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Original Study

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

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A B S T R A C T

Objectives: To investigate the association between a wide set of baseline characteristics (age, sex, rehabilitation discipline), functional scores [Functional Independence Measure (FIM), cumulative Illness Rating Scale (CIRS)], diseases, and administered drugs and incident delirium in rehabilitation inpatients and, 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 January 1, 2015, and December 31, 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% CIs of exposures that were recorded in $\geq$5 cases and controls.
Results: Among a total of 10,503 rehabilitation stays, we identified 125 validated cases. Older age, undergoing neurologic 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 1.14-3.10) during rehabilitation, or an increased anticholinergic burden (ACB $\geq$ 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.

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.[1,2] 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 neurologic disorders or infections, dehydration, malnutrition, immobility, prolonged hospital stay, and polypharmacy.[3-10] 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.[11-17]

In the inpatient rehabilitation setting, as in the acute setting, delirium has been associated with a longer duration of stay and higher mortality.[18-23] Because of the inability of delirious patients to follow

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the challenging interdisciplinary therapeutic schedule, delirium has also been associated with poor functional rehabilitation outcome.[24,25] 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.[26,27]

Older age is a common risk factor for delirium among rehabilitation inpatients.[26-29] 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.[29]

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 of ZURZACH Care, Rehaklinik Bad Zurzach, an inpatient rehabilitation clinic in Switzerland. Electronic health records comprise medical notes (suggestive of incident delirium, as validated in a previous study),[30] 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 *International Classification of Diseases, Tenth Revision (ICD-10)* codes],[2] administered drugs [recorded as Anatomical Therapeutic Chemical (ATC) codes],[31] FIM,[32] and the Cumulative Illness Rating Scale (CIRS).[33] 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 January 1, 2015, and December 31, 2018. Single patients may have contributed to more than 1 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 data set has been described in detail previously.[30] Briefly, we defined 15 keywords commonly used to describe delirious patients in medical notes. Profiles of patients with at least 2 recorded keywords and no diagnosis of delirium at admission were reviewed by at least 2 independent physicians, based on predefined evaluation criteria to confirm or refute the diagnosis of delirium. In confirmed cases, the first recorded keyword was defined as the date of onset of delirium (index date). Eligible controls were patients who did not have any record of delirium predictive keywords in their electronic health records and no diagnosis of delirium at admission. For each validated case, we matched 4 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*,[34] 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 Supplementary Table 1 for the complete *ICD-10* codes list).

Additionally, we assessed the number of administered drugs at admission as continuous variable, and the administered drug classes that were recorded in ≥5 cases and controls at any time between admission and index date (see Supplementary Table 2 for the complete ATC codes list). We defined "users" of the above drugs as patients with at least 1 administration between admission and index date, and "nonusers" 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 or <3).[35]

Statistical Analysis

We summarized continuous variables providing means and SDs, and categorical variables as absolute and relative frequencies.

We conducted unconditional logistic regression analyses to calculate odds ratios with 95% 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 2 matching factors (index date and time span between admission and index date).[36]

All statistical analyses were conducted using SAS 9.4 (SAS Institute). Graphics were composed using Prism GraphPad 9.4 (GraphPad Software).

Results

Of 9406 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 (Supplementary Figure 1). Patients and rehabilitation characteristics of cases and controls are reported in Table 1. 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 (Supplementary Table 3).

Older age and undergoing neurologic rehabilitation were associated with increased risks of incident delirium (Table 1).

Severe functional impairment (FIM ≤ 65) and severe burden of disease (CIRS ≥ 14) were also associated with increased risks of incident delirium (Table 2).

Several comorbidities were associated with an increased risk of incident delirium during inpatient rehabilitation (Figure 1; see Supplementary Table 4 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,

Table 1
Odds Ratios of Baseline Characteristics Among Cases With Incident Delirium and Matched Controls

Characteristic	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, y				
<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, y, 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)
Nonneurology†	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

n/a, not applicable; ref., referent.
Values are n (%) unless otherwise noted. 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/nonneurology); age adjusted on sex, rehabilitation discipline (neurology/nonneurology); rehabilitation discipline adjusted on age, sex.
†Frequencies (%) within nonneurology 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.

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 (AOR 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 2; see Supplementary Table 5 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 non-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 3).

