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ORIGINAL RESEARCH

Delirium in the geriatric unit: proton-pump inhibitors and other risk factors

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Background: Delirium remains a major nosocomial complication of hospitalized elderly. Predictive models for delirium may be useful for identification of high-risk patients for implementation of preventive strategies.

Objective: Evaluate specific factors for development of delirium in a geriatric ward setting.

Methods: Prospective cross-sectional study comprised 675 consecutive patients aged 79.2±7.7 years (66% women and 34% men), admitted to the subacute geriatric ward of a multiprofile university hospital after exclusion of 113 patients treated with antipsychotic medication because of behavioral disorders before admission. Comprehensive geriatric assessments including a structured interview, physical examination, geriatric functional assessment, blood sampling, ECG, abdominal ultrasound, chest X-ray, Confusion Assessment Method for diagnosis of delirium, Delirium-O-Meter to assess delirium severity, Richmond Agitation-Sedation Scale to assess sedation or agitation, visual analog scale and Doloplus-2 scale to assess pain level were performed.

Results: Multivariate logistic regression analysis revealed five independent factors associated with development of delirium in geriatric inpatients: transfer between hospital wards (odds ratio [OR] =2.78; confidence interval [CI] =1.54–5.01; P=0.001), preexisting dementia (OR =2.29; CI =1.44–3.65; $P<0.001$), previous delirium incidents (OR =2.23; CI =1.47–3.38; $P<0.001$), previous fall incidents (OR =1.76; CI =1.17–2.64; P=0.006), and use of proton-pump inhibitors (OR =1.67; CI =1.11–2.53; P=0.014).

Conclusion: Transfer between hospital wards, preexisting dementia, previous delirium incidents, previous fall incidents, and use of proton-pump inhibitors are predictive of development of delirium in the geriatric inpatient setting.

Keywords: delirium, geriatric ward, comprehensive geriatric assessment, Confusion Assessment Method, Delirium-O-Meter, Richmond Agitation-Sedation Scale

Introduction

Delirium is an acute decline in cognitive function of multifactorial etiology associated with increased risk of death, prolonged hospitalization, dementia, and admission to long-term care centers.[1–7] Delirium remains a major nosocomial complication of hospitalized elderly patients that represents significant health care costs.[8,9] Siddiqi et al[10] reported 10%–31% prevalence of delirium at hospital admission, 3%–29% incidence of delirium during admission, and 11%–42% prevalence rate per hospital admission. Similar results were obtained by Ryan et al[11] who diagnosed delirium in 17.6%–19.6% (depending on the method used) of general hospital adult inpatients, with prevalence as high as 34.8% in patients older than 80 years. Multicomponent nonpharmacological interventions may reduce delirium incidents among elderly inpatients by up to 44%.[12,13] As expected, discontinuation of certain medication

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reduced the incidence of delirium in elderly living in long-term care facilities.[14] The 2015 American Geriatrics Society (AGS) Beers Criteria recommend that elderly at high risk of delirium avoid medications such as anticholinergics, benzodiazepines, corticosteroids, H2-receptor antagonists, meperidine, and sedative hypnotics because of their potential to induce or worsen symptoms of delirium.[15] Knowledge of risk factors is essential for delirium prevention: dementia; cognitive impairment; prior delirium incident; presence of functional, visual, or hearing impairment; comorbidity or severe illness; depression; prior transient cerebral ischemia or stroke; alcohol misuse; and age ≥75 years are considered predisposing factors, while polypharmacy; treatment with psychoactive drugs, sedatives, or hypnotics; use of physical restraints; use of bladder catheters; presence of metabolic disorders; infections; surgeries; trauma or urgent admission; and coma are considered precipitating factors.[5] However, risk factors for delirium may differ between treatment centers. Comprehensive geriatric assessment (CGA) may be useful in predicting incidents of delirium.[16] We performed an observational, prospective study to analyze the factors predictive of delirium in patients admitted to the geriatric ward, including CGA results. Predictive models of delirium may be useful for identification of high-risk patients for proactive implementation of delirium preventive strategies and for determination of clinical trial eligibility. Delirium risk stratification may also be suitable for documenting estimates of hospital course and help propagate a better understanding of potential hospitalization outcomes for the patient and patient's family.[5]

