthermore, Puelle et al.[110] published a list of delirium predictive key words, which, combined with the method of Inouye, may serve as a starting point for developing an automated chart-based method to detect delirium episodes within a database of

electronic medical records. A similar automated chart-based method to detect patients with dementia was already developed and validated.[111]

ZURZACH Care is a Swiss group of hospitals and outpatient institutions specialized in inpatient and outpatient rehabilitation and prevention. Patient data have been recorded electronically since 2015 and comprise patient demographics, free-text medical notes, administered drugs, diagnoses and laboratory values. This data may be used to perform observational studies to better understand the incidence of delirium and related risk factors in the rehabilitation setting.

The first aim of this study was to develop an automated chart-based method to identify potentially incident delirium episodes within the electronic database of ZURZACH Care, based on the approach of identifying delirium predictive key words in the medical charts of patients. Secondly, this study aimed to i) validate this method by calculating the positive predictive value (PPV) of the chart-based method compared to confirmed incident delirium episodes and ii) to compare the percentage of through expert review identified confirmed incident delirium episodes with the percentage of recorded delirium discharge diagnoses in the claims data. Thirdly, this study aimed to identify validated incident delirium episodes within the ZURZACH Care database for further research purposes, as example to get insights into clinical implications of delirium.

Materials and Methods

Data Source and Study Design

We conducted a validation study based on data derived from the electronic clinical database of ZURZACH Care between 2015 and 2018. Charts comprise patient demographics such as date of birth, sex and patient identification number, and inpatient care data such as case number (assigned per rehabilitation stay), rehabilitation program, and admission and discharge dates. During inpatient care, subjective and objective observations of nurses, physicians and therapists are documented as free-text medical notes, including date and time. Additionally, drug prescriptions including brand name, ATC-code[112], dosage, posology, time of prescription start, stop and administration are also documented. At admission, all diagnoses deriving from the former care provider (i.e., acute hospital) are documented as free-text in the electronic clinical database, while at discharge, pre-existing and new diagnoses are coded within the ICD-10 classification system[96] and archived as claims data.

Study Population

We included all patients who underwent ≥1 rehabilitation stay in angiology, cardiology, neurology, rheumatology, orthopaedics or headache or pain programs at the ZURZACH Care, Rehaklinik Bad Zurzach, Switzerland, between 1 January 2015 and 31 December 2018. We considered each single rehabilitation stay of patients who were referred to inpatient rehabilitation several times during the study period.

Identification and Classification of Potential Incident Delirium Episodes

We performed the process to identify potential incident delirium episodes and to classify them in two steps: in a first step, experts performed review on a sample of identified episodes. The knowledge gained in the sample review was implemented to improve the identification accuracy for the main review (second step).

Sample Review

Within the study population, we identified all rehabilitation stays with ≥1 recorded delirium predictive key word in the free-text medical notes (henceforth called “potential

delirium episodes"). We defined delirium predictive key words (henceforth abbreviated "key words") as the German translation of any of the terms reported in the study of Puelle et al.[110] plus additional common terms used to describe patients experiencing delirium in the acute neurorehabilitation unit of ZURZACH Care. Additional terms were identified based on independent interviews with the head nurse of this unit and the medical director of neurology of ZURZACH Care. The resulting list of key words is provided in Table 5A.

We defined the date of the first key word record during a potential delirium episode as the index date. As we intended to validate algorithms to capture incident delirium episodes during rehabilitation, we excluded all rehabilitation stays whose admission date was the same date as the index date, or whose free-text admission diagnoses comprised the terms for delirium used in German language ("Delir" or "Delirium").

Among the identified potential incident delirium episodes, we randomly selected a sample of 100 episodes for review by two medical experts, a senior neurologist and a junior physician, both working in a neurological rehabilitation unit of ZURZACH Care. To achieve a standardized approach to the review process, we performed two specific training sessions with the experts, where they defined common evaluation strategies for the classification of potential delirium episodes.

For the review, profiles comprised the admission date and a chronological list of all medical notes registered at and after the index date. To limit the risk of observer bias by the experts due to identification of patients and recollection of associated medical events, we replaced the patient identification number and the case number by a neutral identification number in the profiles.

Based on clinical knowledge and pre-defined evaluation strategies, both physicians independently classified each potential incident delirium episode as "confirmed incident delirium episode", "no incident delirium episode", or "uncertain incident delirium episode". If the classification was discordant between the two physicians, they had to find a verbal consensus ("confirmed incident delirium episode" or "no incident delirium episode"). Because our rehabilitation database lacks validated delirium screening results, and as the diagnosis of delirium in inpatients is often based on subjective clinical observations rather than on biological markers, we considered expert review to be the most accurate and feasible way to classify potential delirium episodes.

Main Review

As a result of the sample review, we identified terms within the initial list of key words (Table 5A) that were not specific enough for delirium detection, namely “unruh…” (German abbreviation for “restless”) because this term was often used to describe patients who were nervous or agitated for reasons other than delirium (e.g., argument with the roommate) or “orient…”, “kooperat…” (German abbreviations for “oriented” and “cooperative”) because these terms often referred to fully oriented and cooperative patients. Therefore, we excluded the term “unruh…” and we added a negation to the other two terms, i.e., substituted “orient…” by “nicht (…) orient…” (German abbreviation for “not oriented”) and “kooperat…” by “nicht (…) kooperat…” (German abbreviation for “not cooperative”). Table 5B provides the modified list of key words used for the main review. The sample review also demonstrated that the reviewers required ≥2 key words (instead of ≥1) to evaluate the characteristic fluctuation of delirium. Moreover, they required knowledge on antipsychotic, anxiolytic or hypnotic drugs (ATC-Codes: “N05Axxx”, “N05Bxxx”, “N05Cxxx”) prescribed within 12 hours before, at, or at any time after the index date and a potential pre-existing diagnosis of dementia (ICD-10 Codes F00 to F03 incl. subgroups), because the differentiation between dementia, delirium and delirium superimposed on dementia or other psychoses is considered very challenging, and above-mentioned clinical data were required to distinguish between these diagnoses.[113]

For the main review, we therefore identified all rehabilitation stays within the initial population with ≥2 key words as defined by the modified list of key words (Table 5B). Within this revised population of potential delirium episodes, we defined the index date and excluded non-incident episodes as described under “Sample review” above.

Based on clinical knowledge and pre-defined evaluation strategies, the same two physicians who performed the sample review independently classified each potential incident delirium episode identified for the main review as “confirmed incident delirium episode”, “no incident delirium episode”, or “uncertain incident delirium episode”. If the classification was discordant, a second senior neurologist independently reviewed the concerned profiles. In these cases, if the classification of the first and the second senior neurologist was concordant, the classification of the junior physician was overruled. If the classification between the two senior neurologists was discordant,

they had to discuss each single potential delirium episode until they found a verbal consensus.

Table 5: List of delirium predictive key words.

A)	**B)**
agress*	agress*
aggress*	aggress*
delir*	delir*
desorient*	desorient*
durcheinand*	durcheinand*
halluzin*	halluzin*
klingelmatte	klingelmatte
konfus*	konfus*
unkoperat*	unkoperat*
unkooperat*	unkooperat*
nestel	nestel
orient*	nicht (...) orient*
koperat*	nicht (...) koperat*
kooperat*	nicht (...) kooperat*
unruh*	
verwirr*	verwirr*

A) Key words derived from the literature and translated to German (**bold**) and further common German terms used to describe patients experiencing delirium.

B) Modified list of delirium predictive key words after the sample review.

* indicates possible different endings. (…): any 0 to 12 characters.

Identification of Recorded Delirium Discharge Diagnoses within the Claims Data

Within the initial study population, we identified all rehabilitation stays with a recorded discharge diagnosis of delirium (ICD-10: "F05.xx") within the claims data. The identified rehabilitation stays comprising a discharge diagnosis of delirium were then compared with the incident delirium episodes confirmed by the medical experts.

Statistical Analysis

We calculated the overall PPV with 95% confidence interval (95% CI) of the described algorithm to identify incident delirium episodes during rehabilitation by dividing the number of (by expert review) confirmed delirium episodes (true positive) by the number of initially identified potential delirium episodes (true positive + false positive). Furthermore, we calculated PPVs with 95% CI of different groups of identified potential delirium episodes according to the number of recorded key words (≥2; ≥3; ≥4; ≥5; ≥6; ≥7; ≥8; ≥9; ≥10) with or without the administration of ≥1 antipsychotic drug (ATC Codes N05Axxx) within 12 hours before, at, or at any time after the index date and according to the rehabilitation discipline.

Results

Between 1 January 2015 and 31 December 2018, we identified 9'406 patients who had a total of 10'515 rehabilitation stays. Baseline characteristics of the study population, median length of rehabilitation stay, and rehabilitation disciplines are reported in Table 6 Within this population we identified 4'910 rehabilitation stays (46.7% of all stays) with ≥1 key word by applying the initial key words list (Table 5A) for the sample review (the results of the sample review are illustrated on Figure 8a). By applying the modified key words list (Table 5B) we identified 1'823 rehabilitation stays (17.3% of all stays) for the main review. We excluded 314 rehabilitation stays because the index date corresponded to the admission date, 230 because the terms „Delir" or „Delirium" were comprised within the free-text admission diagnoses, and 725 because only 1 key word was recorded in the medical notes. This left us with 554 (5.3% of all stays) potential incident delirium episodes for experts' review, 53 episodes (9.6%) of patients with dementia, and 501 (90.4%) without dementia (Figure 8b).
Overall the two experts agreed in the classification of 405 episodes (93 classified as incident delirium episodes and 312 as no incident delirium episodes), and disagreed in the classification of 149 episodes (70 were classified as incident delirium episodes only by the senior neurologist, 69 were classified as incident delirium episodes only by the junior physician, and 10 were classified as uncertain by one of the two medical experts, and as no incident delirium episodes by the other) resulting in an agreement in 73.1% episodes. The patient profiles of the 149 episodes for which the two experts disagreed were reviewed by the second senior neurologist. For 49 episodes (32.9%), the two senior neurologists agreed on the classification and overruled the classification of the junior physician, while for 100 episodes (67.1%), the two senior neurologists had to reach a verbal consensus on the classification. Table 7 shows that 125 potential delirium episodes were classified as incident delirium episodes and 429 as no incident delirium episodes, resulting in a PPV of 0.23 (95% CI 0.19-0.26). Considering subjects with ≥6 recorded key words only, the PPV increased in those without or with ≥1 administered antipsychotic drugs within 12 hours before, at, or at any time after the index date, to 0.55 (95% CI 0.46-0.64) and 0.69 (95% CI 0.56-0.79), respectively. Table 8 shows that both the PPV and the cumulative delirium incidence were highest among the rehabilitation discipline neurology, although differences of PPVs between rehabilitation disciplines and overall were small and statistically not significant.

Within the initially identified 10’515 rehabilitation stays, we identified 111 stays (1.1%) for which a discharge diagnosis of delirium was recorded in the claims data. Of these, 12 (10.8%) stays corresponded to an incident delirium episode confirmed by the medical experts.

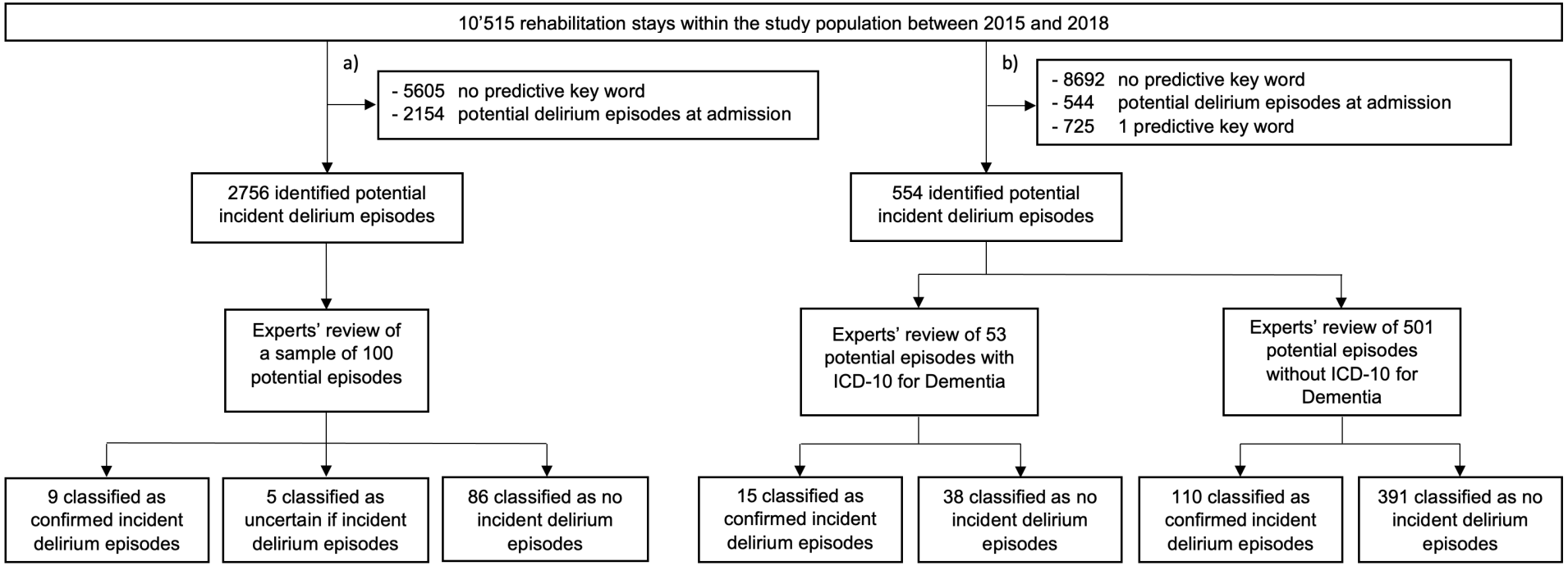

Figure 8: Selection and review process of potential incident delirium episodes within the initial population of rehabilitation stays.

a) Identification of patients based on the original delirium predictive key words list for the sample review (Table 5A)

b) Identification of patients based on the modified delirium predictive key words list for the main review (Table 5B)

Table 6: Baseline characteristics of the study population.

	Study population (n = 10'515)
Male	4683 (44.54 %)
Median length of stay in days (IQR)	22 (10)
Median age at admission in years (IQR)	70 (23)
Age at admission, years	
< 40	700 (6.66 %)
40-49	822 (7.82 %)
50-59	1684 (16.02 %)
60-69	1925 (18.31 %)
70-79	2913 (27.70 %)
80-89	2238 (21.28 %)
> 90	233 (2.22 %)
Rehabilitation discipline	
Angiology	631 (6.00 %)
Cardiology	1127 (10.72 %)
Headache program	450 (4.28 %)
Neurology	3458 (32.89 %)
Orthopedics	2964 (28.19 %)
Pain program	510 (4.85 %)
Rheumatology	1095 (10.41 %)
Others	280 (2.66 %)

IQR: interquartile range.

Table 7: Number of potential and confirmed incident delirium episodes with positive predictive values (PPV) and 95% confidence intervals (95% CI) by number of recorded delirium predictive key words and by administration of at least one antipsychotic drug within 12 hours before, at, or at any time after the index date.

Number of delirium predictive key words	≥ 1 antipsychotic drug after index date	Potential incident delirium episodes	Classified incident delirium episodes	PPV (95% CI)
≥ 2	No	554	125	0.23 (0.19 - 0.26)
	Yes	152	80	0.53 (0.45 - 0.61)
≥ 3	No	312	100	0.32 (0.27 - 0.37)
	Yes	110	63	0.57 (0.48 - 0.67)
≥ 4	No	197	85	0.43 (0.36 - 0.50)
	Yes	88	57	0.65 (0.55 - 0.75)
≥ 5	No	141	68	0.48 (0.40 - 0.57)
	Yes	68	46	0.68 (0.56 - 0.79)
≥ 6	No	105	58	0.55 (0.46 - 0.65)
	Yes	61	42	0.69 (0.57 - 0.81)
≥ 7	No	78	43	0.55 (0.44 - 0.66)
	Yes	51	33	0.65 (0.51 - 0.78)
≥ 8	No	61	33	0.54 (0.41 - 0.67)
	Yes	42	27	0.64 (0.49 - 0.79)
≥ 9	No	53	29	0.55 (0.41 - 0.69)
	Yes	38	24	0.63 (0.47 - 0.79)
≥ 10	No	42	22	0.52 (0.37 - 0.68)
	Yes	30	18	0.60 (0.41 - 0.79)

Table 8: Number of rehabilitation stays, potential and confirmed incident delirium episodes, cumulative delirium incidence and positive predictive values (PPV) with 95% confidence intervals (95% CI) by rehabilitation discipline and overall.

Rehabilitation discipline	Rehabilitation stays	Potential incident delirium episodes	Classified incident delirium episodes	Cumulative delirium incidence	PPV (95% CI)
Cardiology	1127	31	6	0.53 %	0.19 (0.04 - 0.35)
Neurology	3458	343	89	2.57 %	0.26 (0.21 - 0.31)
Orthopedics	2964	111	19	0.64 %	0.17 (0.10 - 0.24)
Others**	2966	69	11	0.37 %	0.16 (0.07 - 0.25)
	10515	**554**	**125**	**1.19 %**	**0.23 (0.19 - 0.26)**

**: Angiology, Headache program, Pain program, Rheumatology, others.

Discussion

Our chart-based method was able to detect 554 potential incident delirium episodes within 10'515 rehabilitation stays (5.3%) in the ZURZACH Care database between 2015 to 2018. Among these, only 125 (1.2% of all stays, 22.6% of identified potential incident delirium episodes) episodes were confirmed as incident delirium episodes by expert review, resulting in a low to moderate accuracy of our chart-based method. The PPV of the method varied from 0.23 (95% CI 0.19-0.26) for potential episodes with ≥2 recorded delirium predictive key words to 0.69 (95% CI 0.56-0.79) for potential episodes with ≥6 recorded key words and ≥1 recording of an administrated antipsychotic drug. The increase of the PPV was inversely related to the absolute number of identified incident delirium episodes. Considering only the rehabilitation discipline neurology, our method detected 343 (9.9% of all stays) potential incident delirium episodes. Among these, 89 (2.6% of all stays) episodes were confirmed as incident delirium episodes by expert review, resulting in PPV of 0.26 (95% CI 0.21-0-31). Both the proportion of detected potential incident delirium episodes and the PPV were higher in the neurology discipline than in non-neurological disciplines. However, it is important to emphasise that the PPV is dependent on the incidence or prevalence of a disease, and in this case, the incidence of delirium in neurology was about 5 times higher than in non-neurological disciplines. We found that for 1.1% of all rehabilitation stays, a discharge diagnosis of delirium was recorded in the claims data after the rehabilitation stay. Although this percentage seems similar to the proportion of confirmed incident delirium episodes in expert review (1.2%), the comparison of the single stays demonstrated a low concordance between the two groups. Only 10.8% of the identified rehabilitation stays with a discharge diagnosis of delirium corresponded to an incident delirium episode. Overall, we identified a study population of 125 validated delirium episodes.