Discussion

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

Table 2
Odds Ratios of FIM and CIRS Scores at Admission Among Cases With Incident Delirium and Matched Controls

Measure	Cases (n = 125)	Controls (n = 499)*	OR (95% CI)	AOR (95% CI)†
FIM score at admission				
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)
CIRS score at admission				
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)

n/a, not applicable; ref., referent.
Values are n (%) unless otherwise noted. 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).
*Missing database entries (FIM and CIRS) for 1 control.
†Adjusted on age, sex, rehabilitation discipline (neurology/nonneurology).

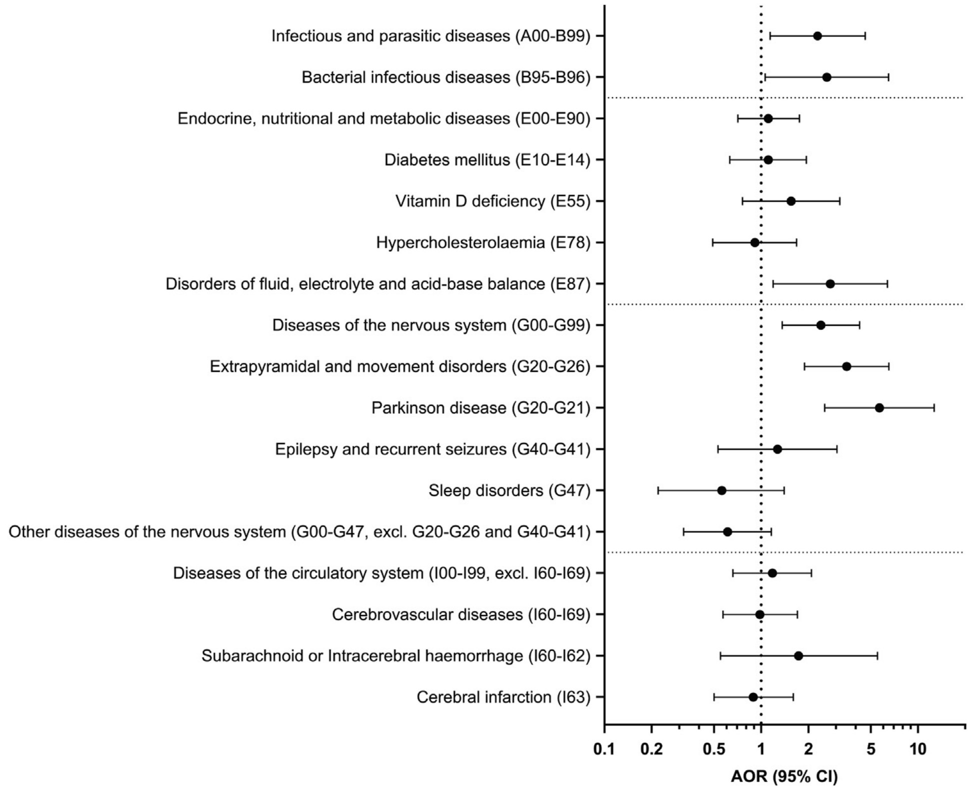

Fig. 1. Forest plot of adjusted odds ratios (95% CIs) among cases with incident delirium and matched controls for exposure to different comorbidities defined as a record of the *International Classification of Diseases, Tenth Revision*, code. Controls were matched to cases on index date (±1 month) and 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/nonneurology).

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 ≥85 years a 13.0-fold increased risk of delirium. The results are consistent with previous studies, which reported that patients who developed delirium during rehabilitation were older[26-29] and more often men[26,28,29] than patients who did not develop delirium. In our study, most cases underwent neurologic 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 neurologic imbalance caused by degenerative neurologic conditions that may trigger the pathophysiology of delirium.[37] 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 an FIM lower than 65 points at admission had a 13.2-fold increased risk of incident delirium as compared to patients with an 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 2 previously published studies that assessed the FIM among patients with and without delirium.[26,27] Bushi et al[26] found that patients with delirium had a significantly lower cognitive and motor 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 neurologic diagnosis for rehabilitation than patients without delirium.[26]

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,[38] who reported a 4.5-fold increased risk of delirium among patients with an elevated Age-Adjusted Charlson Index.