Methods

Design

This prospective observational study was performed in the Department of Geriatrics at University Hospital No 7 SUM Uppersilesian Medical Center in Katowice, Poland, a subacute geriatric ward at a multiprofile university hospital. All reported tests were performed according to clinical indications, and no test was performed in case of refusal by the patient or care giver. No procedure exceeded beyond the scope of standard care in the ward. In 2013, a "Standard Operational Procedure for Delirium Prophylaxis" program was initiated by unit staff and approved by hospital management for use in the ward. In addition to commonly accepted delirium prophylaxis strategies,[6,17] this program added Confusion Assessment Method (CAM),[18] Delirium-O-Meter,[19] and Richmond Agitation-Sedation Scale[20] as additional delirium prevention methods. Implementation of the program was preceded by geriatrician-led staff training.

Participants

Primary analysis consisted of 788 consecutive patients aged 79.5±7.6 years ($\bar{x}$ ±SD) within a range of 60 to 100 years, among them 66% were women and 34% were men. Participants were admitted to the Department of Geriatrics at University Hospital No 7 SUM Uppersilesian Medical Center in Katowice, Poland, an acute geriatric ward at a multiprofile university hospital, between June 2013 and June 2014.

We excluded 113 patients who had been treated with antipsychotic medications because of behavioral disorders before admission and/or presented with signs of delirium on admission (five subjects). Final analysis consisted of 675 patients aged 79.2±7.7 years ($\bar{x}$ ±SD) within a range of 60 to 100 years, among them 443 (66%) were women and 232 (34%) were men.

Measurements

GCA was performed for all the patients, including a structured interview, physical examination, geriatric functional assessment, blood sampling, electrocardiogram (ECG), abdominal ultrasound, and chest X-ray. Mini-Mental State Examination (MMSE)[21] was used to assess global cognitive performance and Geriatric Depression Scale-Short Form (GDS-SF)[22] to identify depression. Barthel Index of Activities of Daily Living (Barthel Index)[23] and Lawton Instrumental Activities of Daily Living Scale (IADL)[24] were used to determine functional status. MMSE scores range from 0 to 30, Barthel Index scores from 0 to 100, and IADL scores from 9 to 27; higher scores indicate better functional state. GDS-SF scores range from 0 to 15 with higher scores indicating higher depression probability. To assess risk of falls, a modified "Get up and Go" test[25] scored from 0 to 10 was employed with lower values indicating higher risk. CAM for diagnosis of delirium[18] was applied. CAM is the most widely used instrument for identification of delirium, which has been validated in high-quality studies.[5] The CAM algorithm includes four criteria: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Confirmation of the diagnosis requires the presence of both the first and the second criteria and of either the third or the fourth criterion. Delirium-O-Meter[19] was used to assess delirium severity. The 12-item behavioral observation scale consists of the following categories: sustained attention, shifting attention, orientation, consciousness, apathy, hypokinesia or psychomotor retardation, incoherence, fluctuating functioning, restlessness, delusions, hallucinations, and anxiety or fear. Total scores range from 0 to 36 with higher values indicating more severe disorders. Richmond Agitation-Sedation Scale[20] was used to assess sedation or agitation. The scale scores from +4 ("combative") to −5 ("unarousable").

Dementia was diagnosed according to recommendations from the National Institute on Aging-Alzheimer's Association.[26] Pain intensity (PI) was assessed with the visual analog scale[27,28] scored from 0 to 10, or with Doloplus-2 scale[29,30] based on the behavioral–observational method and scored from 0 to 30 points (with a higher score indicating more severe pain) in patients who were unable to report PI because of cognitive impairment. To harmonize both scales, for further analysis, Doloplus-2 values were divided by a factor of 3, and PI was scored from 0 to 10 in each patient. A body mass index (BMI) was calculated in all the subjects.

Data collection

Data were collected by three research nurses and entered into forms prepared for research purposes.