The low to moderate accuracy of our chart-based method may be explained by the similar clinical manifestation of delirium with other neurological impairments due to pathologies such as stroke, status epilepticus, or dementia. These differential diagnoses result in the recording of similar key words as delirium and therefore have been captured as well by the chart-based method. Because such differential diagnoses are more common within neurologic rehabilitation, our thesis is supported by the higher proportion of 'no incident delirium episodes' (false positives) within this

discipline (254 out of 3458 stays [7.3%]) compared to the other rehabilitation disciplines (175 out of 7057 [2.5%]). Differentiation between delirium episodes and differential diagnoses of delirium was only possible during the experts' review process. Depending on the clinical setting and the average age of the investigated populations, reported delirium incidence for non-intensive care inpatients vary between 3% and 51%.[35,36,114] Considering these data, the 1.2% of confirmed incident delirium episodes that we observed within all rehabilitation stays was lower than expected but may be explained by considering the differences in studied populations and methodologies. We assessed the incidence of delirium in a rehabilitation setting across all age groups (around 50% of our study population was < 70 years old), whereas most previous studies assessed the incidence of delirium only in elderly populations (> 65 years old) and non-rehabilitation settings.[35,36,103] Additionally, most of the previous studies that were summarized in systematic reviews did not assess the patients' history of delirium or assessed delirium symptoms at admission, which, due to the transient nature of delirium, may have led to inclusion of prevalent delirium episodes.[35,36] We placed emphasis on detecting only new episodes of delirium by excluding those stays already comprising a record of a delirium diagnosis or key words at admission date (5.2% of all rehabilitation stays). Finally, the large variation in the incidence of delirium reported in pre-existing literature is questionable and highlights a considerable heterogeneity in the methodology used to assess delirium.

The low concordance between the rehabilitation stays with a discharge diagnosis of delirium recorded in the claims data and those with an incident delirium episode confirmed by the medical experts might have different reasons. First, some discharge diagnoses may originate from diagnoses made during the acute care hospitalisation prior to rehabilitation start. Second, unlike in the acute setting, where the focus is on diagnosis, the focus in rehabilitation is set on therapeutic aspects. Third, because reimbursement rates in Swiss rehabilitation are currently independent of new diagnoses made during rehabilitation, there is no direct financial interest to transfer new diagnoses, such as delirium, into the claims data. This result demonstrates that claims data are unsuitable to identify incident delirium episodes within such a database. This is compatible with a previous study, in which only 18% of all patients with assessed delirium, based on the prospective interview-based screening instrument CAM, also had a discharge diagnosis of delirium recorded in the claims data.[115] In addition, the percentage of rehabilitation stays with a discharge diagnosis

of delirium recorded in the claims data was considerably lower than the delirium prevalence range reported in the literature, supporting the thesis that the prevalence of recorded delirium diagnoses in electronic real-world databases is severely underestimated.[35,103]

We compared our results with those of Inouye et al.[106] who developed and prospectively validated a similar chart-based delirium detection method within 919 inpatients of a general medicine ward, achieving a PPV of 0.39 (95% CI 0.32-0.45) by comparing the chart-based method to the validated interview-based instrument CAM. In contrast to our method, the chart-reviewers manually searched for potential delirium episodes, whereby they not only searched for delirium key terms but also for any evidence of "acute confusional state" presents in all sections of the patient chart. In addition, they were able to calculate a sensitivity of 0.74 (95% CI 0.65-0.81) and a specificity of 0.83 (95% CI 0.80-0.86) of the chart-based method. Thus, although the sensitivity and specificity of their method was adequate, the PPV was not much higher than the overall PPV we calculated in our study, because of the low delirium prevalence in their study population. Because we did not review rehabilitation stays for which no key words were recorded in the medical notes (and therefore did not assess true negative or false negative episodes), we were not able to calculate the sensitivity and specificity of our method. Therefore, although the two studies had different aims, a different design and a different setting, the results of both studies demonstrate the limited suitability of clinical databases to detect delirium retrospectively, based exclusively on notes of evidence of confusional state.

The following limitations of our study have to be mentioned. First, the detection of potential incident delirium episodes was based on identification of defined key words recorded in medical notes. The recording of medical notes is a non-standardized procedure and affected by interpersonal, interprofessional and interdisciplinary heterogeneity, as shown by the lower PPV within non-neurological disciplines. Therefore, in case of insufficient recording or use of non-considered key words, we could have missed some delirium episodes. We tried to limit this issue by reviewing medical notes of all rehabilitation staff including other specialists or therapists. Second, because the clinical manifestation of delirium is, as already mentioned, similar to other neurological impairments due to pathologies such as stroke, status epilepticus, or dementia, some key words were not specific enough to differentiate between delirium and its differential diagnoses. We attempted to improve the PPV of

delirium diagnosis by considering only potential delirium episodes that were accompanied by records of antipsychotic drug administration shortly prior or at any time after the first registered key word, as this class of drugs is often used to treat delirium in clinical practice. While this approach led to a moderate improvement of the PPV, it especially led to a loss of chart-review confirmed incident delirium episodes for which no antipsychotics were prescribed. This indicates a non-specific use of antipsychotic drugs in clinical practice, and that not every delirium episode is treated with antipsychotic drugs, but also with behavioural and environmental interventions. Third, because our method relies on the records of behavioural observations in medical notes, less noticeable episodes of hypoactive delirium could have been missed. Fourth, although we consider the review of at least two independent and specifically trained medical experts suitable to validate delirium episodes based on medical charts, their expertise remains subjective, as shown by the moderate concordance during the review process, which was around 73% and comparable with previous studies.[116] We tried to limit this subjectivity by involving a second senior neurologist who conducted an independent review and found a verbal consensus with the first senior neurologist on each single episode where the classification was discordant. Fifth and already mentioned, because expert review was based on the interpretation of key words in the clinical context and therefore charts without key words were not reviewed, we were not able to determine the false negatives episodes and thus to calculate the sensitivity and specificity, as well as the negative predictive value (NPV), of our method. However, based on the experience of past studies and on our effort to maximize delirium detection by adapting the initial list of key words, we can expect a limited number of false negative delirium episodes.[106] Last, because we defined delirium-predictive key words in German language and completed the key words list with terms typically used to describe delirious patients in rehabilitation settings, the generalizability of our study findings is limited to the rehabilitation setting of German speaking countries.

Our data suggest that retrospective detection of incident delirium episodes within routinely collected clinical data remains challenging. From our perspective, a chart-based delirium detection method based on key words used to describe delirium symptoms can be useful to pre-select potential delirium episodes for research purposes. It will thus reduce time-effort but will not replace expert profile review, which is expensive and not suitable for large databases. Our results are consistent with other

studies, suggesting that strategies used to identify incident delirium in large clinical or claims databases by identifying recorded diagnoses are not sufficiently effective, because delirium is severely underdiagnosed in clinical practice.[103,117] There is a need to implement standardized delirium assessment and documentation methods during inpatient rehabilitation in order to improve the validity of delirium diagnoses within electronic databases. These standardized data would facilitate the investigation of delirium incidence and associated risk factors in rehabilitation, and thus have therapeutic implications.

Conclusions

Our chart-based method based on identifying delirium-predictive key words in the medical notes was able to detect incident delirium episodes within inpatients undertaking rehabilitation with low to moderate accuracy. Our chart-based method contributes towards an automated detection of potential incident delirium episodes that, supplemented with expert review, efficiently yields a validated population of incident delirium episodes for research purposes.

Second Project

Potential Risk Factors for, and Clinical Implications of, Delirium during Inpatient Rehabilitation: A Matched Case-Control Study

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Abstract

Objectives

To investigate the association between a wide set of baseline characteristics (age, sex, rehabilitation discipline), functional scores (FIM [functional independence measure], CIRS [cumulative illness rating scale]), diseases, and administered drugs and incident delirium in rehabilitation inpatients. Furthermore, to assess clinical implications of developing delirium during rehabilitation.

Design

Matched case-control study based on electronic health record data.

Setting and Participants

We studied rehabilitation stays of inpatients admitted between 1 January 2015 and 31 December 2018 to ZURZACH Care, Rehaklinik Bad Zurzach, an inpatient rehabilitation clinic in Switzerland.

Methods

We conducted unconditional logistic regression analyses to estimate adjusted odds ratios (AORs) with 95 % confidence intervals (CIs) of exposures that were recorded in ≥5 cases and controls.

Results

Among a total of 10’503 rehabilitation stays, we identified 125 validated cases. Older age, undergoing neurological rehabilitation, a low FIM, and a high CIRS were associated with an increased risk of incident delirium. Being diagnosed with a bacterial infection (AOR 2.62 [95% CI 1.06 – 6.49]), a disorder of fluid, electrolyte, or acid-base balance (AOR 2.76 [95% CI 1.19 – 6.38]), Parkinson’s disease (AOR 5.68 [95% CI 2.54 – 12.68]), and administration of antipsychotic drugs (AOR 8.06 [95% CI 4.26 – 15.22]), antiparkinson drugs (AOR 2.86 [95% CI 1.42 – 5.77]), drugs for constipation (AOR 2.11 [95% CI 1.25 – 3.58]), heparins (AOR 2.04 [95% CI 1.29 – 3.24]), or antidepressant drugs (AOR 1.88 [95% CI 1.14 – 3.1]) during rehabilitation, or an

increased anticholinergic burden (ACB ≥ 3) (AOR 2.59 [95% CI 1.41 – 4.73]) were also associated with an increased risk of incident delirium.

Conclusions and Implications

We identified a set of factors associated with an increased risk of incident delirium during inpatient rehabilitation. Our findings contribute to detect patients at risk of delirium during inpatient rehabilitation.

Introduction

Delirium is an etiologically nonspecific organic cerebral syndrome characterized by concurrent impairment of consciousness, attention, perception, thinking, memory, psychomotor behavior, emotions, and the sleep-wake cycle and can vary in duration and severity.[25,26] The underlying pathomechanisms are likely multifactorial, and identified risk factors in a hospital setting are older age, male sex, decreased functional ability, high burden of disease, comorbidities such as degenerative neurological disorders or infections, dehydration, malnutrition, immobility, prolonged hospital stay, and polypharmacy.[35,101,119–124] Several studies have suggested that acetylcholine deficiency may be involved in the pathophysiology of delirium, and that the use of anticholinergic medications may increase the risk of delirium.[125–131]

In the inpatient rehabilitation setting, as in the acute setting, delirium has been associated with a longer duration of stay and higher mortality.[83,85,86,92–94] Due to the inability of delirious patients to follow the challenging interdisciplinary therapeutic schedule, delirium has also been associated with poor functional rehabilitation outcome.[132,133] Two studies assessing the Functional Independence Measure (FIM) of patients undergoing rehabilitation showed that patients who developed delirium during the stay had a more severe impairment at the beginning, and a more limited FIM improvement during rehabilitation than patients who did not.[134,135]

Older age is a common risk factor for delirium among rehabilitation inpatients.[100,134–136] Also, a retrospective study identified traumatic brain injury, depression, diabetes mellitus and musculoskeletal disorders, as well as several out-of-range laboratory parameters as risk factors for delirium among rehabilitation inpatients.[100]

Identifying risk factors for incident delirium during rehabilitation, including specific conditions and administered drugs, is useful to detect patients who are susceptible to develop delirium.

The aim of this study was to explore the association between incident delirium during inpatient rehabilitation and a wide range of factors such as patient characteristics, rehabilitation discipline, functional scores at admission, diagnoses, and administered drugs. Furthermore, this study aimed to describe functional rehabilitation outcome and length of rehabilitation stay in patients who developed delirium and in patients who did not.

Methods

Data Source and Study Design

We conducted a retrospective matched case-control study using data from the electronic health records (EHRs) of ZURZACH Care, Rehaklinik Bad Zurzach, an inpatient rehabilitation clinic in Switzerland. EHRs comprise medical notes (suggestive of incident delirium, as validated in a previous study),[95] patient- and rehabilitation-specific characteristics such as age, sex, rehabilitation discipline and length of stay, as well as clinical data such as diagnoses (recorded as ICD-10 codes),[25] administered drugs (recorded as ATC-codes),[137] FIM,[18] and the Cumulative Illness Rating Scale (CIRS).[21] This study was approved by the Ethics Committee Northwest/Central Switzerland (Project-ID 2018-01351).

Study Population

We included all rehabilitation stays of patients who were admitted for inpatient rehabilitation between 1 January 2015 and 31 December 2018. Single patients may have contributed to more than one rehabilitation stay, if they were referred for rehabilitation several times during the study period. We excluded all stays with missing patient characteristics such as age, sex, or rehabilitation discipline.

Cases and Controls

Cases were patients who developed delirium at some point after the admission date. The definition and validation of delirium in the dataset has been described in detail previously.[95] Briefly, we defined 15 key words commonly used to describe delirious patients in medical notes. Profiles of patients with at least two recorded key words and no diagnosis of delirium at admission were reviewed by at least two independent physicians, based on predefined evaluation criteria to confirm or refute the diagnosis of delirium. In confirmed cases, the first recorded key word was defined as the date of onset of delirium (index date). Eligible controls were patients who did not have any record of delirium predictive key words in their EHRs and no diagnosis of delirium at admission. For each validated case, we matched four controls on calendar time (by assigning the index date [+/- 1 month] of the cases to their controls) and time span between admission date and index date.

Exposure

For cases and controls, we assessed age and length of stay as continuous variables, and sex (male; female), age groups (<65; 65-74; 75-84; ≥85 years), rehabilitation discipline (neurology; non-neurology) and primary diagnosis for rehabilitation as categorical variables. Furthermore, we assessed FIM, including cognitive FIM (C-FIM) and motoric FIM (M-FIM) in categories of severity, adapted from the German Modification of the ICD-10,[138] and evaluated its change between admission and discharge. We assessed disease burden at admission, by categorizing the CIRS into quartiles. We assessed the prevalence of comorbidities recorded in ≥5 cases and controls (see Table 9 for the complete ICD-10 codes list).

Additionally, we assessed the number of administered drugs at admission as continuous variable, and the administered drugs classes that were recorded in ≥5 cases and controls at any time between admission and index date (see Table 10 for the complete ATC-codes list). We defined “users” of the above drugs as patients with at least one administration between admission and index date, and “non-users” as those with no recorded administration in the same interval. Lastly, we calculated the Anticholinergic Cognitive Burden (ACB) at admission and assessed whether cases and controls were exposed to an increased ACB (≥3/<3).[139]

Table 9: List of assessed comorbidities, inclusive ICD-10 codes and subcodes.

Comorbidities	**ICD-10 codes**
Infectious and parasitic diseases	A00-B99
Bacterial infectious diseases	B95-B96
Endocrine, nutritional and metabolic diseases	E00-E90
Diabetes mellitus	E10-E14
Vitamin D deficiency	E55
Hypercholesterolemia	E78
Disorders of fluid, electrolyte and acid-base balance	E87
Diseases of the nervous system	G00-G99
Extrapyramidal and movement disorders	G20-G26
Parkinson disease	G20-G21
Epilepsy and recurrent seizures	G40-G41
Sleep disorders	G47
Other diseases of the nervous system	G00-G47, excl. G20-G26; G40-G41
Diseases of the circulatory system	I00-I99, excl. I60-I69
Cerebrovascular diseases	I60-I69
Subarachnoid or Intracerebral hemorrhage	I60-I62
Cerebral infarction	I63

Table 10: List of assessed co-administered drug classes inclusive ATC-codes and subcodes.

Administered drug classes	**ATC-codes**
Proton pump inhibitors	A02BC
Drugs for constipation	A06
Insulins and analogues	A10A
Blood glucose lowering drugs, excl. insulins	A10B
Vitamin K antagonists	B01AA
Heparin group	B01AB
Platelet aggregation inhibitors, excl. heparin	B01AC
Direct factor Xa inhibitors	B01AF
Cardiac therapy	C01
Diuretic drugs	C03
Beta blocking agents	C07
Calcium channel blockers	C08
Agents acting on the renin-angiotensin system	C09
Lipid modifying agents	C10
Drugs for urinary frequency and incontinence	G04BD
Drugs used in benign prostatic hypertrophy	G04C
Corticosteroids systemic	H02
Thyroid therapy	H03
Antibacterial for systemic use	J01
Antigout preparations	M04
Analgesics	N02
Opioid drugs	N02A
Other analgesic and antipyretics	N02B
Antiepileptic drugs	N03
Dopaminergic agents	N04B
Antipsychotic drugs	N05A
Benzodiazepine derivatives	N05BA
Hypnotics and sedatives	N05C
Antidepressant drugs	N06A
Dementia drugs	N06D
Other nervous system drugs	N07
Drugs for obstructive airways diseases	R03

Statistical Analysis

We summarized continuous variables providing means and standard deviations (SDs), and categorical variables as absolute and relative frequencies.

We conducted unconditional logistic regression analyses to calculate odds ratios (ORs) with 95 % confidence intervals (CIs) for each exposure variable. We adjusted all analyses for sex, age, and rehabilitation discipline to calculate adjusted odds ratios (AORs) with 95 % CIs. Given the unconditional analysis of matched sets, we also adjusted all analyses for the two matching factors (index date and time span between admission and index date).[140]

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA), Graphics were composed using Prism GraphPad 9.4 (GraphPad Software, San Diego, California, USA).

Results

Of 9'406 patients who underwent a total of 10'503 rehabilitation stays during the study period, we identified 125 validated incident delirium episodes and 500 matched controls (Figure 9). Patients and rehabilitation characteristics of cases and controls are reported in Table 11. Diseases of the nervous system (53.6%), among these, cerebral infarction (26.4%) were the most frequent primary diagnoses for rehabilitation among cases. Diseases of the musculoskeletal system (48.0%), among these spondylopathies (7.4%) and other dorsopathies (12.8%), were the most frequent primary diagnoses for rehabilitation among controls (Table 12).

Older age and undergoing neurological rehabilitation were associated were associated with increased risks of incident delirium (Table 11).

Severe functional impairment (FIM ≤ 65) and severe burden of disease (CIRS ≥ 14) were also associated with increased risks of incident delirium (Table 13).

Several comorbidities were associated with an increased risk of incident delirium during inpatient rehabilitation (Figure 10, see Table 14 for exact numbers). Being diagnosed with bacterial infections or disorders of fluid, electrolyte and acid-base balance was associated with a moderately increased risk of incident delirium (AORs 2.62 [95% CI 1.06 – 6.49] and 2.76 [95% CI 1.19 – 6.38], respectively), compared to not having these diagnoses. Parkinson's disease, and more generally extrapyramidal and movement disorders, were strongly associated with the risk of incident delirium compared to not having these conditions (AORs 5.68 [95% CI 2.54 – 12.68] and 3.51 [95% CI 1.89 – 6.52], respectively). Other comorbidities were not associated with incident delirium after adjusting for sex, age, and rehabilitation discipline.

Cases had a higher number of administered drugs at admission compared to controls (mean [SD], 9.0 [3.4] vs. 6.7 [3.8]). The administration of different drug classes was associated with an increased risk of incident delirium (Figure 11, see Table 15 for exact numbers). The use of drugs for constipation (AOR 2.11 [95% CI 1.25 – 3.58]), heparins (AOR 2.04 [95% CI 1.29 – 3.24]), and antidepressants (AOR 1.88 [95% CI 1.14 – 3.10]) was associated with a moderately increased risk of incident delirium, whereas the use of dopaminergic agents and antipsychotic drugs was associated with a markedly increased risk of incident delirium compared to no use of these drug classes (AOR 2.86 [95% CI 1.42 – 5.77] and 8.06 [95% CI 4.26 – 15.22], respectively).

Several drug classes were not associated with incident delirium after adjusting for sex, age and rehabilitation discipline.

The ACB was higher within cases than controls (mean [SD], 0.9 [1.3] vs. 0.6 [1.1]) and having a high ACB (≥3) was associated with an increased risk of delirium compared to having a low ACB (<3) (AOR 2.59 [95% CI 1.41 – 4.73]).

Cases had a longer mean rehabilitation stay than controls (mean days [SD], 33.1 [18.7] vs. 27.8 [16.5]) and the FIM of cases improved less between admission and discharge (Δ FIM [SD], 7.4 [17.1] vs. 17.9 [12.6]) than that of controls (Figure 12).