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.[29] Jang et al[29] 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, erythrocyte sedimentation

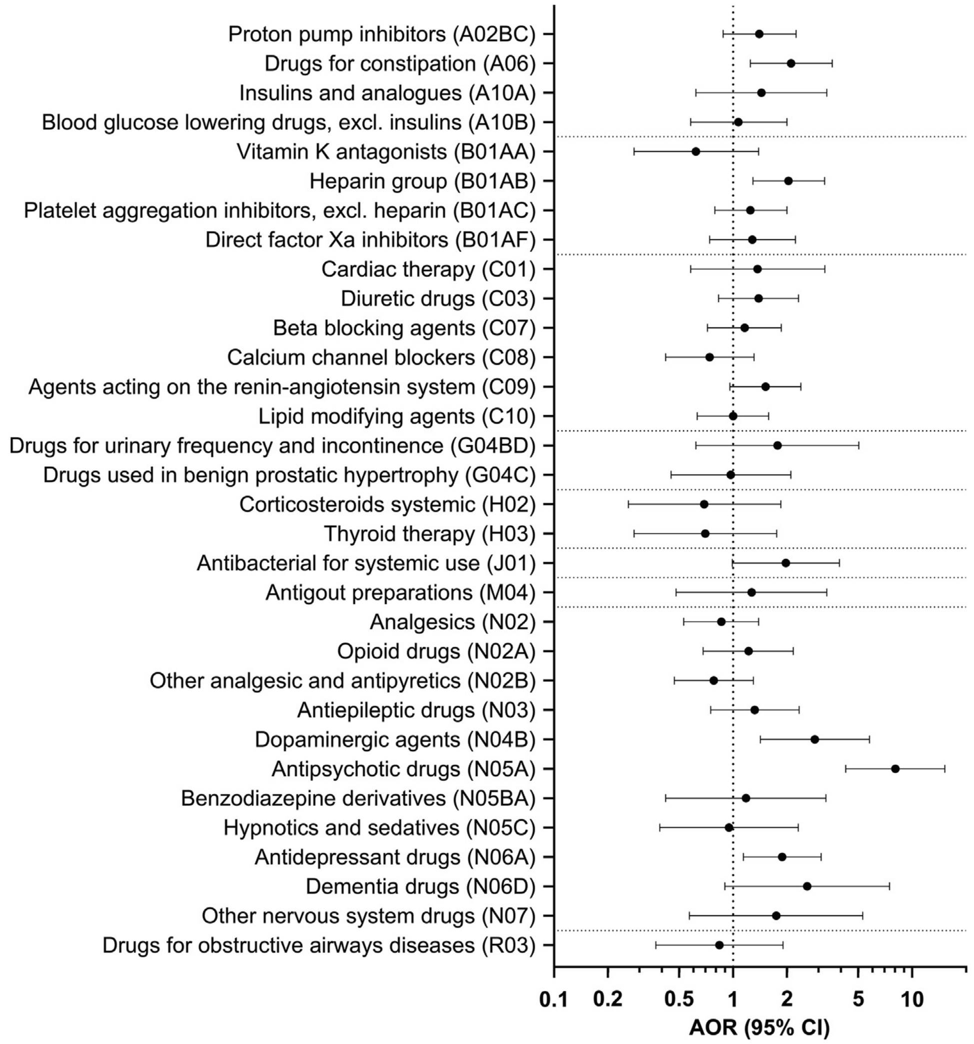

Fig. 2. Forest plot of adjusted odds ratios (95% CIs) among cases with incident delirium and matched controls for exposure to selected drug groups defined as at least 1 record of an administered code of the respective Anatomical Therapeutic Chemical (ATC) class at any time from the admission date until 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/nonneurology).

rate, C-reactive protein and decreased potassium and phosphorus levels.[29] 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 (ie, white blood cells, erythrocyte sedimentation rate, and C-reactive protein) observed by Jang et al[29] 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 favorable conditions for the development of delirium.[37]

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.[10-17,37]

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 nonuse of these drug classes. From a pharmacologic point of view, only some of these results are attributable to the direct effect of these drug classes on the onset of delirium, whereas others may be indirectly but not causally associated with delirium. For instance, in inpatient setting, heparins are often used to prevent thromboembolic conditions,[39] 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 pharmacologic point