Statistical analysis

The obtained data were analyzed using STATISTICA version 10 (StatSoft, Inc., Tulsa, OK, USA). Chi-square test, V-square test, and Fisher's exact test were used for categorical variables and nonparametric Mann–Whitney *U*-test for quantitative variables to compare patients who developed delirium during hospitalization with those who did not. Multivariate binary logistic regression was performed to assess measures associated with delirium development. The variables were adjusted to clinical, functional, and laboratory factors. Multivariate analysis with backward elimination included variables that yielded *P*-values of 0.1 or lower in the initial univariate analysis. The Kaplan–Meier method was used to estimate probability of delirium-free hospitalization in subgroups of patients with respect to selected variables, while differences between these subgroups were assessed with the Wilcoxon–Gehan statistic. Variables were tested to define the value corresponding with the lowest *P* level. *P*-values <0.05 were considered statistically significant.

Ethics

The study protocol was registered with the Bioethical Committee of the Medical University of Silesia in Katowice. In a statement, the committee wrote "the study is characterized by record review and in the context of law is not a medical experiment and does not require assessment by the bioethical committee" (Letter KNW/0022/KB/79/I/13). Based on this decision, written informed consent was not required of our study nor was separate patient consent required for our statistical analysis or research, since patient data are not disclosed outside internal hospital ward staff.

Results

Symptoms suggestive of delirium were reported, but not documented, by 2.79% of the 788 study participants before admission to the geriatric ward. Ten patients (1.27%) died during the study period. Delirium developed in 35 out of the 675 patients (5.2%) who had not been previously treated with neuroleptics (Figure 1). Approximately, 42.8% of the 675 patients were treated with diuretics, 41% with

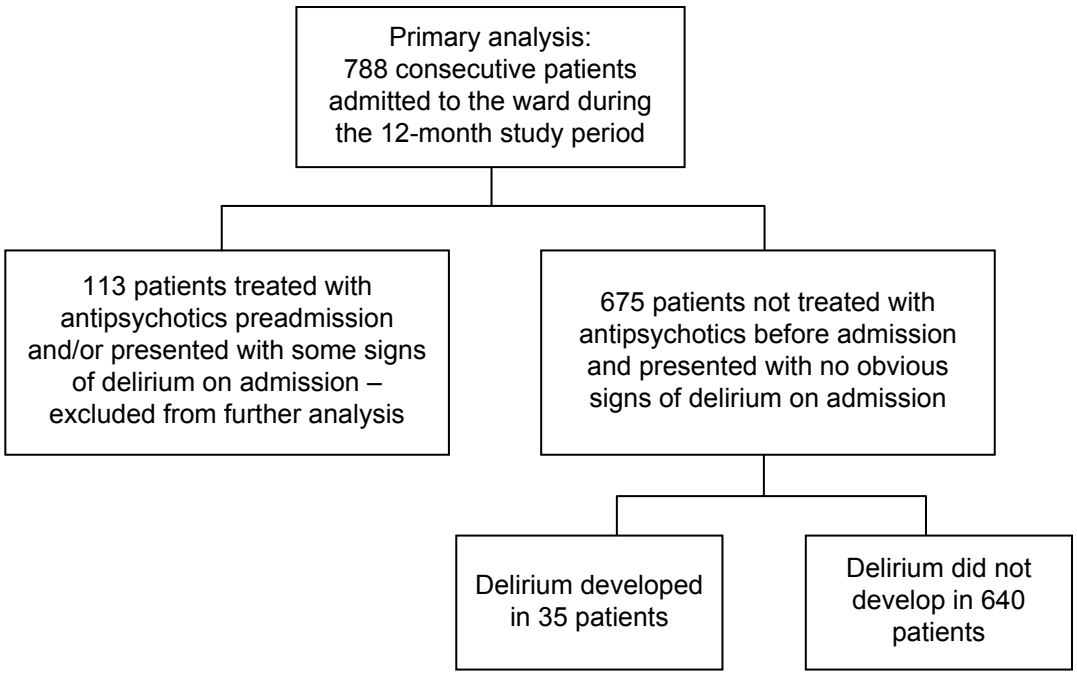

Figure 1 Recruitment of the study participants.