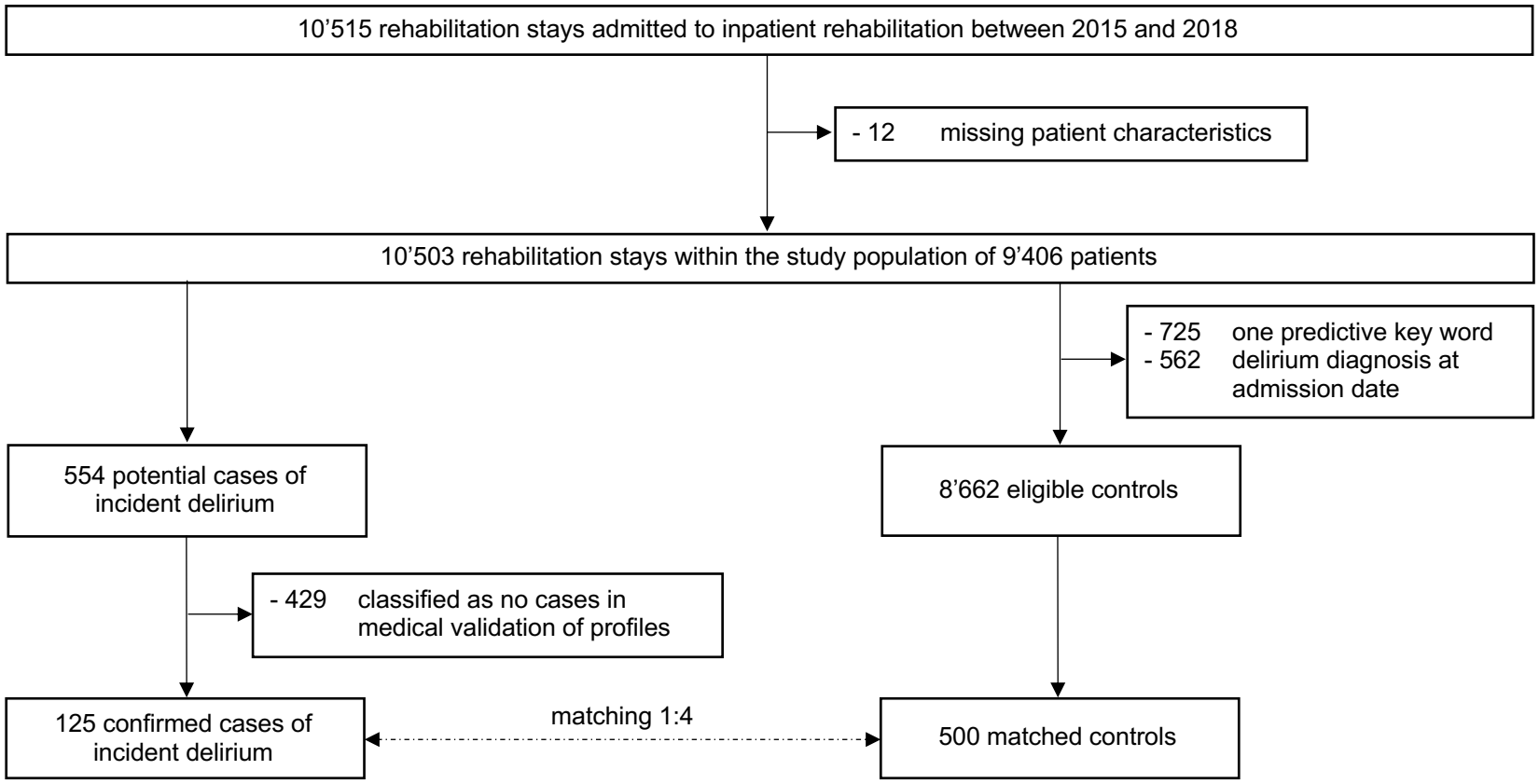

Figure 9: Flowchart of case and control selection. Cases were patients with at least 2 recorded delirium predictive key words (commonly used terms to describe delirious patients) who were classified as incident delirium episodes by two to three independent physicians as defined in a previous validation study.[95] Eligible controls were patients in the study population who did not have any record of delirium predictive key words in their medical notes or a diagnosis of prevalent delirium on admission. Each case was matched to four controls on calendar time (by assigning the index date [+/- 1 month] of the cases to their controls) and time between admission date and index date.

Table 11: Odds ratios of baseline characteristics among cases with incident delirium and matched controls.

	Cases (n= 125)	**Controls (n= 500)**	**OR (95% CI)**	**AOR (95% CI) ***
Sex				
Female	55 (44.0%)	275 (55.0%)	1 ref.	1 ref.
Male	70 (55.0%)	225 (45.0%)	1.56 (1.05 - 2.31)	1.39 (0.89 - 2.17)
Age, years				
<65	13 (10.4%)	227 (45.4%)	1 ref.	1 ref.
65-74	23 (18.4%)	110 (22.0%)	3.67 (1.79 - 7.53)	3.54 (1.69 - 7.45)
75-84	62 (49.6%)	128 (25.6%)	8.48 (4.49 - 16.02)	9.06 (4.68 - 17.56)
≥85	27 (21.2%)	35 (7.0%)	13.64 (6.42 - 28.99)	12.99 (5.89 - 28.67)
Age, mean (SD)	77.2 (9.9)	64.6 (15.7)	n/a	n/a
Rehabilitation discipline				
Neurology	89 (71.2%)	167 (33.4%)	4.97 (3.23 - 7.65)	4.89 (3.07 - 7.79)
Non-Neurology †	36 (28.8%)	333 (66.6%)	1 ref.	1 ref.
Days between admission date and index date, mean (SD)	10.3 (10.3)	10.3 (10.3)	n/a	n/a

Controls were matched to cases on index date (+/- 1 month) and time between the admission date and the index date (days between admission date and index date). All ORs were calculated with unconditional logistic regression and adjusted for matching factors (index date and exposure time).

* Sex adjusted on age, rehabilitation discipline (Neurology / non-Neurology); Age adjusted on sex, rehabilitation discipline (Neurology / non-Neurology); Rehabilitation discipline adjusted on age, sex.

† Frequencies (%) within non-Neurology disciplines (cases / controls): angiology (4.0 / 7.4), cardiology (4.8 / 9.6), rheumatology (1.6 / 9.8), orthopedics (15.2 / 26.2), headache (0 / 4.0) or pain (0.8 / 7.4) programs.

Table 12: Primary diagnosis for rehabilitation of cases with incident delirium and matched controls.

Primary diagnoses for rehabilitation (ICD-10)	**Cases (n=125) n (%)**	**Controls (n=500) n (%)**
Neoplasms (C00-D48)	6 (4.8)	10 (2.0)
Diseases of the nervous system (G00-G99, I60-I63)	67 (53.6)	138 (27.6)
Morbus Parkinson or other extrapyramidal disorders (G20-G26)	14 (11.2)	5 (1.0)
Multiple sclerosis or other demyelinating diseases (G35-G37)	1 (0.8)	5 (1.0)
Migraine or other headache syndromes (G43-G44)	0	25 (5.0)
Guillain–Barré syndrome and other polyneuropathies (G61-G62)	1 (0.8)	3 (0.6)
Cerebral palsy and other paralytic syndromes (G80-G83)	1 (0.8)	9 (1.8)
Cerebral haemorrhage (I60-I62)	7 (5.6)	7 (1.4)
Cerebral infarction (I63)	33 (26.4)	60 (12.0)
Other diseases of the nervous system[1]	10 (8.0)	24 (4.8)
Diseases of the circulatory system (I00-I99, excl. I60-I63)	14 (11.2)	79 (15.8)
Ischemic heart diseases (I20-I25)	4 (3.2)	21 (4.2)
Valvular heart diseases (I05-I08, I34-I36)	1 (0.8)	11 (2.2)
Other forms of heart disease[2]	1 (0.8)	22 (4.4)
Peripheral artery disease (I73)	4 (3.2)	6 (1.2)
Lymphoedema or other noninfective disorders of lymphatic vessels (I89)	1 (0.8)	18 (3.6)
Other diseases of the circulatory system[3]	3 (2.4)	1 (0.2)
Diseases or injuries of the musculoskeletal system (M00-M99, S00-T98)	34 (27.2)	240 (48.0)
Coxarthrosis (M16)	0	23 (4.6)
Gonarthrosis (M17)	2 (1.6)	28 (5.6)
Arthrosis or other arthropathies (M18-M19)	0	5 (1.0)
Spondylopathies (M45-M49)	4 (3.2)	37 (7.4)
Other dorsopathies[4]	1 (0.8)	64 (12.8)
Myalgia or rheumatism (M79)	1 (0.8)	8 (1.6)
Osteopathies and chondropathies (M80-M94)	2 (1.6)	2 (0.4)
Intracranial injury (S06)	10 (8.0)	4 (0.8)
Fracture of femur (S72)	4 (3.2)	15 (3.0)
Fracture of lower leg (S82)	0	8 (1.6)
Other fractures or injuries (S00-S99, excl. S06, S72, S82)	6 (4.8)	29 (5.8)
Complication of internal joint prosthesis (T84)	4 (3.2)	17 (3.4)
Other diseases[5]	4 (3.2)	33 (6.6)

[1] Meningitis and other neurologic inflammatory diseases (G00-G09); Atrophies primarily affecting the central nervous system (G10-G14); Nerve and plexus disorders (G50-G59); Myopathies (G72); Hydrocephalus (G91) or Cerebral cysts (G93).

[2] Endocarditis (I33, I38-I39); Dilated cardiomyopathy (I42); Arrhythmias (I49).

[3] Aortic aneurysm or dissection (I71); Venous thromboembolism (I82).

[4] Cervicalgia (M50); Intervertebral disc disorders (M51); Sciatica (M54.3); Lumbago (M54.5).

[5] Infections (A00-B99); Endocrine, nutritional and metabolic diseases (E00-E90); Diseases of the digestive system (K00-K93); Diseases of the respiratory system (J00-J99).

Table 13: Odds ratios of Functional Independence Measure (FIM) and Cumulative Illness Rating Scale (CIRS) at admission among cases with incident delirium and matched controls.

	Cases (n= 125)	**Controls (n= 499) †**	**OR (95% CI)**	**AOR (95% CI) ***
Functional Independence Measure				
FIM, mean (SD)	45.6 (18.4)	78.7 (19.3)	n/a	n/a
Cognitive FIM, mean (SD)	13.2 (5.7)	22.3 (5.4)	n/a	n/a
Motor FIM, mean (SD)	32.5 (15.0)	56.4 (15.5)	n/a	n/a
FIM low to medium impairment (66 - 126)	16 (12.8%)	382 (76.6%)	1 ref.	1 ref.
FIM high impairment (18 - 65)	109 (87.2%)	117 (23.4%)	25.88 (14.42 - 46.46)	13.19 (7.03 - 24.72)
Cognitive FIM low to medium impairment (11 - 35)	73 (58.4%)	488 (97.8%)	1 ref.	1 ref.
Cognitive FIM high impairment (5 - 10)	52 (41.6%)	11 (2.2%)	32.37 (16.08 - 65.16)	19.11 (8.64 - 42.27)
Motor FIM low to medium impairment (27 - 91)	76 (60.8%)	471 (94.4%)	1 ref.	1 ref.
Motor FIM high impairment (13 - 26)	49 (39.2%)	28 (5.6%)	11.50 (6.73 - 19.64)	6.75 (3.65 - 12.51)
Cumulative Illness Rating Scale				
CIRS, mean (SD)	18.8 (8.2)	15.1 (9.6)	n/a	n/a
CIRS low severity (0 - 8)	10 (8.0%)	141 (28.3%)	1 ref.	1 ref.
CIRS medium severity (9 - 13)	23 (18. 4%)	131 (26.3%)	2.70 (1.23 - 5.92)	1.63 (0.69 - 3.83)
CIRS high severity (14 - 20)	45 (36.0%)	102 (20.4%)	6.98 (3.31 - 14.70)	2.95 (1.29 - 6.74)
CIRS very high severity (21 - 56)	47 (37.6%)	125 (25.1%)	6.12 (2.90 - 12.90)	2.65 (1.16 - 6.07)

Controls were matched to cases on index date (+/- 1 month) and time between the admission date and the index date (days between admission date and index date). All ORs were calculated with unconditional logistic regression and adjusted for matching factors (days between admission date and index date).

* Adjusted on age, sex, rehabilitation discipline (Neurology / non-Neurology).

† Missing database entries (FIM and CIRS) for 1 control.

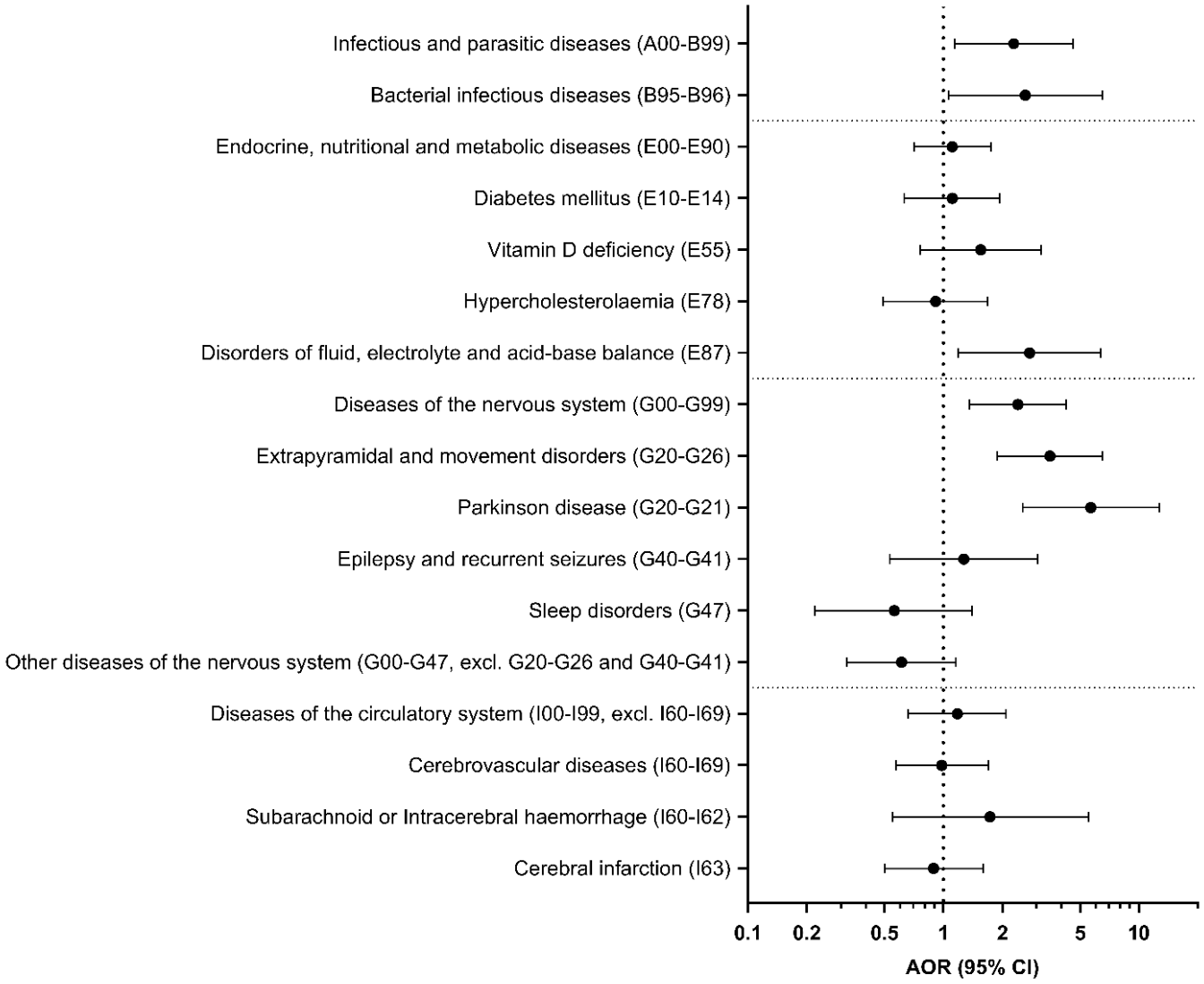

Figure 10: Forest plot of adjusted odds ratios (95% CI) among cases with incident delirium and matched controls for exposure to different comorbidities defined as a record of the ICD-10 code. Controls were matched to cases on index date (+/- 1 month) and days between the admission date and the index date. Odds ratios were calculated with unconditional logistic regression and adjusted for matching factors, age, sex and rehabilitation discipline (Neurology / non-Neurology).

Table 14: Odds ratios of comorbidities among cases with incident delirium and matched controls.

Comorbidities (ICD-10 codes)	Cases n (%) (n= 125)	Controls n (%) (n= 500)	OR (95% CI)	AOR (95% CI)[1]
Infectious and parasitic diseases (A00-B99)				
No[2]	105	470	1 ref.	1 ref.
Yes[3]	20	30	3.06 (1.66 - 5.64)	2.29 (1.14 - 4.61)
Bacterial infectious diseases (B95-B96)				
No[2]	112	486	1 ref.	1 ref.
Yes[3]	13	14	4.16 (1.88 - 9.21)	2.62 (1.06 - 6.49)
Endocrine, nutritional and metabolic diseases (E00-E90)				
No[2]	58	274	1 ref.	1 ref.
Yes[3]	67	226	1.41 (0.95 - 2.09)	1.11 (0.71 - 1.75)
Diabetes mellitus (E10-E14)				
No[2]	100	414	1 ref.	1 ref.
Yes[3]	25	86	1.20 (0.73 - 1.98)	1.11 (0.63 - 1.94)
Vitamin D deficiency (E55)				
No[2]	109	461	1 ref.	1 ref.
Yes[3]	16	39	1.75 (0.94 - 3.27)	1.55 (0.76 - 3.17)
Hypercholesterolemia (E78)				
No[2]	106	436	1 ref.	1 ref.
Yes[3]	19	64	1.23 (0.70 - 2.14)	0.91 (0.49 - 1.68)
Disorders of fluid, electrolyte and acid-base balance (E87)				
No[2]	110	484	1 ref.	1 ref.
Yes[3]	15	16	4.15 (1.99 - 8.67)	2.76 (1.19 - 6.38)
Diseases of the nervous system (G00-G99)				
No[2]	30	263	1 ref.	1 ref.
Yes[3]	95	237	3.55 (2.27 - 5.56)	2.40 (1.36 - 4.24)
Extrapyramidal and movement disorders (G20-G26)				
No[2]	92	471	1 ref.	1 ref.
Yes[3]	33	29	5.93 (3.42 - 10.29)	3.51 (1.89 - 6.52)
Parkinson disease (G20-G21)				
No[2]	101	488	1 ref.	1 ref.
Yes[3]	24	12	9.87 (4.76 - 20.46)	5.68 (2.54 - 12.68)
Epilepsy and recurrent seizures (G40-G41)				
No[2]	114	483	1 ref.	1 ref.
Yes[3]	11	17	2.79 (1.26 - 6.15)	1.27 (0.53 - 3.04)
Sleep disorders (G47)				
No[2]	118	459	1 ref.	1 ref.
Yes[3]	7	41	0.66 (0.29 - 1.52)	0.56 (0.22 - 1.40)

Other diseases of the nervous system (G00-G47, excl. G20-G26 and G40-G41)				
No[2]	109	401	1 ref.	1 ref.
Yes[3]	16	99	0.59 (0.34 - 1.05)	0.61 (0.32 - 1.16)
Diseases of the circulatory system (I00-I99, excl. I60-I69)				
No[2]	24	200	1 ref.	1 ref.
Yes[3]	101	300	2.82 (1.74 - 4.56)	1.18 (0.66 - 2.09)
Cerebrovascular diseases (I60-I69)				
No[2]	75	413	1 ref.	1 ref.
Yes[3]	50	87	3.18 (2.07 - 4.87)	0.98 (0.57 - 1.70)
Subarachnoid or Intracerebral hemorrhage (I60-I62)				
No[2]	118	492	1 ref.	1 ref.
Yes[3]	7	8	3.65 (1.30 - 10.28)	1.73 (0.55 - 5.51)
Cerebral infarction (I63)				
No[2]	87	439	1 ref.	1 ref.
Yes[3]	38	61	3.17 (1.99 - 5.06)	0.89 (0.50 - 1.60)

Controls were matched to cases on index date (+/- 1 month) and days between the admission date and the index date. All ORs were calculated with unconditional logistic regression and adjusted for matching factors. Main categories are depicted in bold.