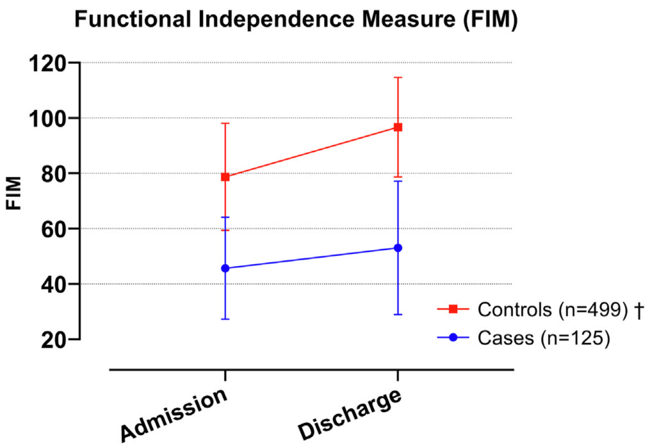

Fig. 3. Functional Independence Measure (FIM) scores at rehabilitation admission and at discharge for cases with incident delirium and matched controls, mean (SD). FIM improvement between admission and discharge, mean (SD): 7.4 (17.1) for cases; 17.9 (12.6) for controls. †Missing database entries for 1 control.

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,[26-29] particularly one study reported a significantly lower change in FIM between admission and discharge for patients with delirium compared with patients without delirium [ΔFIM (SD), 10.5 (13.1) vs 19.4 (15.4)].[27]

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. Because of the nonspecific and off-label use of antipsychotic drugs in clinical practice and 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, because of 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, neurologic rehabilitation, reduced FIM, and high disease or anticholinergic burden, as well as a number of prevalent comorbidities and coadministered 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.[40] Furthermore, modifiable risk factors such as new drug prescriptions or the anticholinergic drug burden should be proactively considered to reduce the risk of incident delirium.

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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. APA Press; 2013.
2. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*. 5th ed. World Health Organization; 2015.
3. Elie M, Cole MG, Primeau FJ, et al. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med*. 1998;13:204–212.
4. 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.
5. 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.
6. 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*. 2019;161:1307–1315.
7. 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.
8. 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.
9. 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.
10. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383:911–922.
11. 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.
12. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: A clinical review. *Clin Interv Aging*. 2009;4:225–233.

13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. McCusker J, Cole M, Abrahamowicz M, et al. Delirium predicts 12-month mortality. *Arch Intern Med*. 2002;162:457–463.
19. 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.
20. Shi Q, Presutti R, Selchen D, et al. Delirium in acute stroke: A systematic review and meta-analysis. *Stroke*. 2012;43:645–649.
21. Mangusan RF, Hooper V, Denslow SA, et al. Outcomes associated with postoperative delirium after cardiac surgery. *Am J Crit Care*. 2015;24:156–163.
22. 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.
23. 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.
24. 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.
25. 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.
26. Bushi S, Barrett AM, Oh-Park M. Inpatient rehabilitation delirium screening: Impact on acute care transfers and functional outcomes. *Pharm Manag PM R*. 2020;12:766–774.
27. 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.
28. 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.
29. 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.
30. 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.
31. WHO Collaborating Centre for Drug Statistics and Methodology. ATC/DDD index. Accessed March 20, 2023. https://www.whocc.no/atc_ddd_index/
32. Granger CV, Hamilton BB, Keith RA, et al. Advances in functional assessment for medical rehabilitation. *Top Geriatr Rehabil*. 1985;1:59–74.
33. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. 1968;16:622–626.
34. 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.
35. 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.
36. Pearce N. Analysis of matched case-control studies. *BMJ*. 2016;352:1–4.
37. Maldonado JR. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry*. 2013;21:1190–1222.
38. 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.
39. 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.
40. Grover S, Kate N. Assessment scales for delirium: A review. *World J Psychiatry*. 2012;2:58–70.

Supplementary Material

Supplementary Table 1
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

ICD-10, International Classification of Diseases, Tenth Revision.

Supplementary Table 2
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

ATC, Anatomical Therapeutic Chemical.

Supplementary Table 3
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*	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†	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 (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§	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‖	4 (3.2)	33 (6.6)

ICD-10, *International Classification of Diseases, Tenth Revision*.

*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).