beta blockers, 30.4% with angiotensin converting enzyme inhibitors (ACEIs), 29.6% with statins, 25% with proton-pump inhibitors, 23.9% with antidiabetic medications, 17.2% with aspirin, 16.6% with pain relievers, 9% with antidepressants, 8.4% with thyroxine, 5.6% with corticosteroids, and 5% with L-DOPA. Compared to the control group, patients who developed delirium were characterized by greater age and increased prevalence of dementia; congestive heart disease; peripheral artery disease; pressure ulcers; urinary incontinence; permanent or prolonged bladder catheterization; delirium and fall incidents; behavioural disorders; lower MMSE, Barthel Index, and Lawton IADL scores; higher white blood cell counts and C-reactive protein levels; lower serum total protein and albumin levels (Table 1).

Table 1 Demographic, clinical, and functional characteristics of the patients who developed delirium during hospitalization (group D) as compared with patients who did not (group C)

Variable	Group D n=35	Group C n=640	Group D vs group C
	Mean ± SD or percentage		*P*-value
Age, years	83.6±4.7	79.0±7.7	>0.001
Sex, percentage of females	74.3	65.2	0.269
Hypertension, %	68.6	77.8	0.204
Diabetes mellitus, %	22.9	32.2	0.248
Myocardial infarction in anamnesis, %	11.4	11.4	0.788
Congestive heart failure, %	58.8	23.4	0.026
Stroke in anamnesis, %	16.7	12.2	0.917
Peripheral artery disease, %	14.3	5.94	0.049
Parkinson's disease, %	5.71	5.94	0.754
Dementia, %	80.0	29.8	>0.001
Delirium in anamnesis, %	8.57	1.72	0.031
Cancer in anamnesis, %	11.4	12.3	0.917
Falls in anamnesis, %	60.0	34.06	0.002
Behavioral disorders in anamnesis, %	34.3	6.25	>0.001
Pressure ulcers, %	14.3	2.03	>0.001
Urinary incontinence, %	57.1	40.3	0.049
Bladder catheterization, %	28.6	5.94	>0.001
Number of used medications	5.23±2.50	4.88±2.54	0.445
Body mass index, kg/m^2	26.32±5.56	28.04±7.24	0.104
Heart rate, beats per minute	73.80±15.56	71.43±12.23	0.259
Systolic blood pressure, mmHg	134.29±25.03	134.63±19.21	0.299
Diastolic blood pressure, mmHg	75.29±8.74	76.77±10.06	0.228
MMSE score	16.80±8.38	23.81±7.22	>0.001
Barthel Index	49.29±30.32	73.27±27.37	>0.001
Lawton IADL	14.03±5.40	19.26±6.19	>0.001
Hemoglobin, mmol/L	7.61±1.40	7.77±1.17	0.491
White blood cells, G/L	10.59±8.47	7.54±3.36	0.001
Total protein, g/L	67.1±0.77	71.1±0.91	0.002
Albumin, g/L	31.3±0.71	35.4±0.61	>0.001
Glucose, mmol/L	6.02±1.82	6.38±2.23	0.227
Bilirubin, µmol/L	11.80±6.50	11.29±9.23	0.288
ALAT, nmol/L/s	307.0±266.9	342.7±382.0	0.197
Creatinine, µmol/L	99.01±54.81	92.82±58.34	0.838
Estimated GFR using BIS_creatinine equation, mL/min/1.73 m^2	57.15±21.18	61.75±25.12	0.434
Thyrotropin, mIU/L	2.22±3.41	2.63±6.82	0.733
Vitamin B12, pmol/L	305.0±206.2	314.4±201.8	0.403
Total cholesterol, mmol/L	4.23±1.17	4.52±1.17	0.480
LDL-cholesterol, mmol/L	2.40±0.80	2.63±0.98	0.450
HDL-cholesterol, mmol/L	1.29±0.52	1.36±0.43	0.730
Triglycerides, mmol/L	1.20±0.38	1.16±0.48	0.344
C-reactive protein, mg/L	47.79±70.28	21.40±44.63	0.019
Sodium, mmol/L	139.8±5.4	139.1±4.0	0.743
Potassium, mmol/L	4.05±0.55	4.20±0.55	0.228
Calcium, mmol/L	2.32±0.33	2.33±0.17	0.019

Abbreviations: ALAT, alanine transaminase; BIS, Berlin Initiative Study; GFR, glomerular filtration rate; SD, standard deviation; MMSE, Mini-Mental State Examination; IADL, Index of Instrumental Activities of Daily Living; LDL, low-density cholestorol; HDL, high-density cholestorol.