[1] Adjusted on age, sex, rehabilitation discipline (Neurology / non-Neurology).

[2] Defined as no read ICD-10 code record of the respective disorder within the claims data

[3] Defined as a read ICD-10 code record of the respective disorder at admission.

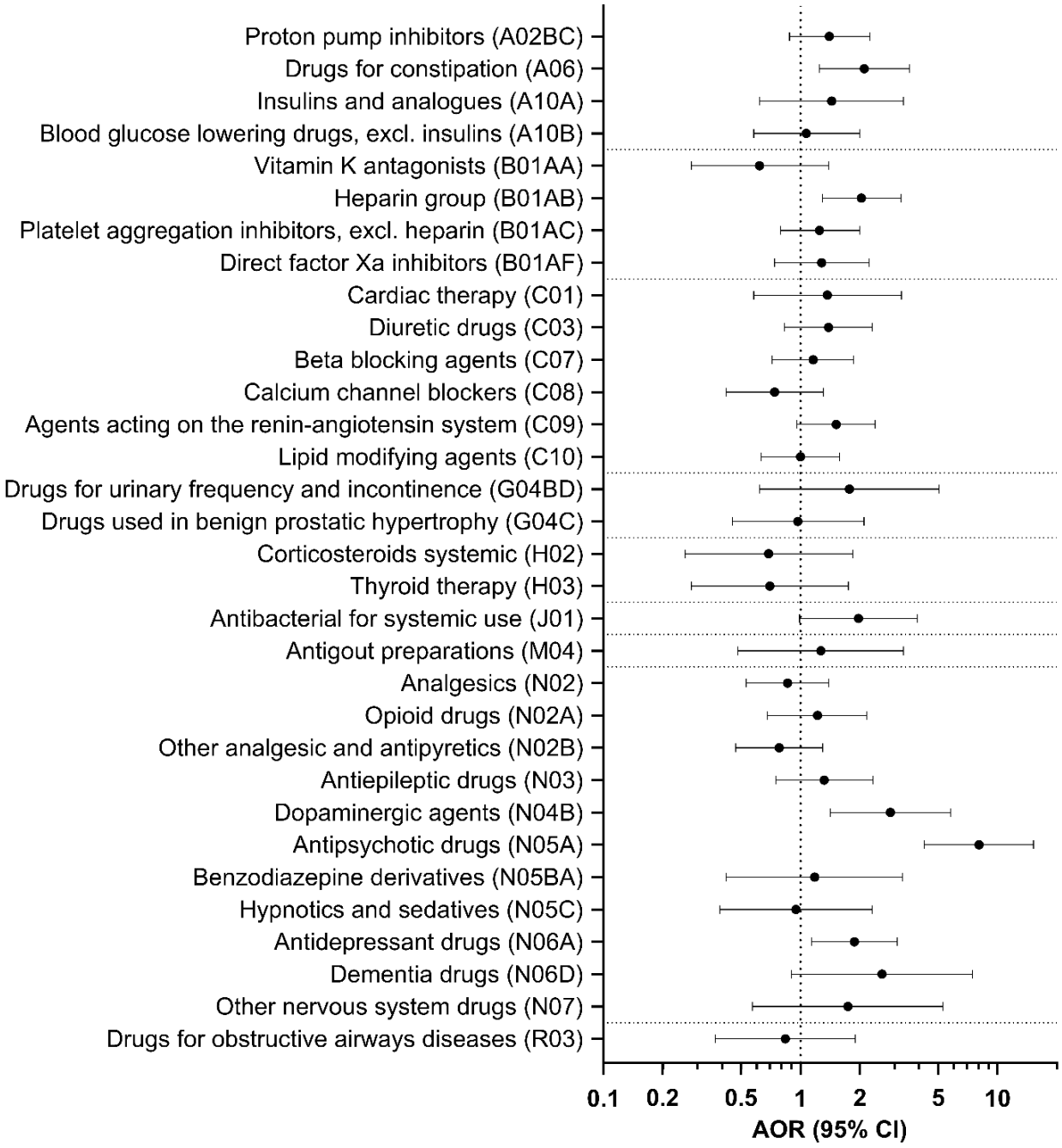

Figure 11: Forest plot of adjusted odds ratios (95% CI) among cases with incident delirium and matched controls for exposure to selected drug groups defined as at least one record of an administered code of the respective ATC-class at any time from the admission date until the index date. Controls were matched to cases on index date (+/- 1 month) and days between the admission date and the index date. Odds ratios were calculated with unconditional logistic regression and adjusted for matching factors, age, sex and rehabilitation discipline (Neurology / non-Neurology).

Table 15: Odds ratios of selected drug classes among cases with incident delirium and matched controls, by users or non-users.

Drug classes (ATC-codes)	Cases n (%) (n= 125)	Controls n (%) (n= 500)	OR (95% CI)	AOR (95% CI)[1]
Proton pump inhibitors (A02BC)				
non-users[2]	66	256	1 ref.	1 ref.
users[3]	59	244	0.94 (0.63 - 1.39)	1.40 (0.88 - 2.25)
Drugs for constipation (A06)				
non-users[2]	91	430	1 ref.	1 ref.
users[3]	34	70	2.30 (1.44 - 3.68)	2.11 (1.25 - 3.58)
Insulins and analogues (A10A)				
non-users[2]	115	473	1 ref.	1 ref.
users[3]	10	27	1.53 (0.72 - 3.27)	1.44 (0.62 - 3.34)
Blood glucose lowering drugs, excl. Insulins (A10B)				
non-users[2]	105	436	1 ref.	1 ref.
users[3]	20	64	1.30 (0.75 - 2.24)	1.07 (0.58 - 2.00)
Vitamin K antagonists (B01AA)				
non-users[2]	115	458	1 ref.	1 ref.
users[3]	10	42	0.95 (0.46 - 1.95)	0.62 (0.28 - 1.39)
Heparin group (B01AB)				
non-users[2]	71	378	1 ref.	1 ref.
users[3]	54	122	2.36 (1.57 - 3.56)	2.04 (1.29 - 3.24)
Platelet aggregation inhibitors, excl. heparin (B01AC)				
non-users[2]	75	353	1 ref.	1 ref.
users[3]	50	147	1.61 (1.07 - 2.42)	1.25 (0.79 – 2.00)
Direct factor Xa inhibitors (B01AF)				
non-users[2]	26	181	1 ref.	1 ref.
users[3]	99	319	2.19 (1.37 - 3.51)	1.28 (0.74 - 2.23)
Cardiac therapy (C01)				
non-users[2]	116	475	1 ref.	1 ref.
users[3]	9	25	1.48 (0.67 - 3.25)	1.37 (0.58 - 3.25)
Diuretic drugs (C03)				
non-users[2]	85	396	1 ref.	1 ref.
users[3]	40	104	1.81 (1.17 - 2.80)	1.39 (0.83 - 2.32)
Beta blocking agents (C07)				
non-users[2]	73	359	1 ref.	1 ref.
users[3]	52	141	1.82 (1.21 - 2.73)	1.16 (0.72 - 1.86)
Calcium channel blockers (C08)				
non-users[2]	99	426	1 ref.	1 ref.

users[3]	26	74	1.51 (0.92 - 2.49)	0.74 (0.42 - 1.31)
Agents acting on the renin-angiotensin system (C09)				
non-users[2]	54	311	1 ref.	1 ref.
users[3]	71	189	2.18 (1.46 - 3.25)	1.52 (0.96 - 2.39)
Lipid modifying agents (C10)				
non-users[2]	63	321	1 ref.	1 ref.
users[3]	62	179	1.78 (1.19 - 2.65)	1.00 (0.63 - 1.58)
Drugs for urinary frequency and incontinence (G04BD)				
non-users[2]	118	486	1 ref.	1 ref.
users[3]	7	14	2.06 (0.81 - 5.23)	1.77 (0.62 - 5.04)
Drugs used in benign prostatic hypertrophy (G04C)				
non-users[2]	110	470	1 ref.	1 ref.
users[3]	15	30	2.14 (1.11 - 4.13)	0.97 (0.45 - 2.10)
Corticosteroids systemic (H02)				
non-users[2]	119	473	1 ref.	1 ref.
users[3]	6	27	0.88 (0.36 - 2.19)	0.69 (0.26 - 1.85)
Thyroid therapy (H03)				
non-users[2]	118	463	1 ref.	1 ref.
users[3]	7	37	0.74 (0.32 - 1.71)	0.70 (0.28 - 1.75)
Antibacterial for systemic use (J01)				
non-users[2]	105	466	1 ref.	1 ref.
users[3]	20	34	2.65 (1.46 - 4.82)	1.97 (0.99 - 3.92)
Antigout preparations (M04)				
non-users[2]	117	481	1 ref.	1 ref.
users[3]	8	19	1.73 (0.74 - 4.06)	1.27 (0.48 - 3.34)
Analgesics (N02)				
non-users[2]	82	283	1 ref.	1 ref.
users[3]	43	217	0.68 (0.45 - 1.03)	0.86 (0.53 - 1.39)
Opioid drugs (N02A)				
non-users[2]	103	397	1 ref.	1 ref.
users[3]	22	103	0.82 (0.50 - 1.37)	1.22 (0.68 - 2.17)
Other analgesic and antipyretics (N02B)				
non-users[2]	92	333	1 ref.	1 ref.
users[3]	33	167	0.71 (0.46 - 1.11)	0.78 (0.47 - 1.30)
Antiepileptic drugs (N03)				
non-users[2]	98	420	1 ref.	1 ref.
users[3]	27	80	1.46 (0.89 - 2.38)	1.32 (0.75 - 2.34)
Dopaminergic agents (N04B)				
non-users[2]	102	477	1 ref.	1 ref.
users[3]	23	23	4.70 (2.54 - 8.72)	2.86 (1.42 - 5.77)

Antipsychotic drugs (N05A)				
non-users[2]	86	471	1 ref.	1 ref.
users[3]	39	29	7.46 (4.37 - 12.74)	8.06 (4.26 - 15.22)
Benzodiazepine derivatives (N05BA)				
non-users[2]	119	475	1 ref.	1 ref.
users[3]	6	25	0.96 (0.38 - 2.39)	1.18 (0.42 - 3.30)
Hypnotics and sedatives (N05C)				
non-users[2]	117	468	1 ref.	1 ref.
users[3]	8	32	1.00 (0.45 - 2.23)	0.95 (0.39 - 2.31)
Antidepressant drugs (N06A)				
non-users[2]	81	367	1 ref.	1 ref.
users[3]	44	133	1.52 (0.99 - 2.31)	1.88 (1.14 - 3.10)
Dementia drugs (N06D)				
non-users[2]	114	493	1 ref.	1 ref.
users[3]	11	7	7.02 (2.64 - 18.69)	2.59 (0.90 - 7.47)
Other nervous system drugs (N07)				
non-users[2]	119	483	1 ref.	1 ref.
users[3]	6	17	1.44 (0.55 - 3.73)	1.74 (0.57 - 5.30)
Drugs for obstructive airways diseases (R03)				
non-users[2]	114	468	1 ref.	1 ref.
users[3]	11	32	1.41 (0.69 - 2.89)	0.84 (0.37 - 1.90)

Controls were matched to cases on index date (+/- 1 month) and days between the admission date and the index date. All ORs were calculated with unconditional logistic regression and adjusted for matching factors.

[1] Adjusted on age, sex, rehabilitation discipline (Neurology / non-Neurology).

[2] Defined as no administration at any time prior the index date

[3] Defined as at least one administration at any time from the admission date until the index date.

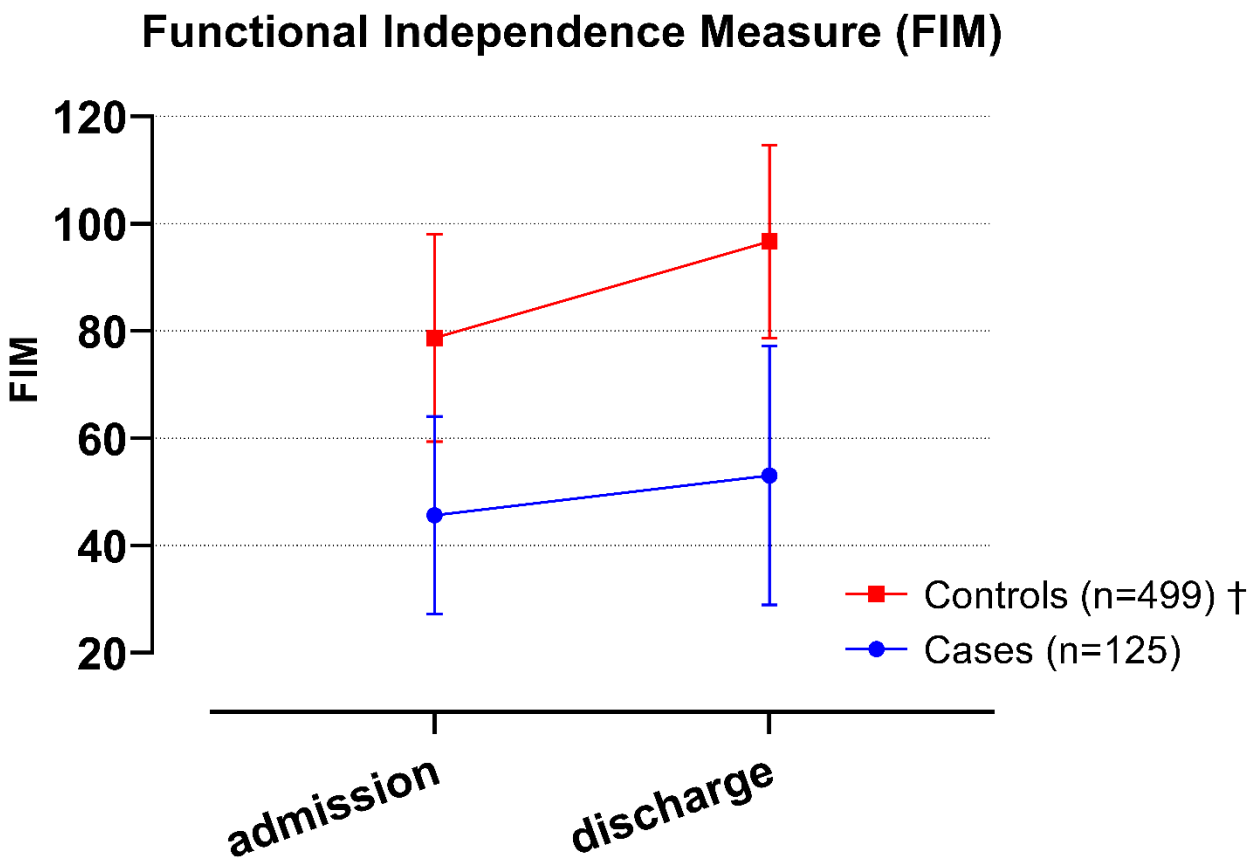

Figure 12: Functional Independence Measure (FIM) at rehabilitation admission and at discharge for cases with incident delirium and matched controls, mean (SD). FIM improvement between admission and discharge, mean (SD): 7.4 (17.1) for cases; 17.9 (12.6) for controls. † Missing database entries for 1 control.

Discussion

In this retrospective matched case-control study based on inpatient clinical data, we identified older age, neurological rehabilitation, reduced FIM, and high disease or anticholinergic burden at admission as factors associated with a considerably increased risk of incident delirium during rehabilitation.

Patients with infectious diseases, disorders of fluid, electrolyte and acid-base balance, and Parkinson's disease at admission, and patients treated with laxatives, heparins, antidepressants, dopaminergic agents and antipsychotics during rehabilitation, were at an increased risk of developing delirium.

Furthermore, patients who developed incident delirium had a longer mean rehabilitation stay and a poorer functional rehabilitation outcome, quantified by the FIM change between admission and discharge, than patients without delirium.

Patient and Rehabilitation Characteristics

Our results suggest that patients who have become delirious during rehabilitation were more frequently men and older than patients who have not. Compared to patients aged <65 years, patients between 65 and 74 years of age had a 3.5-fold increased risk, patients aged between 75 and 84 years a 9.1-fold increased risk, and patients above 85 years a 13.0-fold increased risk of delirium. The results are consistent with previously studies, which reported that patients who developed delirium during rehabilitation were older[100,134–136] and more often men[100,134,136] than patients who did not develop delirium. In our study, most cases underwent neurological rehabilitation, and patients among this rehabilitation discipline had a 4.9-fold increased risk of incident delirium compared to patients among other rehabilitation disciplines. This observation could be explained by neurological imbalance caused by degenerative neurological conditions that may trigger the pathophysiology of delirium.[48] The cognitive and motoric FIM at admission was lower among cases than controls (mean [SD], 13.2 [5.7] vs. 22.3 [5.4] and 32.5 [15.0] vs. 56.4 [15.5], respectively), and patients with a FIM lower than 65 points at admission had a 13.2-fold increased risk of incident delirium as compared to patients with a FIM higher than 65 points. These results suggest that patients with an impaired functional degree are more likely to develop delirium during rehabilitation, which is consistent with two previously published studies that assessed the FIM among patients with and without delirium.[134,135] Bushi et al.

found that patients with delirium had a significantly lower cognitive and motoric FIM on admission than patients without delirium (mean [SD], 15.2 [5.8] vs. 24.2 [6.0] and 24.3 [9.6] vs. 31.3 [9.1], respectively), and that patients with delirium more often had a primary neurological diagnosis for rehabilitation than patients without delirium.[134]

Burden of Disease and Comorbidities

We observed a 2.6 to 2.9-fold increased risk of delirium among patients with an increased burden of disease (CIRS) compared to patients with low burden of disease. This is comparable with the observations of Stelmokas et al., who reported a 4.5-fold increased risk of delirium among patients with an elevated Age-Adjusted Charlson Index.[141]

Patients with prevalent infectious diseases had a 2.3-fold increased risk of delirium, patients with disorders of fluid, electrolyte and acid-base balance had a 2.7-fold increased risk of delirium, and patients with extrapyramidal and movement disorders even had a 3.5-fold (among them, patients with Parkinson's disease a 5.7-fold) increased risk of delirium compared with patients who did not have a diagnosis of these conditions. These results are only partially comparable to those of a previous study, which assessed comorbidities and laboratory parameters as potential risk factors for delirium in the rehabilitation setting.[100] Jang et al. observed an increased risk of delirium among patients with traumatic brain injuries, depression, diabetes mellitus and musculoskeletal disorders, as well as among patients with increased white blood cells (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and decreased potassium and phosphorus levels.[100] In our study we could not assess brain injuries, depression, and musculoskeletal disorders (<5 observations for cases and/or controls), and we did not observe an increased risk of delirium among patients with diabetes mellitus. Nevertheless, the increased inflammatory or infectious parameters (WBC, ESR, CRP) observed by Jang et al. are consistent with the increased risk of delirium we observed among patients with infectious diseases, and the decreased potassium and phosphorus levels are consistent with the increased risk we observed among patients with disorders of fluid, electrolyte and acid-base balance. These findings are consistent with the current state of research suggesting that neurodegenerative diseases affecting dopamine levels and conditions of inflammation or electrolyte imbalance are favourable conditions for the development of delirium.[48]

Anticholinergic Burden and Comedications

Among our study population, cases on average used more drugs than controls. The resulting anticholinergic burden was higher among cases than controls, and patients with an ACB of ≥3 points had a 2.6-fold increased risk of incident delirium compared to patients with an ACB <3. These observations support the hypothesis of several studies that polypharmacy, particularly involving drugs with anticholinergic potential, may cause neurotransmitter imbalance and thus promote the pathophysiology of delirium.[35,48,125–131]

Patients who used laxatives, heparins or antidepressants had an approximately 2-fold increased risk of developing delirium, patients who used dopaminergic agents had a 2.9-fold increased risk, and those who used antipsychotics had an approximately 8-fold increased risk compared with non-use of these drug classes. From a pharmacological point of view, only some of these results are attributable to the direct effect of these drug classes on the onset of delirium, while others may be indirectly, but not causally associated with delirium. For instance, in inpatient setting, heparins are often used to prevent thromboembolic conditions,[142] and laxatives to prevent constipation among patients with reduced mobility. It is reasonable to assume that the observed association is rather due to the prolonged immobility than to a direct pathogenic effect of these classes of drugs on delirium. We also observed a statistically significant association of both Parkinson's disease and dopaminergic drugs with an increased risk of delirium. Although this may be plausible from a pharmacological point of view, the association between dopaminergic drugs and increased risk of delirium could reflect that almost all Parkinson's patients receive this drug class as a standard treatment.

