Outcome of Older Patients with Acute Neuropsychological Symptoms Not Fulfilling Criteria of Delirium

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OBJECTIVES: Although delirium is often investigated, little is known about the outcomes of patients having acute neuropsychological changes at a single time point without fulfilling the criteria of full delirium. Our aim was to determine point prevalence, predictors, and long-term outcomes of delirium and acute neuropsychological changes in patients aged 60 years and older across different departments of a university hospital with general inpatient care.

DESIGN: Prospective observational study.

SETTING: University hospital excluding psychiatric wards.

PARTICIPANTS: At baseline, 669 patients were assessed, and follow-ups occurred at months 6, 12, 18, and 36.

MEASUREMENTS: Measurements were obtained using the Confusion Assessment Method (CAM), comprehensive geriatric assessment, health-related quality of life, functional state (month 6), and mortality rates (months 6, 12, 18, and 36). Subjects were classified into (1) patients with delirium according to the CAM, (2) patients with only two positive CAM items (2-CAM state), and (3) patients without delirium.

RESULTS: Delirium was present in 10.8% and the 2-CAM state in an additional 12.7% of patients. Highest prevalence of delirium was observed in medical and surgical intensive care units and neurosurgical wards. Cognitive restrictions, restricted mobility, electrolyte imbalance, the number of medications per day, any fixations, and the presence of a urinary catheter predicted the presence of delirium and 2-CAM-state. The mean Karnofsky Performance Score and EuroQol-5D were comparable between delirium and the 2-CAM state after 6 months. The 6-, 12-, 18-, and 36-month mortality rates of patients with delirium and the 2-CAM state were comparable. The nurses’ evaluation of distinct patients showed high specificity (89%) but low sensitivity (53%) for the detection of delirium in wide-awake patients.

CONCLUSION: Patients with an acute change or fluctuation in mental status or inattention with one additional CAM symptom (ie, disorganized thinking or an altered level of consciousness) have a similar risk for a lower quality of life and death as patients with delirium. J Am Geriatr Soc 68:1469-1475, 2020.

Keywords: Confusion Assessment Method; cognition; outcome; mortality

INTRODUCTION

Delirium comprises an acute disturbance in attention and cognitive performance and has a multifactorial etiology. It is mostly unrecognized and associated with poor outcomes and increased mortality.1,2 In the past, the prevalence of and risk factors for the development of delirium were investigated in specific selected high-risk (hospital) populations (eg, surgical units or intensive care units [ICUs]).3 Whereas in general medical and geriatric wards, the prevalence of delirium ranges from 18% to 35%, the highest incidence rates were observed in the ICU, postoperative, and palliative care settings.4 Various prediction models have been proposed for surgery-based, procedure-specific, and disease-specific subgroups of patients.5-7 However, more comprehensive data on the risk factors and long-term outcomes of delirium in older patients are
needed. Although a large body of evidence has shown that delirium is associated with poor outcomes, less is known about the impact of subsyndromal delirium on the survival, functional state, and quality of life in older subjects. Subsyndromal delirium is characterized by the presence of specific symptoms of delirium that do not fulfill the definition of full-blown delirium. The detection of subsyndromal delirium requires repeated assessments because subsyndromal delirium and delirium are thought to exist on a continuum. However, there are several practical limitations of repeated measurements in older people. Thus we performed a prospective observational study to determine the outcomes of patients with symptoms not fulfilling the criteria for full delirium at one time point. In addition, we aimed to (1) derive an estimate of the point prevalence of delirium across all medical disciplines in inpatients aged 60 years or older, (2) analyze predictors of delirium in the same group of patients, and finally (3) measure the long-term effects of delirium regarding functionality, health-related quality of life, and mortality.

METHODS

Study Design

This trial was approved by the local ethics committee of the Jena University Hospital and registered at the German Clinical Trial Register (DRKS-ID: DRKS00006545). It was designed as a prospective observational single-center study in a university hospital (excluding psychiatric wards). The point prevalence and risk factors of delirium were assessed during the patients’ stay at the Jena University Hospital (45 general wards, 4 ICUs, and 2 intermediate care units [IMCs]) between October 14, 2014, and October 16, 2014. Outcome scores were assessed after 6, 12, 18, and 36 months. Of the 669 inpatients aged 60 years or older, 611 (91.3%) patients were assessed. Subjects were classified into (1) patients with full delirium according to the Confusion Assessment Method (CAM), (2) patients having only two positive items on the CAM (2-CAM; see later), and (3) patients without delirium.