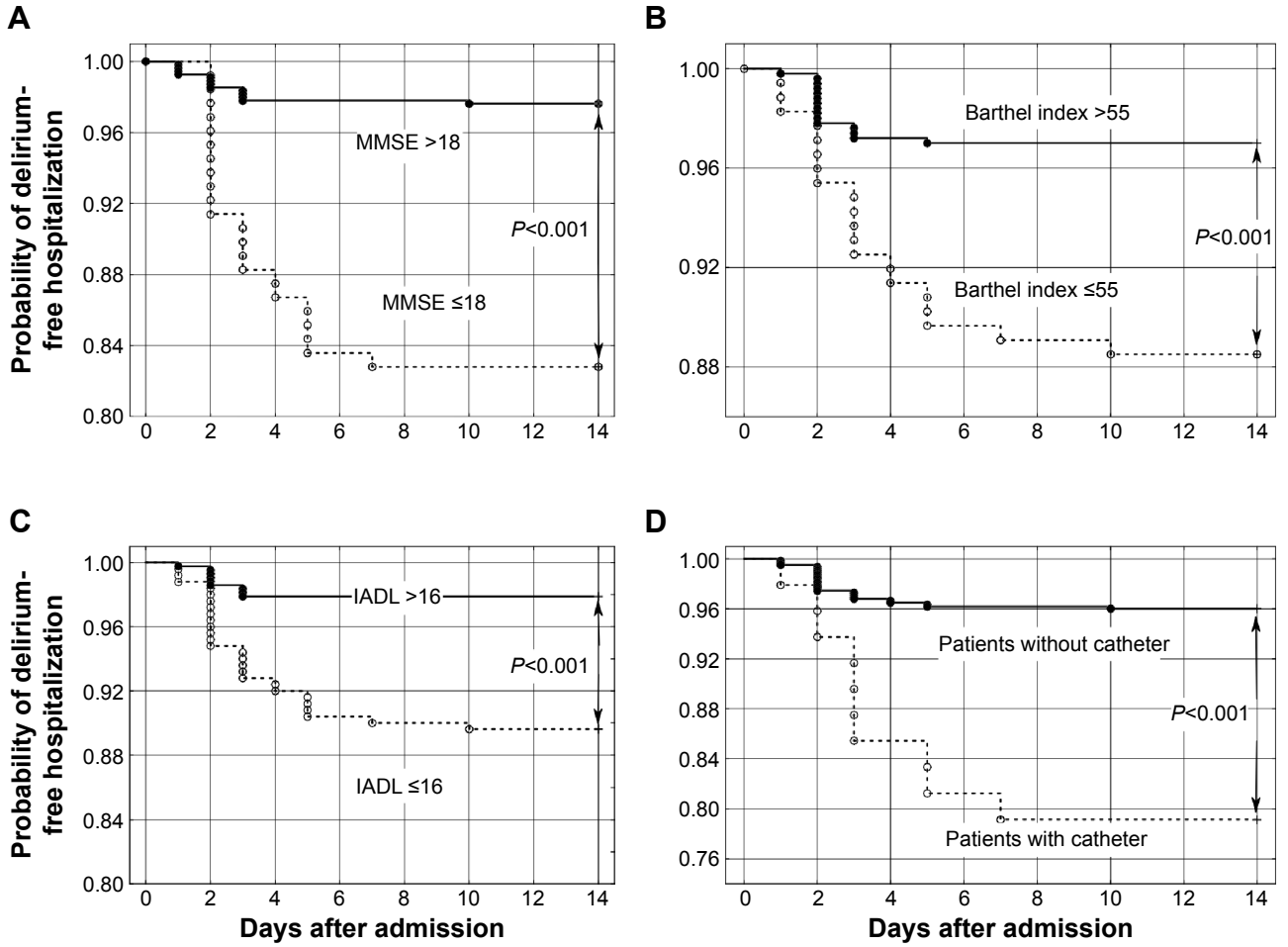

Figure 2 Probability of delirium-free hospitalization in geriatric ward patients.
Notes: Probability according to (**A**) Mini-Mental State Examination (MMSE) scores >18 versus lower values, (**B**) Barthel Index of Activities of Daily Living (Barthel Index) >55 versus lower values, (**C**) Lawton Index of Instrumental Activities of Daily Living (Lawton IADL) >16 versus lower values and (**D**) bladder catheterization versus noncatheterization.

According to the Wilcoxon–Gehan test, individuals with MMSE scores >18 points had higher probability of delirium-free hospitalization ($P<0.001$) similar to those with Barthel Index scores >55 points ($P<0.001$), Lawton IADL scores >16 points ($P<0.001$), and patients without bladder catheterization ($P<0.001$) (Figure 2). Higher probability of delirium-free hospitalization was also associated with WBC count <9.7 G/L ($P<0.002$), C-reactive protein serum concentration <33 mg/L ($P<0.001$), serum total protein concentration >64 g/L ($P<0.001$), and albumin concentration >30 g/L ($P<0.001$) (Figure 3). Multivariate logistic regression analysis included eleven quantitative variables and 30 categorical variables that yielded *P*-values of 0.1 or lower in the initial univariate analysis. Five factors associated with the development of inpatient delirium were included in the final multivariate logistic regression analysis: transfer between hospital wards (odds ratio [OR] =2.78; confidence interval [CI] =1.54–5.01; $P=0.001$), preexisting dementia (OR =2.29; CI =1.44–3.65; $P<0.001$), previous delirium incidents (OR =2.23; CI =1.47–3.38; $P<0.001$), previous fall incidents (OR =1.76; CI =1.17–2.64; $P=0.006$), and use of proton-pump inhibitors (OR =1.67; CI =1.11–2.53; $P=0.014$).

Discussion

Development of delirium is a major nosocomial complication of the hospitalized elderly patients.[7,31] Prevention of this condition is a major priority for hospitalized elderly patients.[32] Predictive models of inpatient delirium incidents may be useful for geriatric admission guidelines. Unfortunately, the pathophysiology of delirium is poorly understood and this disorder is frequently unrecognized or overlooked.[5] Delirium is often characterized by fluctuating psychological symptom progression that is difficult to assess subjectively. Complicating assessment further, various subtypes of delirium[33,34] have been defined. Preexisting dementia is the leading risk factor for development of delirium in geriatric inpatients, and distinguishing between these in the clinical setting may be