Clinical Implications

We observed that patients who experienced incident delirium during rehabilitation on average had a 5 days longer rehabilitation stay and a poorer functional rehabilitation outcome at discharge (Δ FIM [SD], 7.4 [17.1] vs. 17.9 [12.6]) than patients who did not. These observations are consistent with previous studies [100,134–136], particularly one study reported a significantly lower change in FIM between admission and discharge for patients with delirium compared with patients without delirium (Δ FIM [SD], 10.5 [13.1] vs. 19.4 [15.4]).[135]

Strengths and Limitations

The following limitations of our study have to be considered. First, our analyses were based on clinical routine data, which were not primarily collected for research purposes. However, the consistency of our results with previous studies corroborates the validity of our data. Second, although we rigorously assessed medication use prior to the index date and time, potential protopathic bias must be considered. For example, the substantially increased risk of delirium observed in association with antipsychotic drugs may be explained by the administration of this drug class to patients presenting with early symptoms of delirium, rather than by a direct association between antipsychotic drug use and delirium. Due to the nonspecific and off-label use of antipsychotic drugs in clinical practice and due to the short follow-up time, we were not able to detect and limit this type of bias by shifting the index date. Third, because the aim of our study was not to test formal hypotheses, we assessed a wide range of potential risk factors simultaneously. Therefore, the results should be considered as a set of factors associated with, rather than causing delirium. Fourth, due to the low prevalence of certain drug classes and also the short observation time of our study, we were not able to differentiate between occasional, prolonged or cumulative use of medication. This would have helped us to understand whether the increased risk of delirium is associated with chronic use of certain drugs, or whether even occasional use is associated with delirium. However, given the pathophysiology of delirium, which typically develops within hours or days, we believe that our approach was appropriate for the assessed drug classes.

An important strength of our study is the high quality of the data set, which comprised accurate and structured entries of each single drug administration and diagnosis record. This allowed us to precisely define exposures without the use of proxy parameters.

Considering the above-mentioned limitations, our study offers a broad overview of the main risk factors for incident delirium during inpatient rehabilitation. Especially, our study adds knowledge to the existing literature regarding associations between administered drug classes and incident delirium during rehabilitation.

Conclusions and Implications

Our study suggests that among inpatients undergoing rehabilitation, older age, neurological rehabilitation, reduced FIM, and high disease or anticholinergic burden, as well as a number of prevalent comorbidities and co-administered drug classes, are potential risk factors for incident delirium. Moreover, incident delirium during rehabilitation seems to be associated with worse functional rehabilitation outcome and longer rehabilitation stay.

These findings may be relevant for health care providers working in the rehabilitation setting. Identifying patients potentially at risk of delirium during rehabilitation by considering a set of risk factors at rehabilitation admission, such as age, functional scores, comorbidities and preexisting drug prescriptions could represent an innovative method compared to the more conventional delirium assessment tools, which are based on the observation of patients over time and are therefore time consuming and require staff training.[38] Furthermore, modifiable risk factors such as new drugs prescriptions or the anticholinergic drug burden should be proactively considered to reduce the risk of incident delirium.

Third Project

Assessing the Risk of Developing Delirium on Admission to Inpatient Rehabilitation: A Clinical Prediction Model

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Abstract

Objectives

To develop a clinical model to predict the risk of an individual patient of developing delirium during inpatient rehabilitation, based on patient characteristics and clinical data available on admission.

Design

Retrospective observational study based on electronic health record data.

Setting and Participants

We studied a previously validated data set of inpatients including incident delirium episodes during rehabilitation. These patients were admitted to ZURZACH Care, Rehaklinik Bad Zurzach, a Swiss inpatient rehabilitation clinic, between 1 January 2015 and 31 December 2018.

Methods

We performed logistic regression analysis using backward and forward selection with alpha=0.01 to remove any non-informative potential predictor. We subsequentially used the Akaike information criterion (AIC) to select the final model among the resulting “intermediate” models. Discrimination of the final prediction model was evaluated using the C-statistic.

Results

Of the 20 candidate predictor variables, 6 were included in the final prediction model: a linear spline of age with one knot at 60 years and a linear spline of FIM with one knot at 64, diagnosis of disorders of fluid, electrolyte and acid-base balance (E87), use of other analgesic and antipyretics (N02B), use of anti-Parkinson drugs (N04B), and an Anticholinergic Burden Score (ACB) of ≥3.

Conclusions and Implications

Our clinical prediction model could, upon validation, identify patients at risk of incident delirium at admission to inpatient rehabilitation, and thus enable targeted prevention strategies.

Introduction

Delirium is defined as an etiologically unspecified organic brain syndrome in which consciousness, attention, perception, thought, memory, psychomotor behaviors, emotions and the sleep-wake cycle are simultaneously impaired. Delirium is reversible, and its duration and severity can range from hours to days.[25,26] Delirium has been associated with a longer duration of stay and higher mortality in both acute hospital and inpatient rehabilitation settings.[83,85,86,92–94] Due to the inability of delirious patients to follow the challenging interdisciplinary therapeutic rehabilitation schedule, delirium has also been associated with poor functional rehabilitation outcomes.[132,133]

Because of the highly fluctuating nature of delirium and several differential diagnoses presenting with similar key symptoms, detecting patients at risk of delirium and diagnosing delirium during inpatient rehabilitation is challenging. Validated screening tools, such as the Confusion Assessment Method (CAM), have been developed to detect delirium in several inpatient settings.[38,40] However, as these tools are only partially validated in the rehabilitation setting, they require specialized training and are time-consuming, and thus standardized delirium screening in rehabilitation remains rare.[91] Being able to detect patients at risk of delirium on admission to inpatient rehabilitation would allow targeted implementation of non-pharmacologic prevention measures for delirium, which have been demonstrated to be more effective than treatment measures.[67]

Clinical prediction models (CPMs) are research-based tools that quantify the contributions of relevant patient characteristics to calculate a numeric probability of the presence or development of a specific disorder; thus, they assist clinicians in making predictions.[143]
In a previous case-control study based on electronic health records (EHRs) of ZURZACH Care, an inpatient rehabilitation clinic in Switzerland, we evaluated a broad spectrum of risk factors for incident delirium during inpatient rehabilitation, including patient characteristics, specific conditions and administered drugs.[118]

Based on the results of the previous case-control study, this study aimed to develop a CPM to predict the risk of an individual patient of developing incident delirium during

an inpatient rehabilitation stay, based on patient characteristics, functional scores, diagnosed conditions, and administered drugs on admission to rehabilitation.

Methods

Source of Data

We used data from the EHRs of ZURZACH Care, Rehaklinik Bad Zurzach, an inpatient rehabilitation clinic in Switzerland. EHRs comprise medical notes (including terms that are suggestive of incident delirium, as validated in a previous study),[95] patient and rehabilitation specific characteristics such as age, sex, and rehabilitation discipline, as well as clinical data such as diagnoses (recorded as ICD-10 codes),[25] administered drugs (recorded as ATC-codes),[137] the Functional Independence Measure (FIM),[18] and the Cumulative Illness Rating Scale (CIRS).[21]

Participants

We included all rehabilitation stays of patients who were admitted for inpatient rehabilitation between 1 January 2015 and 31 December 2018. Single patients may have contributed to more than one rehabilitation stay, if they were referred for rehabilitation several times during the study period. We excluded all stays of patients with missing information on age, sex, and rehabilitation discipline. This study was approved by the Ethics Committee Northwest/Central Switzerland (Project-ID 2018-01351).

Outcome

The outcome was defined as an incident delirium at some point during the rehabilitation stay. The definition and validation of the outcome delirium in this dataset has been described in detail previously.[95] Briefly, we defined 15 key words commonly used to describe delirious patients in medical notes. Profiles of patients with at least two recorded key words during rehabilitation and no diagnosis of delirium on admission were reviewed by at least two independent physicians, based on predefined evaluation criteria to confirm or refute the diagnosis of delirium. Patients with only one delirium predictive key word in their EHRs, patients whose potential delirium diagnosis was refuted in medical review, and patients with prevalent delirium (record of a delirium diagnosis on admission) were excluded from the study population.

Predictor Variables

Based on the results of our previous case-control study,[118] evidence in the literature[100,134,135] and clinical expertise of a senior neurologist (P.S.S), we selected the following variables as potential predictors for the development of our model:[144] sex, age on admission, rehabilitation discipline (neurology / non-neurology), FIM[18] and CIRS[21] assessed on admission, records of any of the following conditions (ICD-10) and/or at least one administration of any of the following drugs classes (*ATC-codes*) on admission: infections (A00-B99 or *J01*), disorders of fluid, electrolyte and acid-base balance (E87), epilepsy (G40-G41), ischemic heart disease (I20-I25), cerebrovascular hemorrhage (I60-I62), cerebral infarction (I63), antidiabetic drugs (*A10A* and *A10B*), drugs for urinary frequency and incontinence (*G04BD*), corticosteroids systemic (*H02*), thyroid therapy (*H03*), opioid drugs (*N02A*), other analgesic and antipyretics (*N02B*), anti-Parkinson drugs (*N04B*), antidepressants (*N06A*), and Anticholinergic Burden Score (ACB)[139] assessed on admission.

Statistical Analysis

We described baseline characteristics of patients with or without incident delirium during rehabilitation using mean and standard deviation (SD) for continuous variables and absolute numbers and frequencies for categorical variables.

ACB was categorized into high (≥ 3) and low (<3) anticholinergic burden, for all other continuous variables (age, FIM and CIRS), the linearity of their relationships with the logit of the outcome probability was assessed using linear splines with an initial number of 19 knots placed at the 5th, 10th, … and 95th percentiles. The respective spline terms were defined as $(x - x_{k\times0.05}) \times (x > x_{k\times0.05})$ for k = 0, 5, …19. The term with k = 0 denotes the respective variable itself. We performed logistic regression analysis using both backward and forward selection with alpha=0.01 to remove any non-informative binary variables and spline terms. Because we aimed to obtain a parsimonious prediction model, we deliberately set a low alpha value as selection criterion. As the models obtained by forward and backward selection differed slightly in the selected spline terms for age, we assessed different “intermediate” models and used the Akaike information criterion (AIC) to select the final model among them. Discrimination of the final prediction model was evaluated using the C-statistic (area

under the Receiver Operating Characteristic [ROC] curve). All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Study Population and Outcome

Of 9'406 patients who underwent a total of 10'515 rehabilitation stays during the study period, we included 8'774 stays for the analysis (Figure 13). Among these, we identified 125 validated incident delirium episodes (outcome). Table 1 provides baseline characteristics at rehabilitation admission of patients with or without incident delirium. Patients with incident delirium during rehabilitation were more often male (56.0% vs. 42.9%), older (mean, 77.2 vs. 65.3 years), had a lower FIM (mean, 45.6 vs. 79.4), a higher CIRS (mean, 18.8 vs. 14.1), and were more often exposed to a high ACB (≥ 3) (22.4% vs. 9.1%) than patients without incident delirium.

Development of the Prediction Model

Of the 20 candidate predictor variables, 6 were included in the prediction model after backward selection: a linear spline of age with one knot at 55 years and a linear spline of FIM with one knot at 64, diagnosis of disorders of fluid, electrolyte and acid-base balance (E87), use of other analgesic and antipyretics (N02B), use of anti-Parkinson drugs (N04B), and ACB ≥3. Initially, age and FIM were included as linear splines with 19 knots (5^{th} to 95^{th} percentiles). Almost the same variables were included after forward selection, except that age >63 years was selected in the forward selection, while age >55 years was selected in the backward selection. We thus ran a model including two knots of age, at 55 and 63 years. Here, the first knot turned out to be statistically highly insignificant so that we kept the knot at 63 years only. However, we then also tested models with knots between 55 and 63 years. Here the model with the knot at 60 years showed the lowest AIC with a value of 959.48 (as compared to 959.53 for the model with the knot at 63 years). We thus considered the model with age >60 years as final. The area under the ROC-curve of this model yielded 0.9167 (value of c) (Figure 14). The resulting prediction function for the logit of the probability of developing delirium (DP) thus equaled:

logit (DP) = -1.5984 - 0.5913 × N02B (yes/no) + 0.8469 × N04B (yes/no)
+ 0.7440 × ACB ≥3 (yes/no) +1.0297× E87 (yes/no)
+ 0.0476 × (age-60) × (age >60) - 0.0466 × FIM
- 0.0788 × (FIM-64) × (FIM >64)

where the variables (x > a) are defined as 1 if x > a and as 0 if x <= a.
The estimated probability of developing delirium is then given by the following equation:

DP = exp(logit(DP)) / (1 + exp(logit(DP)))

We subsequently implemented the prediction function of delirium within an Excel file, in order to render it user-friendly (Figure 15).

Table 16: Baseline characteristics of the incident delirium group and the non-delirium group at rehabilitation admission.

Characteristics	**Non-delirium (n=8'649)**	**Incident delirium (n=125)**
Sex, N (%)		
Female	4937 (57.08)	55 (44.00)
Male	3712 (42.92)	70 (56.00)
Age, mean (SD)	65.28 (15.86)	77.17 (9.88)
Age group, N (%)		
<65	3710 (42.90)	13 (10.40)
65-74	2026 (23.42)	23 (18.40)
75-84	2190 (25.32)	62 (49.60)
≥85	723 (8.36)	27 (21.60)
Rehabilitation disciplines, N (%)		
Angiology	554 (6.41)	5 (4.00)
Cardiology	967 (11.18)	6 (4.80)
Headache program	430 (4.97)	0
Neurology	2429 (28.08)	89 (71.20)
Orthopedics	2578 (29.81)	19 (15.20)
Pain program	467 (5.40)	1 (0.80)
Rheumatology	1008 (11.65)	2 (1.60)
Others	216 (2.50)	3 (2.40)
FIM at admission, mean (SD)	79.38 (19.43)	45.64 (18.40)
CIRS at admission, mean (SD)	14.14 (8.63)	18.77 (8.19)
ACB at admission, N (%)		
high anticholinergic last (≥ 3)	790 (9.13)	28 (22.40)
low anticholinergic last (<3)	7859 (90.87)	97 (77.60)

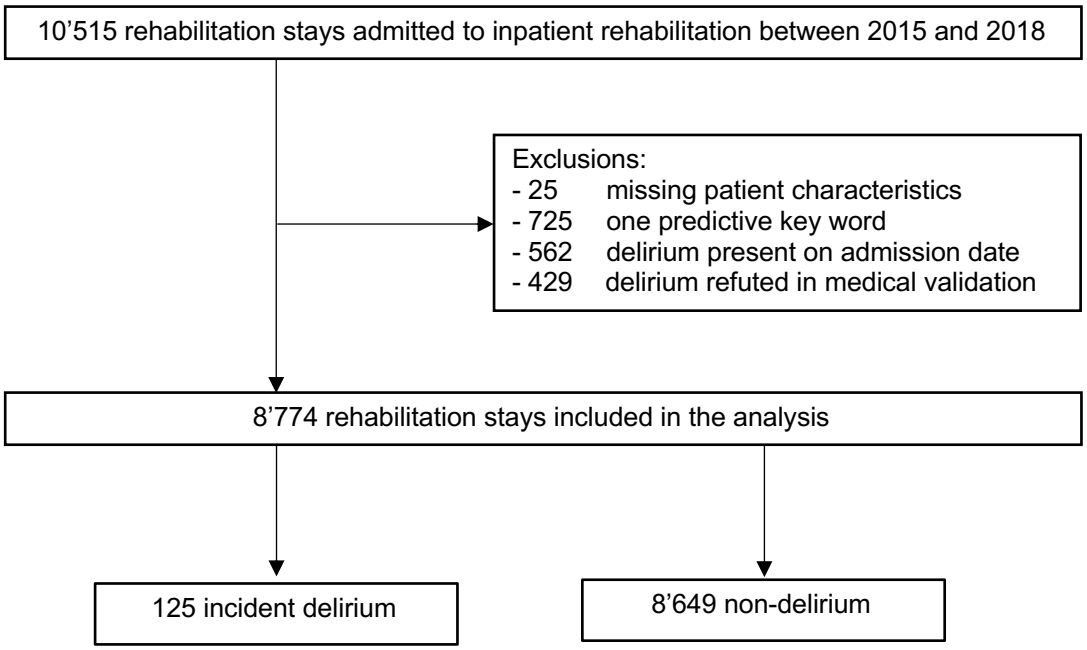

Figure 13: Flowchart of study population selection. Patients with incident delirium had at least 2 recorded delirium predictive key words (commonly used terms to describe delirious patients) who were classified as incident delirium episodes by two to three independent physicians as defined in a previous validation study.[95] Patients with non-delirium did not have any record of delirium predictive key words in their medical notes or a diagnosis of prevalent delirium on admission.

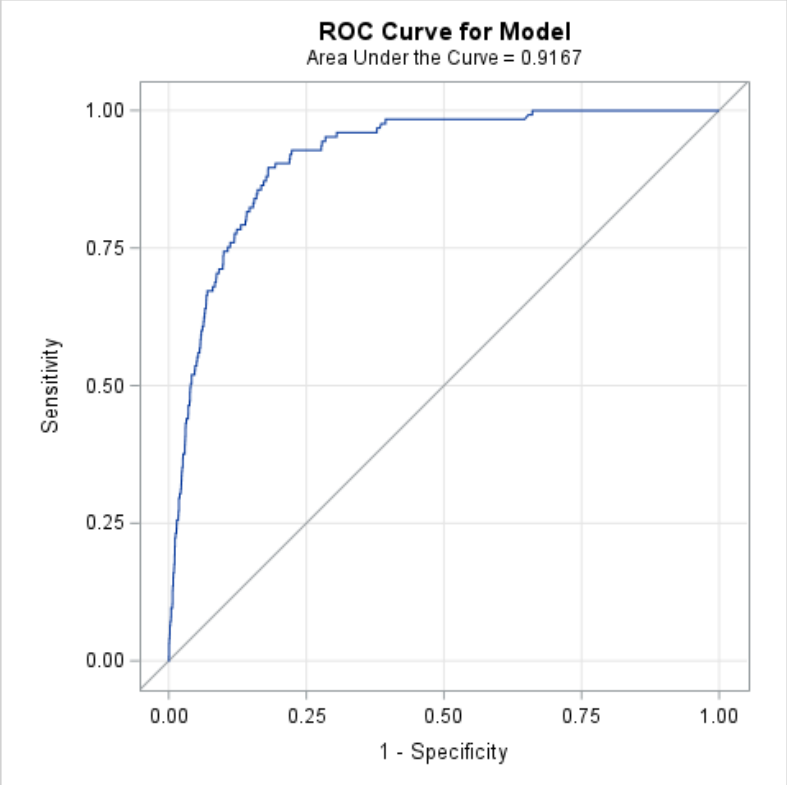

Figure 14: Receiver operating characteristics (ROC)-curve of the final model.