†Endocarditis (I33, I38-I39); Dilated cardiomyopathy (I42); Arrhythmias (I49).

‡Aortic aneurysm or dissection (I71); Venous thromboembolism (I82).

§Cervicalgia (M50); Intervertebral disc disorders (M51); Sciatica (M54.3); Lumbago (M54.5).

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

Supplementary Table 4
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)*
Infectious and parasitic diseases (A00-B99)				
No†	105	470	1 ref.	1 ref.
Yes‡	20	30	3.06 (1.66-5.64)	2.29 (1.14-4.61)
Bacterial infectious diseases (B95-B96)				
No†	112	486	1 ref.	1 ref.
Yes‡	13	14	4.16 (1.88-9.21)	2.62 (1.06-6.49)
Endocrine, nutritional and metabolic diseases (E00-E90)				
No†	58	274	1 ref.	1 ref.
Yes‡	67	226	1.41 (0.95-2.09)	1.11 (0.71-1.75)
Diabetes mellitus (E10-E14)				
No†	100	414	1 ref.	1 ref.
Yes‡	25	86	1.20 (0.73-1.98)	1.11 (0.63-1.94)
Vitamin D deficiency (E55)				
No†	109	461	1 ref.	1 ref.
Yes‡	16	39	1.75 (0.94-3.27)	1.55 (0.76-3.17)
Hypercholesterolemia (E78)				
No†	106	436	1 ref.	1 ref.
Yes‡	19	64	1.23 (0.70-2.14)	0.91 (0.49-1.68)
Disorders of fluid, electrolyte and acid-base balance (E87)				
No†	110	484	1 ref.	1 ref.
Yes‡	15	16	4.15 (1.99-8.67)	2.76 (1.19-6.38)
Diseases of the nervous system (G00-G99)				
No†	30	263	1 ref.	1 ref.
Yes‡	95	237	3.55 (2.27-5.56)	2.4 (1.36-4.24)
Extrapyramidal and movement disorders (G20-G26)				
No†	92	471	1 ref.	1 ref.
Yes‡	33	29	5.93 (3.42-10.29)	3.51 (1.89-6.52)
Parkinson disease (G20-G21)				
No†	101	488	1 ref.	1 ref.
Yes‡	24	12	9.87 (4.76-20.46)	5.68 (2.54-12.68)
Epilepsy and recurrent seizures (G40-G41)				
No†	114	483	1 ref.	1 ref.
Yes‡	11	17	2.79 (1.26-6.15)	1.27 (0.53-3.04)
Sleep disorders (G47)				
No†	118	459	1 ref.	1 ref.
Yes‡	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†	109	401	1 ref.	1 ref.
Yes‡	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†	24	200	1 ref.	1 ref.
Yes‡	101	300	2.82 (1.74-4.56)	1.18 (0.66-2.09)
Cerebrovascular diseases (I60-I69)				
No†	75	413	1 ref.	1 ref.
Yes‡	50	87	3.18 (2.07-4.87)	0.98 (0.57-1.70)
Subarachnoid or Intracerebral hemorrhage (I60-I62)				
No†	118	492	1 ref.	1 ref.
Yes‡	7	8	3.65 (1.30-10.28)	1.73 (0.55-5.51)
Cerebral infarction (I63)				
No†	87	439	1 ref.	1 ref.
Yes‡	38	61	3.17 (1.99-5.06)	0.89 (0.5-1.60)

AOR, adjusted odds ratio; *ICD-10*, *International Classification of Diseases, Tenth Revision*; OR, odds ratio; ref. referent.
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.

*Adjusted on age, sex, and rehabilitation discipline (neurology/nonneurology).

†Defined as no-read *ICD-10* code record of the respective disorder within the claims data.

‡Defined as a read *ICD-10* code record of the respective disorder at admission.