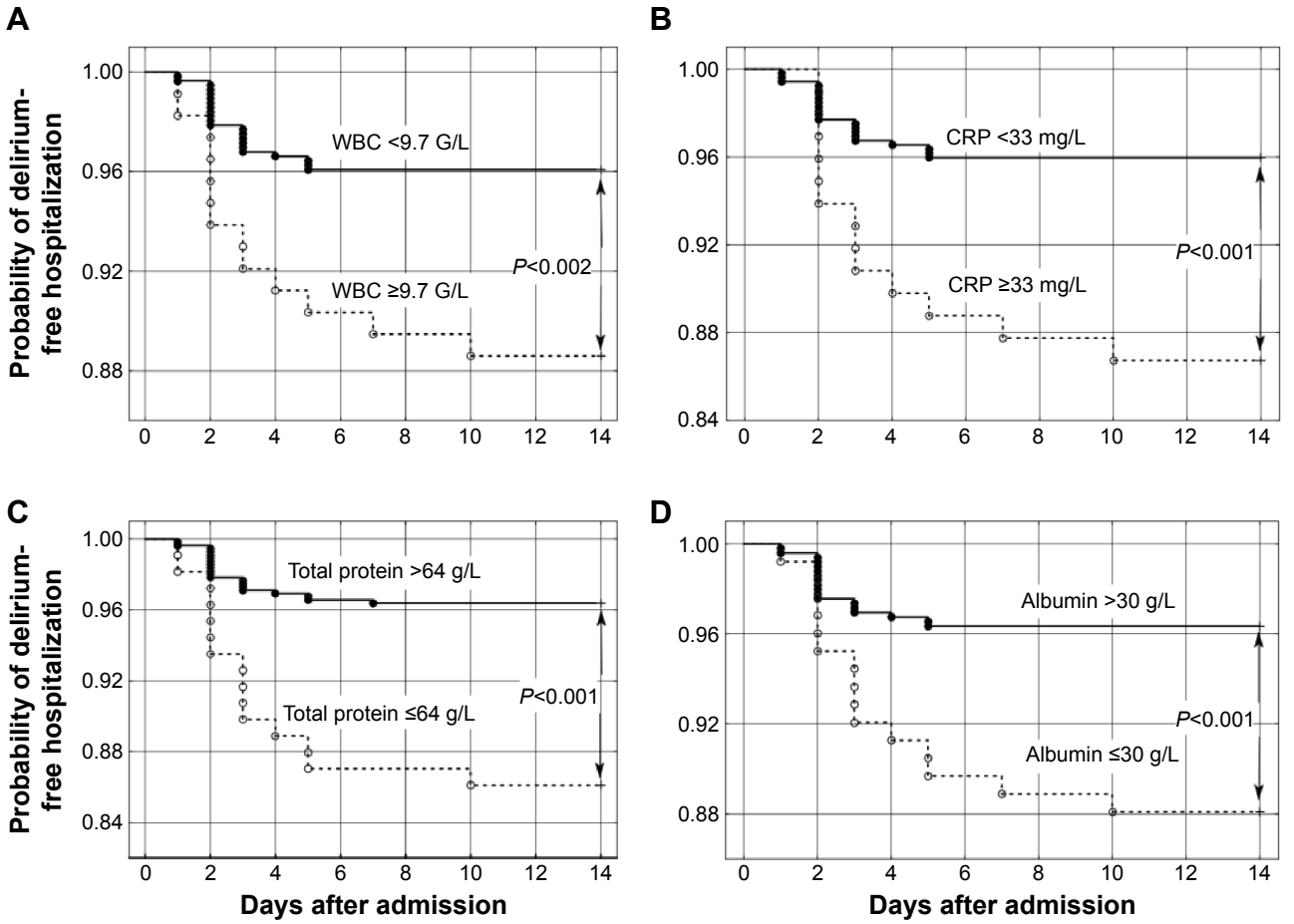

Figure 3 Probability of delirium-free hospitalization in geriatric ward patients according to WBC, CRP, and total serum protein and serum albumin levels.
Notes: (**A**) White blood cells (WBC) <9.7 G/L versus higher values, (**B**) C-reactive protein (CRP) <33 mg/L versus higher values, (**C**) total serum protein level >64 g/L versus lower values, and (**D**) serum albumin level >30 g/L versus lower values.

difficult, even for experienced clinicians.[35] Numerous factors may affect delirium, among them are psychoactive agents, especially antipsychotic medications used to treat behavioral and psychological disorders associated with psychogeriatric syndromes.[36–39] None of the 788 study participants had documented delirium incidents before admission to the geriatric ward. However, 113 patients were undergoing treatment with antipsychotic medication, and it is likely that a portion of these patients were receiving treatment for delirium. Since antipsychotics may hinder the recognition of delirium, we excluded patients treated with antipsychotic medications (14.3% of all patients admitted to the ward during the observation period). Consequently, the number of patients who developed delirium during hospitalization may not reflect the total incidence of this syndrome. Prevalence of delirium at admission to the geriatric ward was assessed in other studies at 12%,[40] 18.5%,[16] and 25%,[41] while incidence during hospitalization was 6.6%,[42] 11.8%,[16] and 13.3%.[43] Similarly, we identified multiple factors associated with increased risk of the development of delirium, some of which have not been previously reported: greater age, dementia, congestive heart disease, peripheral artery disease, pressure ulcers, urinary incontinence, permanent or prolonged bladder catheterization, history of delirium episodes, behavioral disorders, history of falls, functional dependence, increased markers of inflammation, and decreased serum total protein and albumin level. Multivariate logistic regression analysis allowed identification of factors predictive of inpatient delirium development, specific for the geriatric ward. Multivariate logistic regression model consisted of five independent variables in relation to the risk of development of delirium: transfer between hospital wards, preexisting diagnosis of dementia, previous delirium incidents, previous fall incidents, and use of proton-pump inhibitors.