Assessments

Of 1,039 hospitalized patients, 669 were assessed (Supplementary Figure S1) by 21 research assistants with the relevant qualifications who documented routinely available data (general demographic data, reasons for hospitalization, diagnoses, presence of a urinary catheter, presence of fixation/physical restraints, laboratory values, ward change) and performed a standardized assessment. The first step comprised assessing consciousness status using the Richmond Agitation-Sedation Scale (RASS). If the patient was alert, the Montreal Cognitive Assessment (MoCA) and CAM were applied; otherwise, the Glasgow Coma Scale and CAM-ICU were used. The CAM, the most frequently used screening tool for delirium, has been validated in high-quality studies. It shows a sensitivity of 94%, a specificity of 89%, and a high interrater reliability. According to the CAM, delirium has four features: (1) acute onset of changes or fluctuations in mental status, (2) inattention, (3) disorganized thinking, and (4) an altered level of consciousness. Delirium was diagnosed when both features 1 and 2, plus either feature 3 or 4, were present. The “2-CAM state” was defined when feature 1 or 2, plus either feature 3 and/or 4, was present, or when features 1 and 2 were present (not fulfilling the criteria for full delirium).

If the patient had cognitive deficits (MoCA <26 points), delirium, or a 2-CAM state, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was applied to the patients’ caregivers. The IQCODE validly reflects past cognitive decline, predicts incident dementia, and correlates with a wide range of cognitive tests. A particular strength of the IQCODE is its relative independence from the educational level of the subject and premorbid ability. Cutoffs for IQCODE were derived from Jorm. The Identification of Seniors at Risk (ISAR) questionnaire was used to assess risk factors of adverse health outcomes in older adults. It assesses functional dependence, recent hospitalization, impaired memory, impaired vision, and polypharmacy (each with yes/no answers), and a score of 2 or higher is regarded as predictive for adverse health outcomes. The state of the decreased functional reserve was assessed using the Study of Osteoporotic Fractures (SOF) frailty index. The SOF frailty index explores (1) unintentional weight loss, (2) inability to rise five times from a chair, and (3) responding with a “no” to the question, “Do you feel full of energy?” If the total score was 2 or 3, the patient was categorized as frail, and if the score was 1, the patient was categorized as pre-frail. The chair rising test was performed, and the time was measured until the patient rose five times from the chair.

Longitudinal outcome measures after 6 months included the Karnofsky Performance Score (KPS), the 3-level EuroQol (EQ)-5D-3L, and mortality as well as the IQCODE for those patients who were assessed with the IQCODE at baseline. The KPS ranges from 100 (perfect health) to 0 (death). The EQ-5D is a standardized, simple, and generic measure of health-related quality of life. The EQ-5D-3L primarily consists of the EQ-5D descriptive system (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the EQ summary index (www.euroqol.org). The longitudinal outcome measure after 12 and 36 months included mortality.

In addition to the standardized assessment, nurses caring for individual patients in the hospital were asked to appraise whether delirium was present in these subjects.

Statistical Analyses

The primary outcomes of this study were delirium, and the 2-CAM-state measured using the CAM and CAM-ICU. All assessed variables were analyzed descriptively for patients with delirium/2-CAM state/without delirium and in total. Data are given as means, standard deviations (SDs), medians, and interquartile ranges for metric and frequency analyses for categorical variables or ordinal variables. Because of the exploratory nature of the observation, no confirmatory tests were performed. The prevalence of delirium and the 2-CAM, including the 95% confidence interval (CI), was evaluated. Exploratory subgroup analyses included cross tabulations for several variables concerning age, the kind of ward, the kind of medical intervention, and the MoCA. Generalized linear models with backward selection for the presence/absence of delirium were fitted regarding Bayesian information criterion (BIC) using a prespecified set of predisposing factors and hospital-acquired (trigger)
factors. These factors were derived from the existing literature. The predisposing risk factors were age, pre-existing cognitive restrictions according to the IQCODE, present cognitive restrictions according to the MoCA, multimorbidity according to ISAR, restricted mobility as determined by the chair rising test (number of seconds or not able to rise), neurologic/psychiatric disease, need of care, and frailty according to the SOF. The hospital-acquired or trigger factors were surgery, infection, stay in ICU/IMC, ward change, electrolyte imbalance, polypharmacy, any fixation/physical restraints, ventilation, and a urinary catheter.

In addition, for all precipitating and hospital-acquired factors, relative risks for the development of delirium, including the 95% CI, were estimated. For this purpose, metric and ordinal factors were dichotomized.

Survival rates were calculated using a Kaplan-Meier analysis. We fitted a Cox proportional hazards regression model for mortality using relevant covariates at the time of enrollment (delirium, age, sex, presence of cancer, surgery, stay in ICU, and ward change) concerning BIC. Hazard ratios (HRs) were evaluated using the final resulting model.