Supplementary Table 5
Odds Ratios of Selected Drug Classes Among Cases With Incident Delirium and Matched Controls, by Users or Nonusers

Drug Classes (ATC Codes)	Cases, n (%) (n = 125)	Controls, n (%) (n = 500)	OR (95% CI)	AOR (95% CI)*
Proton pump inhibitors (A02BC)				
Nonusers†	66	256	1 ref.	1 ref.
Users‡	59	244	0.94 (0.63-1.39)	1.4 (0.88-2.25)
Drugs for constipation (A06)				
Nonusers†	91	430	1 ref.	1 ref.
Users‡	34	70	2.30 (1.44-3.68)	2.11 (1.25-3.58)
Insulins and analogues (A10A)				
Nonusers†	115	473	1 ref.	1 ref.
Users‡	10	27	1.53 (0.72-3.27)	1.44 (0.62-3.34)
Blood glucose lowering drugs, excl. Insulins (A10B)				
Nonusers†	105	436	1 ref.	1 ref.
Users‡	20	64	1.30 (0.75-2.24)	1.07 (0.58-2.00)
Vitamin K antagonists (B01AA)				
Nonusers†	115	458	1 ref.	1 ref.
Users‡	10	42	0.95 (0.46-1.95)	0.62 (0.28-1.39)
Heparin group (B01AB)				
Nonusers†	71	378	1 ref.	1 ref.
Users‡	54	122	2.36 (1.57-3.56)	2.04 (1.29-3.24)
Platelet aggregation inhibitors, excl. heparin (B01AC)				
Nonusers†	75	353	1 ref.	1 ref.
Users‡	50	147	1.61 (1.07-2.42)	1.25 (0.79-2.00)
Direct factor Xa inhibitors (B01AF)				
Nonusers†	26	181	1 ref.	1 ref.
Users‡	99	319	2.19 (1.37-3.51)	1.28 (0.74-2.23)
Cardiac therapy (C01)				
Nonusers†	116	475	1 ref.	1 ref.
Users‡	9	25	1.48 (0.67-3.25)	1.37 (0.58-3.25)
Diuretic drugs (C03)				
Nonusers†	85	396	1 ref.	1 ref.
Users‡	40	104	1.81 (1.17-2.80)	1.39 (0.83-2.32)
Beta blocking agents (C07)				
Nonusers†	73	359	1 ref.	1 ref.
Users‡	52	141	1.82 (1.21-2.73)	1.16 (0.72-1.86)
Calcium channel blockers (C08)				
Nonusers†	99	426	1 ref.	1 ref.
Users‡	26	74	1.51 (0.92-2.49)	0.74 (0.42-1.31)
Agents acting on the renin-angiotensin system (C09)				
Nonusers†	54	311	1 ref.	1 ref.
Users‡	71	189	2.18 (1.46-3.25)	1.52 (0.96-2.39)
Lipid modifying agents (C10)				
Nonusers†	63	321	1 ref.	1 ref.
Users‡	62	179	1.78 (1.19-2.65)	1 (0.63-1.58)
Drugs for urinary frequency and incontinence (G04BD)				
Nonusers†	118	486	1 ref.	1 ref.
Users‡	7	14	2.06 (0.81-5.23)	1.77 (0.62-5.04)
Drugs used in benign prostatic hypertrophy (G04C)				
Nonusers†	110	470	1 ref.	1 ref.
Users‡	15	30	2.14 (1.11-4.13)	0.97 (0.45-2.10)
Corticosteroids systemic (H02)				
Nonusers†	119	473	1 ref.	1 ref.
Users‡	6	27	0.88 (0.36-2.19)	0.69 (0.26-1.85)
Thyroid therapy (H03)				
Nonusers†	118	463	1 ref.	1 ref.
Users‡	7	37	0.74 (0.32-1.71)	0.7 (0.28-1.75)
Antibacterial for systemic use (J01)				
Nonusers†	105	466	1 ref.	1 ref.
Users‡	20	34	2.65 (1.46-4.82)	1.97 (0.99-3.92)
Antigout preparations (M04)				
Nonusers†	117	481	1 ref.	1 ref.
Users‡	8	19	1.73 (0.74-4.06)	1.27 (0.48-3.34)
Analgesics (N02)				
Nonusers†	82	283	1 ref.	1 ref.
Users‡	43	217	0.68 (0.45-1.03)	0.86 (0.53-1.39)
Opioid drugs (N02A)				
Nonusers†	103	397	1 ref.	1 ref.
Users‡	22	103	0.82 (0.50-1.37)	1.22 (0.68-2.17)
Other analgesic and antipyretics (N02B)				
Nonusers†	92	333	1 ref.	1 ref.
Users‡	33	167	0.71 (0.46-1.11)	0.78 (0.47-1.30)
Antiepileptic drugs (N03)				
Nonusers†	98	420	1 ref.	1 ref.
Users‡	27	80	1.46 (0.89-2.38)	1.32 (0.75-2.34)
Dopaminergic agents (N04B)				