	A	B
1	**Parameters**	
3	Age (years)	70
4	FIM (points)	35
5	**Diseases and Conditions (ICD-10)**	
6	Disorders of fluid, electrolyte and acid-base balance (E87)	N
7	**Prescribed Drugs (ATC)**	Y
8	Analgesic and antipyretics (excl. Opioid) (N02B)	N Y
9	Anti-Parkinson drugs (N04B)	N
10	Anticholinergic Burden Score (ACB) ≥3	N
11		
12		
13	**Risk of developing delirium during inpatient rehabilitation stay:**	**3.41%**
14		

Figure 15: Example of risk calculation on excel sheet according to prediction function of the final model.

Discussion

In this observational study based on EHRs, we developed a clinical prediction model to predict the risk of an individual patient of developing incident delirium during inpatient rehabilitation. Age, FIM, diagnoses of disorders of fluid, electrolyte and acid-base balance (E87), use of other analgesic and antipyretics (N02B) or anti-Parkinson drugs (N04B) on admission, and an ACB ≥3 were selected as predictor parameters. The measured area under the ROC curve of the final model was 0.916 (value of c), which indicates a very good level of discrimination between positive and negative predictions.

Age and FIM showed proportional resp. inversely proportional associations with the risk of delirium, but only above resp. below certain values (age >60 years and FIM <64). Advanced age (>60 to >70 years, depending on the study) has repeatedly been reported as a risk factor for delirium within the rehabilitation setting.[100,134–136] A previous study also suggested that FIM is associated with an increased risk of delirium. Patients who developed incident delirium during inpatient rehabilitation had a significantly lower FIM on admission compared to patients who did not develop delirium.[134] Interestingly, we observed that use of analgesics and antipyretics (N02B) was associated with a lower risk of delirium. This indicates that an effective pain management may reduce the risk of delirium not only within postoperative settings,[145] but also in rehabilitation. Four previous studies reported a clinical prediction model for the risk of incident delirium in non-rehabilitation settings.[146–149] Two of them were performed in an acute hospital,[147,148] one in intensive care,[146] and the last one among patients after a stroke.[149] Excluding age, which was included in three[146,147,149] out of the four models, the included predictive parameters were highly heterogeneous across studies. Of the two models developed in acute hospital settings, the first one (among trauma patients >18 years of age) included the Glasgow Coma Scale, the BMI, the Clinical Frailty Score and two laboratory parameters (fibrinogen degradation products and lactate);[148] the second model (among patients >60 years of age) included age, the C-reactive protein (CRP), the blood urea level, the number of prescribed drugs, and use of one of the following drug classes (ATC-Code): anxiolytics (N05B), anti-dementia drugs (N06D), antidepressants (N06A), anti-Parkinson drugs (N04), drugs used in diabetes (A10), antipsychotics (N05A), opioids (N02A), hypnotics and sedatives (N05C) as predictive parameters for the risk of delirium.[147] The model

developed in the intensive care included the medical discipline (internal medicine, surgery, traumatology or neurology), the diagnoses of infection or metabolic acidosis, the use of morphine or sedatives and the urea blood level.[146] Finally, the model based on patients after a stroke included age, the presence of cerebral hemorrhage, or a brain lesion volume of >40 cm^3 and two laboratory parameters (gamma-glutamyl transferase and bilirubin).[149] Despite the fact that all models were developed based on high mathematical accuracy, it seems that the subjectivity in the preselection of potential predictive parameters due to different settings and parameters available had a great influence on the final prediction parameters included in the models. However, some of these parameters are common for conditions that are associated with delirium, as the CRP value for infections, lactate or urea values for metabolic acidosis or acid-base regulation imbalance, or the number of prescribed drugs for the dopaminergic system or the anticholinergic burden on the central nervous system. Our model also partially includes parameters related to some of these conditions (electrolyte and acid-base balance [E87], use of anti-Parkinson drugs [N04B] and ACB ≥3), with the exception of infections. This may be due to the different settings, with a lower incidence of infections in the rehabilitation setting than in acute hospital or intensive care.

Strengths and Limitations

The following limitations of our study must be considered. First, our analyses were based on routine clinical data, which were not primarily collected for research purposes. However, the cases of delirium were validated in a previous study, [95] and the same database was also used for a case-control study, in which results showed consistency with published literature.[118] Second, although we used a systematic method to pre-select predictive parameters, based on literature and expert opinion, we were restricted to available data in the database; thus it is possible that some parameters selected in prediction models of other studies were not considered, although they are associated with the risk of incident delirium. Third, although the statistical parameters indicate very good robustness of our model, the model has not yet been externally validated. An external validation would confirm the sensitivity and specificity of our model and should be performed before implementing the model in clinical practice.

An important strength of our model is the suitability to be used directly on admission to inpatient rehabilitation, as the parameters necessary for prediction are part of routine clinical data and already available at that time.

Conclusions and Implications

In our study, we developed a clinical prediction model to predict the risk of an individual patient of developing delirium during inpatient rehabilitation, based on patient characteristics, functional scores, diagnosed conditions, and administered drugs recorded in the EHRs of patients on admission to the rehabilitation facility. Considering the above-mentioned limitations, and after performing external validation as a further step, our model could provide an innovative method to screen patients for the risk of developing delirium during rehabilitation, based on factors present at admission to inpatient rehabilitation, and thus allow a targeted implementation of well-established delirium prevention strategies.[67]

General Discussion

Within inpatient rehabilitation, the knowledge about risk factors that lead some patients to develop delirium and the negative impact that delirium has on functional rehabilitation outcomes is limited. Improving this knowledge could raise awareness about this debilitating brain syndrome. It would also facilitate the identification of patients who are susceptible to developing delirium during rehabilitation and would allow the implementation of targeted delirium prevention measures.

The primary goal of this thesis was to identify a set of risk factors for the development of incident delirium during inpatient rehabilitation. Furthermore, this thesis aimed to describe the impact of delirium on functional rehabilitation outcomes and length of rehabilitation stay, and to develop a clinical prediction model based on parameters available on admission able to quantify an individual's risk of developing delirium during rehabilitation.

Because incident delirium episodes were not recorded systematically in the EHRs of our study population, comprising patients who underwent rehabilitation at ZURZACH Care, Rehaklinik Bad Zurzach, an inpatient rehabilitation clinic in Switzerland, between 1 January 2015 and 31 December 2018, in the first project of this thesis, we developed and validated a chart-based method able to detect incident delirium episodes within EHRs of inpatients undertaking rehabilitation. This method, based on the identification of delirium predictive key words within medical notes, was able to detect incident delirium episodes with low to moderate accuracy only (overall PPV 0.23 [95% CI 0.19–0.26]). However, supplemented with expert review, the developed method efficiently yielded a validated population of 125 incident delirium episodes for further research purposes.

The subsequent project, a retrospective matched case-control study based on routinely collected clinical data of inpatients and the previously validated case definition of patients with delirium, identified older age, neurological rehabilitation,

reduced FIM, and high disease (CIRS) or anticholinergic burden (ACB) at admission as factors associated with a considerably increased risk of incident delirium during rehabilitation. More specifically, patients with infectious diseases, disorders of fluid, electrolyte and acid-base balance, and Parkinson's disease at admission, and patients treated with laxatives, heparins, antidepressants, dopaminergic agents, and antipsychotics during rehabilitation, were at an increased risk of developing delirium compared with patients without these conditions or patients not receiving these drug classes. Furthermore, patients who became delirious during rehabilitation had a longer mean stay and a poorer functional rehabilitation outcome, quantified by the FIM improvement between admission and discharge, than patients without delirium.

In the third and last part of this thesis, we developed a clinical prediction model based on parameters available at rehabilitation admission to calculate the risk of an individual patient of developing incident delirium during inpatient rehabilitation. Age, FIM, diagnoses of disorders of fluid, electrolyte and acid-base balance, use of other analgesic and antipyretics or anti-Parkinson drugs on admission, and an ACB ≥3 were selected as predictor parameters. The subsequent implementation of the prediction function of delirium within an Excel file allows, upon validation of the model, user-friendly calculation of an individual's risk of developing incident delirium during inpatient rehabilitation.

Challenges and Opportunities of using Real-World Data for Epidemiological Research

As a result of global digitalization, the availability of real-world data (RWD) has increased exponentially in recent years in various areas of the healthcare system as well as in daily life. RWD are defined by the FDA as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources”.[150] Sources of RWD are typically EHRs, claims and billing databases, disease registries, and patient-generated data such as health data from wearable devices (Figure 16).[151]

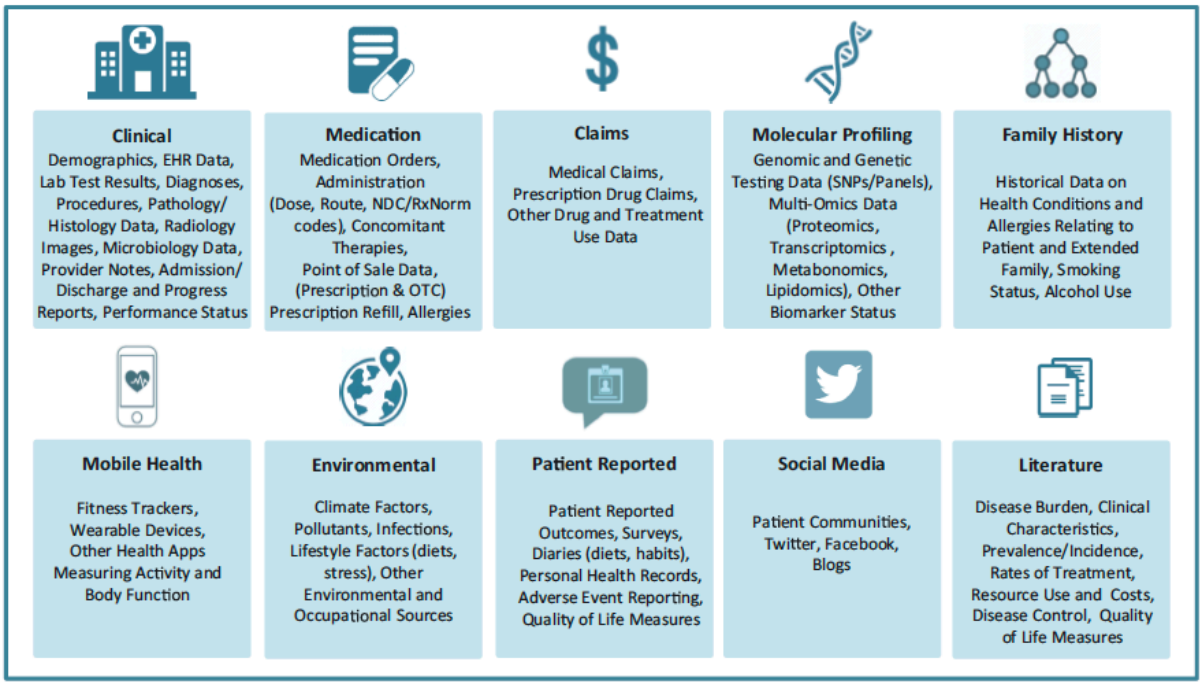

Figure 16: An overview of types and sources of real-world data. (Swift et al.[151])

Due to the lower costs and the increasing accessibility of RWD compared to traditional data collected in clinical trials, the interest of the scientific community in analyzing these data to generate real-world evidence (RWE), namely the clinical evidence regarding the usage and the potential benefits or risks of a medical product derived from the analysis of RWD, has increased parallely.[152]

However, if compared with data from traditional clinical trials, RWD have several limitations, which have to be addressed properly, i.e., by pre-processing RWD, to avoid misinterpretation of research findings. First of all, RWDs are often unstructured

(e.g., free-text entries, or use of different codes or scores) and sometimes inconsistent due to interpersonal, interprofessional, and interdisciplinary heterogeneity in recording these data. Second, RWD may be incomplete by missing data entries or by lacking relevant data, such as a diagnosis of interest. Third, RWD can be affected by different types of bias or measurement errors. For example, RWD may not be representative of a population of interest if the data are collected only from a subset of this population (e.g., by using health data from smartwatches, which are more popular among young people). Fourth, the amount of data available is often much larger than the number of variables needed for the analysis. Errors may therefore occur during data reduction or selection. Fifth, as information from RWD is often sensitive (e.g., medical histories, disease status, financial situations, and social behaviors) privacy and ethical issues may limit the accessibility to such databases.[152] Researchers should make every effort to ensure that RWD collection, storage, sharing, and analysis follow established data privacy principles, on the other hand, policymakers should facilitate access to RWD for researchers that fulfill these privacy standards.

It is fundamental to maintain scientific rigor during the RWE generation process from RWD. Results would require medical validation either using expert knowledge or conducting reproducibility and replicability studies before they are used for decision-making.[153] Engagement of key stakeholders (i.e., regulatory or government agencies, research institutes, or industries) should be encouraged to establish data quality standards for RWD. In Switzerland, the further use of health-related personal data for research projects is currently difficult for legal as well as structural reasons. However, the Federal Council has recently decided on a new strategy to facilitate the use of linked health data for research purposes. This includes common standards for data exchange and the creation of legal bases for facilitated data access and further use.[154] This may allow, on the one hand, a more efficient and linked use of existing databases, such as disease registers and statistics, and health insurance billing data, and on the other hand, a better sharing of the huge amount of health data generated by health care providers that currently remain unused.

If the above-mentioned limitations of RWD are appropriately taken into account in the planning and conduct of a study, they may also offer advantages over data collected in traditional clinical trials. For example, RWD from clinical routines, such as from EHRs, allow assessing outcomes in real-life conditions, including certain population groups which are normally excluded due to ethical reasons from clinical trials (i.e.,

pregnant women, children, elderly, and polymorbid patients). For this reason, clinical prediction models which require real-world conditions, are also often based on EHRs data.[155] A further field of application of RWD is in the study of rare diseases, where classical clinical trials are often too small to investigate outcomes (e.g., drug effects) among patients with a rare disease. The use of rare disease registries instead allows the collection of sufficient information to conduct such studies.[156] Furthermore, the use of claims data allows the study of outcomes in outpatient settings, such as medication usage or adherence.[157]

There are several methods to analyze RWD and their choice often depends on the source and type of available RWD. When RWD are particularly voluminous, messy, or unstructured, machine learning (ML) methods are particularly useful for pre-processing and analyzing such data. For example, natural language processing (NLP) is based on sophisticated ML algorithms, which can process unstructured free text or semi-structured clinical data (e.g., medical notes) from EHRs into structured outcomes, such as disease diagnoses or exact values.[158] Furthermore, modern ML techniques are able to elaborate very voluminous and dynamic databases, such as mobile health data.[152]

In our study, we primarily used RWD from EHRs and claims data. Part of the data, such as patient characteristics, medication use, and functional scores were well-structured and reliable. By contrast, the medical notes we used to identify incident delirium episodes were unstructured and affected by interpersonal and interdisciplinary heterogeneity. Because we found more than one publication demonstrating that delirium or dementia can be detected with elevated sensitivity and specificity by screening medical charts,[106,111] and a further study published a list of key words suggestive of delirium episodes,[110] we developed our chart-based method to detect incident delirium episodes based on this latter approach, rather than using more complex ML methods. Looking back and considering the low-to-moderate accuracy demonstrated by our chart-based method, ML, specifically NLP, could have been used to improve the accuracy of our method. Thanks to a higher level of complexity, NLP learns to identify signs of diseases from text patterns, and, above all, it can adapt itself to pattern variations and thus deal with heterogeneity issues. However, it is important to consider that very large databases are needed to ensure a good degree of reliability

of ML methods, so the question if the use of NLP would have yielded better results than our chart-based method remains difficult to answer.[159] We also compared our findings with the diagnoses of delirium extracted from the claims data to establish whether this latter data source could be alternatively used to identify delirium episodes. However, as mentioned in the discussion of the first project, we observed that claims data were unsuitable to identify incident delirium episodes.

Common Sources of Error in Epidemiological Studies

When interpreting the findings of an epidemiological study, one should always be aware that an observed association may not represent the true effect of exposure but simply the result of an error due to chance (random error), bias, or confounding.[160]

Random Error

Random error is the result of variability that occurs by chance and can affect the accuracy of the analysis in two ways: a study outcome suggests an association between variables that does not exist (type 1 error), or there is an association between variables, which is not detected by the analysis (type 2 error). The risk of false positive associations (type 1) occurs frequently in clinical studies that analyze a large number of associations simultaneously. The random error depends primarily on the sample size and can be estimated and quantitatively expressed using p-values and confidence intervals. Although it cannot be eliminated, it can be controlled using larger sample sizes and efficient statistical analysis.[160]

Bias

Bias is defined as “any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure’s effect on the risk of disease”.[161] Several types of bias have been recognized in epidemiological studies, but generally, they can be classified into two main categories: selection bias and information bias. Selection bias occurs when the characteristics of individuals within the comparison groups (affecting comparability) or the characteristics of individuals participating in the study and those not participating (affecting generalizability) differ systematically. Information bias occurs when the means used to obtain information on exposure or outcome are inadequate or differ systematically between comparison groups. Consequently, this may lead to the misclassification of subjects concerning exposure and/or outcome (misclassification bias).[161] As mentioned in the introduction, the most common types of bias for case-control studies are selection bias and recall bias, a subtype of information bias.[8] Regarding the first one, the process of control selection of a case-control study must be carefully conducted. In the ideal scenario, a control is as similar as possible to its own case except for the absence of the outcome. For this

purpose, controls should be selected from the same source population (e.g., the same setting) as cases to have similar characteristics.

In our case-control study, we selected cases and controls from the same population within rehabilitation settings; however, to minimize the risk of classifying a delirium case as a control (misclassification bias), we deliberately excluded patients with any evidence of delirium from the selection pool of controls: i) patients who became cases at any time during the rehabilitation stay, ii) patients with potential prevalent delirium episodes (i.e., patients who already had a delirium diagnosis at admission date or patients who already had delirium predictive key words detected on admission), iii) patients with uncertain delirium episodes (i.e., patients with only 1 detected delirium predictive key word), and iv) patients with unconfirmed delirium episodes (i.e., patients with at least 2 detected delirium predictive key words, who were classified as no incident delirium by the expert review). This approach may have introduced a potential selection bias as approximately 20% of the source population was excluded from the selection pool of controls.

A further critical process in the design of a case-control study is the assessment of the exposures. During exposures assessment, metrics and time must be defined to quantify whether a subject is exposed or unexposed: for example, to assess exposure to drugs, it may be necessary to define a temporal window as well as the number of administrations, or the cumulative dose required to consider a subject exposed. The appropriate quantification of exposure depends on the knowledge about the supposed biological mechanism inducing a health effect or disease but is often limited by data availability.[162]

As described in the introduction, the pathogenesis of delirium is usually multifactorial and based on the interactions between pre-existing, predisposing factors, and acute or sub-acute precipitating factors.[44–46] Without the availability of pre-admission data, our approach in the case-control study was therefore to consider measurable exposures on admission, such as comorbidities and degree of comorbidities as pre-existing factors, and during rehabilitation measurable exposures, such as drug administration, as acute (and possibly precipitating) factors. This approach could have introduced some misclassification bias as this generalization is only partly extendible to all disorders or drug classes included in the analysis. For example, we considered an individual to be exposed to an acute infection even if the delirium episode occurred weeks after admission when the infection was probably already cured.

Concerning recall bias, it is unlikely that our study is affected by this systematic error since our analyses were based on EHRs systematically recorded data rather than patient-reported data.

Confounding

Confounding is one of the most concerning issues in observational studies and may distort the observed measure of association. A confounder is a known risk factor for a certain outcome, which is also associated with the assessed exposure, without being a direct consequence of this exposure. Confounding can be identified by stratifying the analysis for the confounder. However, methods to reduce confounding are only applicable to known and measurable confounders. Since in observational studies, the study groups are not allocated by randomization, residual confounding due to unmeasurable factors can never be completely ruled out. For this reason, observational studies are normally unsuitable to conclude causative associations.[161]
As explained in the discussion of the case-control study, some of the observed associations, for example, the one between heparins or laxatives and incident delirium, could be the result of a confounding factor, such as the patients' immobility in the given example. However, such confounders can be relativized if we consider the exploratory (hypothesis-generating) purpose of our study, which did not aim to prove a causal inference of singular risk factors.