It may be assumed that patient transfers from other hospital wards are associated with delirium risk factors such as poor general health, increased prevalence of major geriatric syndromes, subsequent change of surroundings, and prolonged hospitalization.[7,31] Dementia, previous delirium, and fall incidents are well-recognized factors associated

with delirium.[1] A pathophysiologic mechanism for the association between proton-pump inhibitors (PPIs) and development of delirium remains elusive. PPIs are used frequently in the geriatric inpatient setting, often for prolonged periods of time and are not necessarily taken according to indications.[44] Increasing evidence suggests that PPIs may trigger potentially serious complications.[45] Some case reports suggest that omeprazole may induce delirium.[46,47] Use of PPIs was associated with increased mortality adjusted for age, sex, comorbidity, delirium, and use of aspirin and SSRIs in patients of acute geriatric wards and nursing homes.[48] In elderly patients discharged from acute care medical wards, high-dose PPI therapy is associated with increased 1-year mortality.[49] Most of our study group patients treated with PPIs prior to admission had used these drugs for unspecified periods of time. Treatment was continued at the ward until indications for further treatment or treatment cessation could be determined. The 2015 AGS Beers Criteria recommend the avoidance of PPI therapy beyond 8 weeks without justification due to the increased risk of *Clostridium difficile* infection, bone loss, and fractures.[15] We observed that proton-pump inhibitors may increase the risk of delirium in hospitalized geriatric unit patients. However, we were unable to determine the mechanism behind the PPI and geriatric mortality association. Prolonged use of PPIs is associated with increased risk of infections (*C. difficile*,[50] salmonellosis,[51] community-acquired pneumonia[52]), vitamin B12 deficiency,[53,54] and hypomagnesemia.[45,55] Infection is a recognized precipitating factor for delirium.[5] Delirium-free hospitalization probability was diminished in patients with increased inflammatory markers (Figure 3). Poor vitamin B12 status increases risk of cognitive decline.[56] Some observations suggest that hypomagnesemia may be a factor precipitating delirium.[57,58] PPIs, especially omeprazole, affect pharmacokinetics of other drugs, among them benzodiazepines and antidepressants,[59] increasing risk of adverse effects. PPIs can cross the blood–brain barrier and block the vacuolar-type ATPase proton pumps leading to decreased degradation of amyloid beta.[60,61] A recent study by Akter et al[62] indicates that even a short course of PPIs may impair cognitive functions in young healthy volunteers. The concept of microbiome gut–brain axis is also intriguing.[63] PPIs significantly influence enteric microbiota,[64,65] and there exists increasing evidence that gut-microbiota signaling to brain by means of neural, endocrine, immune, and humoral links may influence brain function.[66] Some observations suggest possible association between gut-microbiota and anxiety or depressive syndromes.[67,68] Thus, the pathophysiology of the relationship between PPI therapy and the risk of delirium may be complex. We were unable to confirm the observation of Goldberg et al[31] that an increased number of room transfers was associated with increased incidence of delirium.

Conclusion

Transfer between hospital wards, preexisting dementia, previous delirium incidents, previous fall incidents, and use of proton-pump inhibitors are predictive of delirium incidents in the geriatric inpatient setting.

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Author contributions

IO and JS contributed to the study conception and design, evaluation of the subjects, data collection, analysis and interpretation of data, and drafting of article. KW performed analysis and interpretation of data, drafting of article, and revising of drafts. All authors approved the final paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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