(*continued on next page*)

Supplementary Table 5 (*continued*)

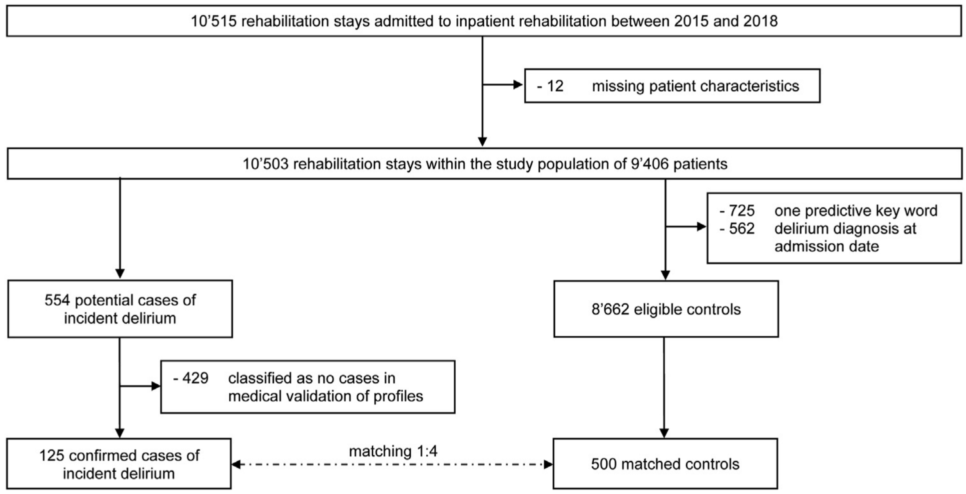
Drug Classes (ATC Codes)	Cases, n (%) (n = 125)	Controls, n (%) (n = 500)	OR (95% CI)	AOR (95% CI)*
Nonusers†	102	477	1 ref.	1 ref.
Users‡	23	23	4.70 (2.54-8.72)	2.86 (1.42-5.77)
Antipsychotic drugs (N05A)				
Nonusers†	86	471	1 ref.	1 ref.
Users‡	39	29	7.46 (4.37-12.74)	8.06 (4.26-15.22)
Benzodiazepine derivatives (N05BA)				
Nonusers†	119	475	1 ref.	1 ref.
Users‡	6	25	0.96 (0.38-2.39)	1.18 (0.42-3.30)
Hypnotics and sedatives (N05C)				
Nonusers†	117	468	1 ref.	1 ref.
Users‡	8	32	1.00 (0.45-2.23)	0.95 (0.39-2.31)
Antidepressant drugs (N06A)				
Nonusers†	81	367	1 ref.	1 ref.
Users‡	44	133	1.52 (0.99-2.31)	1.88 (1.14-3.10)
Dementia drugs (N06D)				
Nonusers†	114	493	1 ref.	1 ref.
Users‡	11	7	7.02 (2.64-18.69)	2.59 (0.90-7.47)
Other nervous system drugs (N07)				
Nonusers†	119	483	1 ref.	1 ref.
Users‡	6	17	1.44 (0.55-3.73)	1.74 (0.57-5.30)
Drugs for obstructive airways diseases (R03)				
Nonusers†	114	468	1 ref.	1 ref.
Users‡	11	32	1.41 (0.69-2.89)	0.84 (0.37-1.90)

AOR, adjusted odds ratio; ATC, Anatomical Therapeutic Chemical; OR, odds ratio.
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.

*Adjusted on age, sex, rehabilitation discipline (neurology/nonneurology).

†Defined as no administration at any time prior the index date.

‡Defined as at least 1 administration at any time from the admission date until the index date.



Supplementary Figure 1. Flowchart of case and control selection. Cases were patients with at least 2 recorded delirium predictive keywords (commonly used terms to describe delirious patients) who were classified as incident delirium episodes by 2 to 3 independent physicians as defined in a previous validation study.[30] Eligible controls were patients in the study population who did not have any record of delirium predictive keywords in their medical notes or a diagnosis of prevalent delirium on admission. Each case was matched to 4 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.