The Impact of the SwissDRG on Delirium Management among Swiss Rehabilitation Facilities

Since the introduction of the SwissDRG system in 2012, the financial remuneration of hospitals in the Swiss healthcare system has radically changed. According to SwissDRG, the remuneration is primarily based on diagnosis-related flat rates that are uniform throughout Switzerland and, therefore, no longer correlated to the time spent in the hospital.[163] The goals of the SwissDRG flat rates were more transparency and a better base for comparing the services of Swiss hospitals. As a consequence, the overall average length of stay in acute hospital has been drastically reduced in the last years (10.1 days in 2006 vs. 8.1 days in 2018),[164] so that patients with a condition requiring rehabilitation, such as a stroke, are transferred earlier to rehabilitation compared to the past. Although an earlier rehabilitation start has been associated with better functional rehabilitation outcomes,[165,166] many clinical issues of the acute setting, including delirium occurrence, were shifted to the rehabilitation setting. Therefore, Swiss rehabilitation clinics are faced more often with patients who experience delirium than in the past and the question remains whether they have also implemented sufficient guidelines for the prevention and management of delirium.

A survey conducted in 2022 in Switzerland showed that only 23% of surveyed rehabilitation clinics have an internal guideline for delirium management and of these, less than half provide systematic screening of patients at risk of delirium. One of the most frequently cited reasons for not having an internal guideline was “no or rare delirious patients, or treatment not possible on site”.[167] These explanations stand in contrast with the high prevalence and incidence of delirium reported among rehabilitation inpatients, especially the elderly,[35,36,83,85] and suggest a lack of awareness in Swiss rehabilitation clinics attributed to this brain syndrome. Furthermore, based on clinical experience within Swiss rehabilitation clinics, it is relatively common for a patient to be transferred back to the acute hospital as soon as a delirium episode occurs, which leads to additional costs, a great effort for all involved, and above all a further change of environment for the already disoriented patient.

By providing a broad overview of the main risk factors for incident delirium in rehabilitation, highlighting the consequences of delirium on rehabilitation outcomes, and developing a clinical prediction model to identify patients at risk of delirium at

admission, we hope to improve the awareness of this condition within the Swiss rehabilitation setting.

Outlook and Translation into Clinical Practice

Chart-Based Method to Identify Patients with Delirium During Rehabilitation

Our first project aimed to develop an automated chart-based method to identify patients with incident delirium within EHRs for further research purposes. This would have facilitated the use of retrospective data to conduct retrospective observational studies, with the final goal of better understanding the incidence and risk factors of delirium in the rehabilitation setting. For reasons described in detail in the discussion of the first project, our chart-based method showed only a low to moderate accuracy and was therefore not suitable for the intended purpose. In clinical practice, where every report of a potential delirium episode is ideally examined by a physician and a suspected false positive diagnosis can be refuted, preventive use of this chart-based tool is imaginable to identify patients with, or in the process of developing, delirium during inpatient rehabilitation. For instance, the chart-based tool could be integrated into the electronic clinical documentation system to generate an automatic alert notification to make the physician in charge and the rest of the clinical staff aware if two or more key words suggestive of delirium are detected in recently documented clinical notes. This would not replace the systematic screening of patients at risk of delirium or the reporting by caregivers of potential delirium episodes but would complement them. As mentioned in the introduction of the first project, chart-based methods have the advantage to detect delirium episodes occurring outside the screening times of interview-based methods,[109] and are more reliable than voluntary reports.

Recommendations based on Individual Delirium Risk Factors

Because of the limited available literature, especially on associations between administered drug classes and the occurrence of incident delirium, our second project aimed to give a broad overview of the main risk factors for incident delirium during inpatient rehabilitation. Therefore, we performed an explorative case-control study assessing all exposures that were sufficiently prevalent among our study population

and only adjusted our analyses for basic covariates (age, gender, discipline of rehabilitation) that we considered potential confounders common to all investigated associations. As a result, the observed associations have to be seen as a set of factors that are crudely, not necessarily causally, associated with incident delirium. None of the associations should therefore be considered individually without the context of all other results.

In the next step, one could select among the observed associations those with more clinical relevance, such as age, functional scores, or some comorbidities, or those modifiable, such as new drugs prescriptions or the ACB score, and test them singularly as risk factors for incident delirium. To do this, it would be necessary to consider each association separately and adjust for its specific set of confounders. The results of such hypothesis-testing studies could, in context with all other available literature on the topic, be used to make clinical recommendations to prevent incident delirium during inpatient rehabilitation.

A project toward this purpose has already started with a medical dissertation at ZURZACH Care, with the final aim of developing delirium management guidelines specific to the rehabilitation setting.

Clinical Prediction Model for the Systematic Delirium Screening on Admission to Inpatient Rehabilitation

The clinical prediction model developed in the third project of the thesis is able to calculate the individual risk of a patient of developing incident delirium during inpatient rehabilitation. However, as stated in the limitations of the study, the model has not yet been validated and a fundamental next step of this project would be external validation. By conducting a validation study in an external dataset with the same available variables and comparing the performance of the clinical prediction model against a gold standard for the delirium diagnosis, such as a prospective screening with a validated delirium screening tool, it would be possible to evaluate sensitivity and specificity of the model and thus enable its implementation in clinical practice. For instance, our model could be used to automatically screen all patients on admission to inpatient rehabilitation and identify patients with a high risk of developing delirium who need preventive measures and special surveillance. An automated prediction model with sufficiently high sensitivity and specificity would save time compared to the

use of classical delirium screening tools and above all would effectively deploy resources to implement effective delirium prevention measures.

References and Tools

1. Cambioli L, Bava M, Bellelli G, et al. “nabucco” by Giuseppe Verdi: A Case of Delirium in an Italian Romantic Opera. *Eur Neurol* 2017;77:180-185. doi:10.1159/000456712
2. Gordis L. Introduction - What is Epidemiology? In: *Epidemiology*. 4th ed. Saunders Elsevier; 2014:3-17.
3. Chidambaram AG, Josephson M. Clinical research study designs: The essentials. *Pediatr Investig* 2019;3:245-252. doi:10.1002/ped4.12166
4. Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312:1215-1218. doi:10.1136/bmj.312.7040.1215
5. Porta M. *A Dictionary of Epidemiology*. 5th ed. Oxford University Press; 2008.
6. Gordis L. Cohort Studies. In: *Epidemiology*. 4th ed. Saunders Elsevier; 2014:167-176.
7. Miller AB, Goff Jr. DC, Bammann K, et al. Cohort Studies. In: Ahrens W, Pigeot I, eds. *Handbook of Epidemiology*. Springer New York; 2014:259-291. doi:10.1007/978-0-387-09834-0
8. Gordis L. Case-Control Studies and Other Study Desgns. In: *Epidemiology*. 4th ed. Saunders Elsevier; 2014:177-200.
9. Strom BL, Kimmel SE, Hennessy S. *Pharmacoepidemiology*. 6th ed. Wiley Blackwell; 2020.
10. Basicmedical Key. Case–control studies. Accessed December 15, 2022. https://basicmedicalkey.com/case-control-studies-3
11. Gordis L. Assessing the Validity and Reliability of Diagnostic and Screening Tests. In: *Epidemiology*. Saunders Elsevier; 2014:85-108.
12. Frey N, Bircher A, Bodmer M, et al. Validation of Stevens–Johnson syndrome or toxic epidermal necrolysis diagnoses in the Clinical Practice Research Datalink. *Pharmacoepidemiol Drug Saf* 2017;26:429-436. doi:10.1002/pds.4124
13. Garbe E, Suissa S. Pharmacoepidemiology. In: Ahrens W, Pigeot I, eds. *Handbook of Epidemiology*. Springer New York; 2014:1875-1925. doi:10.1007/978-0-387-09834-0
14. Sjölund BH. Rehabilitation. In: *Encyclopedia of Behavioral Medicine*. Springer New York; 2013:1634-1638. doi:10.1007/978-1-4419-1005-9_924
15. World Health Organization. *World Report on Disability*. World Health Organization; 2011. https://onlinelibrary.wiley.com/doi/10.1111/j.1741-1130.2011.00320.x
16. Bachmann S, Graf C, Goetz S, et al. *DefReha Stationäre Rehabilitation: Definition Und Mindestanforderungen*.; 2021.
17. World Health Organization. *International Classification of Functioning, Disability and Health: ICF*.; 2001. https://apps.who.int/iris/handle/10665/42407
18. Granger C V., Hamilton BB, Keith RA, et al. Advances in functional assessment for

medical rehabilitation. *Top Geriatr Rehabil* 1985;1:59-74. doi:10.1097/00013614-198604000-00007

19. SwissDRG AG. ST Reha 1.0 Definitionshandbuch Abrechnungsversion (2022/2022). Published online 2022.
20. Tesio L. Inpatient Rehabilitation Units: Age and Comorbidities Are Not Relevant if Admission Fits the Mission. In: *Rehabilitation Medicine for Elderly Patients. Practical Issues in Geriatrics*. Springer; 2018:521-529. doi:10.1007/978-3-319-57406-6_54
21. Linn BS, Linn MW, Gurel L. Cumulative Illness Rating Scale. *J Am Geriatr Soc* 1968;16:622-626. doi:10.1111/j.1532-5415.1968.tb02103.x
22. Parmelee PA, Thuras PD, Katz IR, et al. Validation of the Cumulative Illness Rating Scale in a Geriatric Residential Population. *J Am Geriatr Soc* 1995;43:130-137. doi:10.1111/j.1532-5415.1995.tb06377.x
23. Hudon C, Fortin M, Vanasse A. Cumulative Illness Rating Scale was a reliable and valid index in a family practice context. *J Clin Epidemiol* 2005;58:603-608. doi:10.1016/j.jclinepi.2004.10.017
24. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified Cumulative Illness Rating Scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc* 2008;56:1926-1931. doi:10.1111/j.1532-5415.2008.01935.x
25. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*. 5th ed. (World Health Organization, ed.).; 2015. https://apps.who.int/iris/handle/10665/246208
26. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. (APA Press, ed.).; 2013. doi:https://doi.org/10.1176/appi.books.9780890425596
27. Savaskan E, Hasemann W. *Leitlinie Delir*. 1th ed. (Savaskan E, Hasemann W, eds.). Hogrefe; 2017. doi:10.1024/85761-000
28. Laurila J V., Pitkala KH, Strandberg TE, et al. The impact of different diagnostic criteria on prevalence rates for delirium. *Dement Geriatr Cogn Disord* 2003;16:156-162. doi:10.1159/000071004
29. O'Keeffe ST. *Clinical Subtypes of Delirium in the Elderly*. Vol 10.; 1999. http://biomednet.com/karger
30. Young J, Inouye SK. Delirium in older people. *BMJ* 2007;334:842-846. doi:10.1136/bmj.39169.706574.AD
31. Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. *Palliat Support Care* 2004;2:171-179. doi:10.1017/s1478951504040234
32. Meagher DJ, Leonard M, Donnelly S, et al. A longitudinal study of motor subtypes in delirium: Relationship with other phenomenology, etiology, medication exposure and prognosis. *J Psychosom Res* 2011;71:395-403. doi:10.1016/j.jpsychores.2011.06.001

33. Turan A, George I, Grossberg T. Delirium: Clinical Features, Diagnosis and Differential Diagnosis. In: Isik AT, Grossberg GT, eds. *Delirium in Elderly Patients*. Springer International Publishing; 2018:19-37. doi:10.1007/978-3-319-65239-9
34. Vasilevskis EE, Han JH, Hughes CG, et al. Epidemiology and risk factors for delirium across hospital settings. *Best Pract Res Clin Anaesthesiol* 2012;26:277-287. doi:10.1016/j.bpa.2012.07.003
35. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911-922. doi:10.1016/S0140-6736(13)60688-1
36. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: A systematic literature review. *Age Ageing* 2006;35:350-364. doi:10.1093/ageing/afl005
37. De Lange E, Verhaak PFM, Van Der Meer K. Prevalence, presentation and prognosis of delirium in older people in the population, at home and in long term care: A review. *Int J Geriatr Psychiatry* 2013;28:127-134. doi:10.1002/gps.3814
38. Grover S, Kate N. Assessment scales for delirium: A review. *World J Psychiatry* 2012;2:58-70. doi:10.5498/wjp.v2.i4.58
39. Helfand BKI, D'Aquila ML, Tabloski P, et al. Detecting Delirium: A Systematic Review of Identification Instruments for Non-ICU Settings. *J Am Geriatr Soc* 2021;69:547-555. doi:10.1111/jgs.16879
40. De J, Wand APF. Delirium Screening : A Systematic Review of Delirium Screening Tools in Hospitalized Patients. *Gerontologist* 2015;55:1079-1099. doi:10.1093/geront/gnv100
41. Shi Q, Warren L, Saposnik G, et al. Confusion assessment method: A systematic review and meta-analysis of diagnostic accuracy. *Neuropsychiatr Dis Treat* 2013;9:1359-1370. doi:10.2147/NDT.S49520
42. Park J, Jeong E, Lee J. The Delirium Observation Screening Scale: A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy. *Clin Nurs Res* 2021;30:464-473. doi:10.1177/1054773820961234
43. Trzepacz PT, Mittal D, Torres R, et al. Validation of the Delirium Rating Scale-Revised-98: Comparison With the Delirium Rating Scale and the Cognitive Test for Delirium. *J Neuropsychiatry Clin Neurosci* 2001;13:229-242. doi:10.1176/jnp.13.2.229
44. Popp J, Arlt S. Prevention and treatment options for postoperative delirium in the elderly. *Curr Opin Psychiatry* 2012;25:515-521. doi:10.1097/YCO.0b013e328357f51c
45. Guenther U, Theuerkauf N, Frommann I, et al. Predisposing and precipitating factors of delirium after cardiac surgery: A prospective observational cohort study. *Ann Surg* 2013;257:1160-1167. doi:10.1097/SLA.0b013e318281b01c
46. Hughes CG, Patel MB, Pandharipande PP. Pathophysiology of acute brain dysfunction: What's the cause of all this confusion? *Curr Opin Crit Care* 2012;18:518-526. doi:10.1097/MCC.0b013e328357effa

47. Popp J. Delirium and cognitive decline: More than a coincidence. *Curr Opin Neurol* 2013;26:634-639. doi:10.1097/WCO.0000000000000030
48. Maldonado JR. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry* 2013;21:1190-1222. doi:10.1016/j.jagp.2013.09.005
49. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *Int J Geriatr Psychiatry* 2018;33:1428-1457. doi:10.1002/gps.4823
50. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. The immunology of delirium. *Neuroimmunomodulation* 2014;21:72-78. doi:10.1159/000356526
51. Cunningham C, MacLullich AMJ. At the extreme end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behaviour response. *Brain Behav Immun* 2013;28:1-13. doi:10.1016/j.bbi.2012.07.012
52. Cerejeira JMS, Nogueira V, Luís P, et al. The cholinergic system and inflammation: Common pathways in delirium pathophysiology. *J Am Geriatr Soc* 2012;60:669-675. doi:10.1111/j.1532-5415.2011.03883.x
53. Cunningham C. Systemic inflammation and delirium: Important co-factors in the progression of dementia. *Biochem Soc Trans* 2011;39:945-953. doi:10.1042/BST0390945
54. Oh ES, Needham DM, Nikooie R, et al. Antipsychotics for preventing delirium in hospitalized adults a systematic review. *Ann Intern Med* 2019;171:474-484. doi:10.7326/M19-1859
55. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2016. doi:10.1002/14651858.CD005563.pub3
56. Kalisvaart KJ, De Jonghe JFM, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: A randomized placebo-controlled study. *J Am Geriatr Soc* 2005;53:1658-1666. doi:10.1111/j.1532-5415.2005.53503.x
57. Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: A randomized controlled trial*. *Crit Care Med* 2012;40:731-739. doi:10.1097/CCM.0b013e3182376e4f
58. Barnes TRE, McPhillips MA. Novel antipsychotics, extrapyramidal side effects and tardive dyskinesia. *Int Clin Psychopharmacol* 1998;13:S49-S58. doi:10.1097/00004850-199803003-00009
59. Hanania M, Kitain E. Melatonin for Treatment and Prevention of Postoperative Delirium. *Anesth Analg* 2002;94:338-339. doi:10.1097/00000539-200202000-00019
60. Chakraborti D, Tampi DJ, Tampi RR. Melatonin and melatonin agonist for delirium in the elderly patients. *Am J Alzheimers Dis Other Demen* 2015;30:119-129. doi:10.1177/1533317514539379
61. Chen S, Shi L, Liang F, et al. Exogenous Melatonin for Delirium Prevention: a Meta-

analysis of Randomized Controlled Trials. *Mol Neurobiol* 2016;53:4046-4053. doi:10.1007/s12035-015-9350-8

62. Hatta K, Kishi Y, Wada K, et al. Preventive effects of ramelteon on delirium: A randomized placebo-controlled trial. *JAMA Psychiatry* 2014;71:397-403. doi:10.1001/jamapsychiatry.2013.3320
63. Shigeta H, Yasui A, Nimura Y, et al. Postoperative delirium and melatonin levels in elderly patients. *Am J Surg* 2001;182:449-454. doi:10.1016/S0002-9610(01)00761-9
64. Khaing K, Nair BR. Melatonin for delirium prevention in hospitalized patients: A systematic review and meta-analysis. *J Psychiatr Res* 2021;133:181-190. doi:10.1016/j.jpsychires.2020.12.020
65. Dang V, Mansukhani MP, Wang Z, et al. Prophylactic Use of Ramelteon for Delirium in Hospitalized Patients: A Systematic Review and Meta-Analyses. *J Acad Consult Psychiatry* 2022;in press. doi:10.1016/j.jaclp.2022.06.002
66. Burton JK, Craig L, Yong SQ, et al. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2021. doi:10.1002/14651858.CD013307.pub3
67. National Institute for Health and Care Excellence. Delirium: prevention, diagnosis and management [CG103]. Published 2010. https://www.nice.org.uk/guidance/cg103
68. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Delirium*. (American Psychiatric Association, ed.).; 1999. http://www.appi.org/CustomerService/Pages/Permissions.aspx.http://www.appi.org/CustomerService/Pages/Permissions.aspx.
69. National Guidelines for Seniors' Mental Health. *The Assessment and Treatment of Delirium*. (Canadian Coalition for Seniors' Mental Health, ed.).; 2006.
70. Burry L, Mehta S, Perreault MM, et al. Antipsychotics for treatment of delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2018;2018. doi:10.1002/14651858.CD005594.pub3
71. Nørgaard A, Jensen-Dahm C, Wimberley T, et al. Effect of antipsychotics on mortality risk in patients with dementia with and without comorbidities. *J Am Geriatr Soc* 2022;70:1169-1179. doi:10.1111/jgs.17623
72. Ralph SJ, Espinet AJ. Increased All-Cause Mortality by Antipsychotic Drugs: Updated Review and Meta-Analysis in Dementia and General Mental Health Care. *J Alzheimer's Dis Reports* 2018;2:1-26. doi:10.3233/adr-170042
73. National Guidelines for Seniors' Mental Health. *The Assessment and Treatment of Delirium: Guideline Update*. (Health CC for SM, ed.).; 2014.
74. Francis J. Delirium and acute confusional states: Prevention, treatment, and prognosis. In: Post TW, ed. *UpToDate*. UpToDate; 2022. https://www.uptodate.com/contents/delirium-and-acute-confusional-states-prevention-treatment-and-

prognosis/print?search=deliriumtreatment&…1/27OfficialreprintfromUpToDatewww.uptodate.com

75. Janssen-Cilag AG. Haldol® Product Information - Swissmedicinfo.ch. Published 2020. Accessed November 11, 2022. https://www.swissmedicinfo.ch
76. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry* 1996;153:231-237. doi:10.1176/ajp.153.2.231
77. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients. *Anesthesiology* 2006;104:21-27. http://pubs.asahq.org/anesthesiology/article-pdf/104/1/21/359676/0000542-200601000-00005.pdf
78. Koponen HJ. Neurochemistry and delirium. *Dement Geriatr Cogn Disord* 1999;10:339-341. doi:10.1159/000017166
79. Wengel SP, Roccaforte WH, Burke WJ. Donepezil Improves Symptoms of Delirium in Dementia: Implications for Future Research. *J Geriatr Psychiatry Neurol* 1998;11:159-161. doi:10.1177/089198879801100308
80. Wengel SP, Burke WJ, Roccaforte WH. Donepezil for postoperative delirium associated with Alzheimer's disease. *J Am Geriatr Soc* 1999;47:379-380. doi:10.1111/j.1532-5415.1999.tb03015.x
81. van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 2010;376:1829-1837. doi:10.1016/S0140-6736(10)61855-7
82. Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry* 2007;22:343-349. doi:10.1002/gps.1679
83. Turco R, Bellelli G, Morandi A, et al. The effect of poststroke delirium on short-term outcomes of elderly patients undergoing rehabilitation. *J Geriatr Psychiatry Neurol* 2013;26:63-68. doi:10.1177/0891988713481265
84. Leslie DL, Marcantonio ER, Zhang Y, et al. One-Year Health Care Costs Associated With Delirium in the Elderly Population. *Arch Intern Med* 2008;168:27. doi:10.1001/archinternmed.2007.4
85. Shi Q, Presutti R, Selchen D, et al. Delirium in acute stroke: A systematic review and meta-analysis. *Stroke* 2012;43:645-649. doi:10.1161/STROKEAHA.111.643726
86. Mangusan RF, Hooper V, Denslow SA, et al. Outcomes associated with postoperative delirium after cardiac surgery. *Am J Crit Care* 2015;24:156-163. doi:10.4037/ajcc2015137
87. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive Trajectories after Postoperative

Delirium. *N Engl J Med* 2012;367:30-39. doi:10.1056/nejmoa1112923

88. Duppils GS, Wikblad K. Patients' experiences of being delirious. *J Clin Nurs* 2007;16:810-818. doi:10.1111/j.1365-2702.2006.01806.x
89. Bruera E, Bush SH, Willey J, et al. Impact of Delirium and recall on the level or distress in patients with advanced cancer and their family caregivers. *Cancer* 2009;115:2004-2012. doi:10.1002/cncr.24215
90. Drews T, Franck M, Radtke FM, et al. Postoperative delirium is an independent risk factor for posttraumatic stress disorder in the elderly patient a prospective observational study. *Eur J Anaesthesiol* 2015;32:147-151. doi:10.1097/EJA.0000000000000107
91. Oh-Park M, Chen P, Romel-Nichols V, et al. Delirium screening and management in inpatient rehabilitation facilities. *Am J Phys Med Rehabil* 2018;97:754-762. doi:10.1097/PHM.0000000000000962
92. McCusker J, Cole M, Abrahamowicz M, et al. Delirium predicts 12-month mortality. *Arch Intern Med* 2002;162:457-463. doi:10.1001/archinte.162.4.457
93. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: An independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010;58:643-649. doi:10.1111/j.1532-5415.2010.02762.x
94. Bellelli G, Frisoni GB, Turco R, et al. Delirium Superimposed on Dementia Predicts 12-Month Survival in Elderly Patients Discharged From a Postacute Rehabilitation Facility. *Journals Gerontol Ser A Biol Sci Med Sci* 2007;62:1306-1309. doi:10.1093/gerona/62.11.1306
95. Ceppi MG, Rauch MS, Sándor PS, et al. Detecting incident delirium within routinely collected inpatient rehabilitation data: Validation of a chart-based method. *Neurol Int* 2021;13:701-711. doi:10.3390/neurolint13040067
96. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Fifth Edition*. WHO; 2015. https://apps.who.int/iris/handle/10665/246208
97. Davis DHJ, Muniz Terrera G, Keage H, et al. Delirium is a strong risk factor for dementia in the oldest-old: A population-based cohort study. *Brain* 2012;135:2809-2816. doi:10.1093/brain/aws190
98. Marcantonio ER, Flacker JM, Michaels M, et al. Delirium Is Independently Associated with Poor Functional Recovery After Hip Fracture Edward. *J Am Geriatr Soc* 2000;48:618-624. doi:10.1111/j.1532-5415.2000.tb04718.x
99. Bellelli G, Frisoni GB, Turco R, et al. Delirium superimposed on dementia predicts 12-month survival in elderly patients discharged from a postacute rehabilitation facility. *Journals Gerontol - Ser A Biol Sci Med Sci* 2007;62:1306-1309. doi:10.1093/gerona/62.11.1306
100. Jang S, Jung KI, Yoo WK, et al. Risk factors for delirium during acute and subacute

stages of various disorders in patients admitted to rehabilitation units. *Ann Rehabil Med* 2016;40:1082-1091. doi:10.5535/arm.2016.40.6.1082

101. Kotfis K, Szylińska A, Listewnik M, et al. Early delirium after cardiac surgery: An analysis of incidence and risk factors in elderly (≥65 years) and very elderly (≥80 years) patients. *Clin Interv Aging* 2018;13:1061-1070. doi:10.2147/CIA.S166909
102. Szylińska A, Rotter I, Listewnik M, et al. Postoperative delirium in patients with chronic obstructive pulmonary disease after coronary artery bypass grafting. *Med* 2020;56:1-11. doi:10.3390/medicina56070342
103. Rudolph JL, Doherty K, Kelly B, et al. Validation of a Delirium Risk Assessment Using Electronic Medical Record Information. *J Am Med Dir Assoc* 2016;17:244-248. doi:10.1016/j.jamda.2015.10.020
104. Leonard MM, Agar M, Spiller JA, et al. Delirium diagnostic and classification challenges in palliative care: Subsyndromal delirium, comorbid delirium-dementia, and psychomotor subtypes. *J Pain Symptom Manage* 2014;48:199-214. doi:10.1016/j.jpainsymman.2014.03.012
105. Inouye SK, Van Dyck CH, Alessi CA, et al. Clarifying confusion: The confusion assessment method: A new method for detection of delirium. *Ann Intern Med* 1990;113:941-948. doi:10.7326/0003-4819-113-12-941
106. Inouye SK, Leo-Summers L, Zhang Y, et al. A chart-based method for identification of delirium: Validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc* 2005;55:312-318. doi:10.1111/j.1532-5415.2005.53120.x
107. Fong TG, Jones RN, Marcantonio ER, et al. Adverse outcomes after hospitalization and delirium in persons with alzheimer disease. *Ann Intern Med* 2012;156:848-856. doi:10.7326/0003-4819-156-12-201206190-00005
108. Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in alzheimer disease. *Neurology* 2009;72:1570-1575. doi:10.1212/WNL.0b013e3181a4129a
109. Saczynski JS, Kosar CM, Xu G, et al. A tale of two methods: Chart and interview methods for identifying delirium. *J Am Geriatr Soc* 2014;62:518-524. doi:10.1111/jgs.12684
110. Puelle MR, Kosar CM, Xu G, et al. The Language of Delirium: Keywords for Identifying Delirium from Medical Records. *J Gerontol Nurs* 2015;41:34-42. doi:10.3928/00989134-20150723-01
111. Ford E, Sheppard J, Oliver S, et al. Automated detection of patients with dementia whose symptoms have been identified in primary care but have no formal diagnosis: A retrospective case-control study using electronic primary care records. *BMJ Open* 2021;11:1-11. doi:10.1136/bmjopen-2020-039248
112. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment*.; 2019. https://www.whocc.no/atc_ddd_index/
113. Morandi A, Davis D, Bellelli G, et al. The Diagnosis of Delirium Superimposed on

Dementia: An Emerging Challenge. *J Am Med Dir Assoc* 2017;18:12-18. doi:10.1016/j.jamda.2016.07.014

114. Voyer P, Richard S, Doucet L, et al. Detecting Delirium and Subsyndromal Delirium Using Different Diagnostic Criteria among Demented Long-Term Care Residents. *J Am Med Dir Assoc* 2009;10:181-188. doi:10.1016/j.jamda.2008.09.006
115. Kim DH, Lee J, Kim CA, et al. Evaluation of algorithms to identify delirium in administrative claims and drug utilization database. *Pharmacoepidemiol Drug Saf* 2017;26:945-953. doi:10.1002/pds.4226
116. Infante MT, Pardini M, Balestrino M, et al. Delirium in the acute phase after stroke: comparison between methods of detection. *Neurol Sci* 2017;38:1101-1104. doi:10.1007/s10072-017-2832-x
117. Hope C, Estrada N, Weir C, et al. Documentation of delirium in the VA electronic health record. *BMC Res Notes* 2014;7:24-26. doi:10.1186/1756-0500-7-208
118. Ceppi MG, Rauch MS, Spöndlin J, et al. Potential Risk Factors for, and Clinical Implications of, Delirium During Inpatient Rehabilitation: A Matched Case-Control Study. *J Am Med Dir Assoc* 2023;24. doi:10.1016/j.jamda.2023.01.012
119. Elie M, Cole MG, Primeau FJ, et al. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med* 1998;13:204-212. doi:10.1046/j.1525-1497.1998.00047.x
120. O'Regan NA, Fitzgerald J, Adamis D, et al. Predictors of delirium development in older medical inpatients: Readily identifiable factors at admission. *J Alzheimer's Dis* 2018;64:775-785. doi:10.3233/JAD-180178
121. Zipser CM, Deuel J, Ernst J, et al. The predisposing and precipitating risk factors for delirium in neurosurgery: a prospective cohort study of 949 patients. *Acta Neurochir (Wien)* 2019;161:1307-1315. doi:10.1007/s00701-019-03927-z
122. Carrasco MP, Villarroel L, Andrade M, et al. Development and validation of a delirium predictive score in older people. *Age Ageing* 2014;43:346-351. doi:10.1093/ageing/aft141
123. Rosted E, Prokofieva T, Sanders S, et al. Serious Consequences of Malnutrition and Delirium in Frail Older Patients. *J Nutr Gerontol Geriatr* 2018;37:105-116. doi:10.1080/21551197.2018.1470055
124. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: Predictive model and interrelationship with baseline vulnerability. *J Am Med Assoc* 1996;275:852-857. doi:10.1001/jama.275.11.852
125. Mach JR, Dysken MW, Kuskowski M, et al. Serum Anticholinergic Activity in Hospitalized Older Persons with Delirium: A Preliminary Study. *J Am Geriatr Soc* 1995;43:491-495. doi:10.1111/j.1532-5415.1995.tb06094.x
126. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging* 2009;4:225-233. doi:10.2147/CIA.S5358
127. Caeiro L, Ferro JM, Claro MI, et al. Delirium in acute stroke: A preliminary study of the role

of anticholinergic medications. *Eur J Neurol* 2004;11:699-704. doi:10.1111/j.1468-1331.2004.00897.x

128. Pasina L, Colzani L, Cortesi L, et al. Relation Between Delirium and Anticholinergic Drug Burden in a Cohort of Hospitalized Older Patients : An Observational Study. *Drugs Aging* 2019;36:85-91. doi:10.1007/s40266-018-0612-9
129. Naja M, Zmudka J, Hannat S, et al. In geriatric patients, delirium symptoms are related to the anticholinergic burden. *Geriatr Gerontol Int* 2016;16:424-431. doi:10.1111/ggi.12485
130. Kolanowski A, Mogle J, Fick DM, et al. Anticholinergic Exposure during Rehabilitation: Cognitive and Physical Function Outcomes in Patients with Delirium Superimposed on Dementia. *Am J Geriatr Psychiatry* 2015;23:1250-1258. doi:10.1016/j.jagp.2015.07.004
131. Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med* 2001;161:1099-1105. doi:10.1001/archinte.161.8.1099
132. Morandi A, Mazzone A, Bernardini B, et al. Association between delirium, adverse clinical events and functional outcomes in older patients admitted to rehabilitation settings after a hip fracture: A multicenter retrospective cohort study. *Geriatr Gerontol Int* 2019;19:404-408. doi:10.1111/ggi.13628
133. Guerini F, Frisoni GB, Morghen S, et al. Clinical instability as a predictor of negative outcomes among elderly patients admitted to a rehabilitation ward. *J Am Med Dir Assoc* 2010;11:443-448. doi:10.1016/j.jamda.2009.10.005
134. Bushi S, Barrett AM, Oh-Park M. Inpatient Rehabilitation Delirium Screening: Impact on Acute Care Transfers and Functional Outcomes. *PM R* 2020;12:766-774. doi:10.1002/pmrj.12304
135. Heyman N, Nili F, Shahory R, et al. Prevalence of delirium in geriatric rehabilitation in Israel and its influence on rehabilitation outcomes in patients with hip fractures. *Int J Rehabil Res* 2015;38:233-237. doi:10.1097/MRR.0000000000000121
136. Gual N, Morandi A, Pérez LM, et al. Risk Factors and Outcomes of Delirium in Older Patients Admitted to Postacute Care with and without Dementia. *Dement Geriatr Cogn Disord* 2018;45:121-129. doi:10.1159/000485794
137. WHO Collaborating Centre for Drug Statistics and Methodology. ATC/DDD index. Published 2018. https://www.whocc.no/atc_ddd_index/
138. ICD-10-GM, International statistical classification of diseases and related health problems, 10th revision. In: German Institute of Medical Documentation and Information (DIMDI) on behalf of the Federal Ministry of Health (BMG); 2018. www.bfarm.de - Coding systems - Services - Downloads - ICD-10-GM
139. Boustani M, Campbell N, Munger S, et al. Impact of anticholinergics on the aging brain: A review and practical application. *Aging health* 2008;4:311-320. doi:10.2217/1745509X.4.3.311

140. Pearce N. Analysis of matched case-control studies. *BMJ* 2016;352:1-4. doi:10.1136/bmj.i969
141. Stelmokas J, Gabel N, Flaherty JM, et al. Delirium detection and impact of comorbid health conditions in a post-acute rehabilitation hospital setting. *PLoS One* 2016;11:1-8. doi:10.1371/journal.pone.0166754
142. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: The Padua Prediction Score. *J Thromb Haemost* 2010;8:2450-2457. doi:10.1111/j.1538-7836.2010.04044.x
143. Beattie P, Nelson R. Clinical prediction rules: What are they and what do they tell us? *Aust J Physiother* 2006;52:157-163. doi:10.1016/S0004-9514(06)70024-1
144. Heinze G, Wallisch C, Dunkler D. Variable selection – A review and recommendations for the practicing statistician. *Biometrical J* 2018;60:431-449. doi:10.1002/bimj.201700067
145. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth* 2020;125:492-504. doi:10.1016/j.bja.2020.06.063
146. Van Den Boogaard M, Pickkers P, Slooter AJC, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: Observational multicentre study. *BMJ* 2012;344:17. doi:10.1136/bmj.e420
147. de Wit HAJM, Winkens B, Mestres Gonzalvo C, et al. The development of an automated ward independent delirium risk prediction model. *Int J Clin Pharm* 2016;38:915-923. doi:10.1007/s11096-016-0312-7
148. Matsuoka A, Miike T, Miyazaki M, et al. Development of a delirium predictive model for adult trauma patients in an emergency and critical care center: A retrospective study. *Trauma Surg Acute Care Open* 2021;6:1-5. doi:10.1136/tsaco-2021-000827
149. Kostalova M, Bednarik J, Mitasova A, et al. Towards a predictive model for post-stroke delirium. *Brain Inj* 2012;26:962-971. doi:10.3109/02699052.2012.660510
150. FDA. Real-World Evidence. Published 2023. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
151. Swift B, Jain L, White C, et al. Innovation at the Intersection of Clinical Trials and Real-World Data Science to Advance Patient Care. *Clin Transl Sci* 2018;11:450-460. doi:10.1111/cts.12559
152. Liu F, Demosthenes P. Real-world data: a brief review of the methods, applications, challenges and opportunities. *BMC Med Res Methodol* 2022;22:1-10. doi:10.1186/s12874-022-01768-6
153. Eichler HG, Koenig F, Arlett P, et al. Are Novel, Nonrandomized Analytic Methods Fit for Decision Making? The Need for Prospective, Controlled, and Transparent Validation. *Clin Pharmacol Ther* 2020;107:773-779. doi:10.1002/cpt.1638
154. Schweizerische Eidgenossenschaft. *Der Bundesrat Will Der Forschung Eine Bessere*

Nutzung von Gesundheitsdaten Ermöglichen.; 2022. https://www.admin.ch/gov/de/start/dokumentation/medienmitteilungen.msg-id-88631.html

155. Wu J, Roy J, Stewart WF. Prediction Modeling Using EHR Data Challenges, Strategies, and a Comparison of Machine Learning Approaches. *Med Care* 2010;48:S106-S113. www.lww-medicalcare.com
156. Jansen-Van Der Weide MC, Gaasterland CMW, Roes KCB, et al. Rare disease registries: Potential applications towards impact on development of new drug treatments. *Orphanet J Rare Dis* 2018;13:1-11. doi:10.1186/s13023-018-0836-0
157. Svarstad BL, Shireman TI, Sweeney JK. Using Drug Claims Data to Assess the Relationship of Medication Adherence With Hospitalization and Costs. *Psychiatr Serv* 2001;52:805-811.
158. Sheikhalishahi S, Miotto R, Dudley JT, et al. Natural language processing of clinical notes on chronic diseases: Systematic review. *JMIR Med Informatics* 2019;7:1-18. doi:10.2196/12239
159. Solomon MD, Tabada G, Allen A, et al. Large-scale identification of aortic stenosis and its severity using natural language processing on electronic health records. *Cardiovasc Digit Heal J* 2021;2:156-163. doi:10.1016/j.cvdhj.2021.03.003
160. Barraza F, Arancibia M, Madrid E, et al. General concepts in biostatistics and clinical epidemiology: Random error and systematic error. *Medwave* 2019;19:e7687. doi:10.5867/medwave.2019.07.7687
161. Gordis L. More on Causal Inferences: Bias, Confounding, and Interaction. In: *Epidemiology*. 4th ed. Saunders Elsevier; 2014:247-264.
162. Garbe E, Suissa S. Exposure Assessment. In: Ahrens W, Pigeot I, eds. *Handbook of Epidemiology*. Springer New York; 2014:613-638. doi:10.1007/978-0-387-09834-0
163. Swiss DRG AG. Fallpauschalen in Schweizer Spitälern. Published online 2015:1-8. http://www.swissdrg.org/assets/pdf/Broschuere/150212_SwissDRG_Broschuere_D.PDF (retrieved June 27, 2016)
164. Bundesamt für Statistik. Patient/innen, Hospitalisierungen. Accessed January 20, 2023. https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/gesundheitswesen/spitaeler/patienten-hospitalisierungen.html
165. Horn SD, DeJong G, Smout RJ, et al. Stroke rehabilitation patients, practice, and outcomes: Is earlier and more aggressive therapy better? *Arch Phys Med Rehabil* 2005;86:101-114. doi:10.1016/j.apmr.2005.09.016
166. Maulden SA, Gassaway J, Horn SD, et al. Timing of initiation of rehabilitation after stroke. *Arch Phys Med Rehabil* 2005;86:34-40. doi:10.1016/j.apmr.2005.08.119
167. Sauter M. *Delir in Der Rehabilitation – Entwicklung Evidenzbasierter Guidelines*. University of Zurich; 2022.

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1. DeepL Translate, Deepl SE: https://www.deepl.com/translator
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