RESULTS

Baseline Characteristics

Table 1 shows the baseline characteristics of patients with delirium, the 2-CAM state, and no delirium. The mean age of the overall cohort was 74.1 years (SD = 8.4; range = 60-101 y). According to the RASS, 550 (90%) were alert; 61 (10%) were sedated. Regarding sociodemographic factors, most patients lived with a spouse/family members (n = 370 [60.6%]) in a private residence (n = 542 [88.7%]). Only a minority received care from a professional service or caregiver (n = 122 [20.0%]). According to the ISAR, 262 (42.9%) were hospitalized during the past 6 months, and 163 (26.7%) needed help regularly before the current admission to the hospital. Of note, 236 (38.6%) took more than six drugs per day. Frailty, according to the SOF frailty index, was observed in 38% and prefrailty in 36.3%. Patients were hospitalized in medical departments (48.6%), major surgical departments (29.6%), minor surgical departments (12.4%), and ICUs (9.3%).

Prevalence of Delirium

In the group of patients with normal consciousness status (n = 550; RASS ≥0), delirium was present in 36 (6.5%). Sixty-six patients (12.0%) were categorized in the 2-CAM state and therefore did not fulfill the criteria for full delirium. The CAM-ICU was used in patients with altered consciousness (n = 61; RASS <0). In patients with altered consciousness, delirium was present in 28 (43.8%) patients, and the 2-CAM state in 9 (12.0%) subjects. Of note, in 20 patients who were deeply sedated or unarousable (RASS ≤−4), the CAM-ICU could not be assessed. In summary, a delirium

| Table 1. Descriptive Statistics of the Subjects |
|------------------------------------------------|
| Enrolled n = 611a | No delirium | 2-CAM state | Delirium |
| N, n (%) | 452 (74.0) | 75 (12.3) | 64 (10.8) |
| Age, mean, y (SD) | 72.9 (8.1) | 77.7 (7.1) | 78.6 (8.5) |
| Sex female, n (%) | 222 (49.1) | 48 (64.0) | 33 (51.6) |
| No. of drugs before hospitalization, n (SD) | 8.3 (4.3) | 10.7 (3.8) | 12.9 (5.1) |
| MoCA sum score, mean (SD) | 21.6 (4.9) | 13.4 (6.6) | 10.1 (5.0) |
| RASS sedated, n (%) | 4 (.9) | 9 (12.0) | 28 (43.8) |
| RASS normal/agitated, n (%) | 448 (99.1) | 66 (88.0) | 36 (56.3) |
| IQCODE baseline, mean(SD) | 3.25 (.32) | 3.75 (.65) | 3.45 (.51) |
| >2.5-3.5, n (%) | 204 (86.8) | 21 (42.0) | 30 (68.2) |
| >3.5-4.5, n (%) | 29 (12.3) | 21 (42.0) | 12 (27.3) |
| >4.5-5, n (%) | 2 (.9) | 8 (16.0) | 2 (4.5) |
| ISAR, total n = 558 | | | |
| Regular need of help before illness, n (%) | 101 (22.3) | 42 (56.0) | 20 (31.3) |
| Need of more help in last 24 h, n (%) | 77 (17.0) | 29 (38.7) | 16 (25.0) |
| Hospitalization in past 6 mo, n (%) | 204 (45.1) | 38 (50.7) | 20 (31.3) |
| Impaired vision, n (%) | 74 (16.4) | 22 (29.3) | 10 (15.6) |
| Impaired memory, n (%) | 36 (8.0) | 21 (28.0) | 15 (23.4) |
| Polypharmacy, >6 drugs, n (%) | 180 (39.8) | 35 (46.7) | 21 (32.8) |
| SOF Frailty Index, total n = 597, n (%) | | | |
| Feeling of exhaustion, n (%) | 181 (40.0) | 47 (62.7) | 25 (39.1) |
| Weight loss, n (%) | 151 (33.4) | 30 (40.0) | 16 (25.0) |
| Inability to rise 5 times, n (%) | 193 (42.7) | 57 (76.0) | 42 (65.6) |
| Chair rising test, s, mean (SD) | 13.3 (6.0) | 16.3 (5.3) | 18.8 (7.3) |

Abbreviations: CAM, Confusion Assessment Method; ICU, intensive care unit; IMC, intermediate care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; ISAR, Identification of Seniors at Risk questionnaire; MoCA, Montreal Cognitive Assessment; RASS, Richmond Agitation-Sedation Scale; SOF, Study of Osteoporotic Fractures frailty index.

aFrequency analysis of total CAM/CAM-ICU assessments (including 20 missing values in deeply sedated or unarousable patients; RASS ≤−4).
detected by a positive CAM or CAM-ICU was present in 64 (10.8%) in the cohort of 591 patients.

In most patients with a normal state of consciousness (RASS ≥ 0), we observed abnormalities in cognitive function. Here, 104 (18.9%) subjects had no cognitive deficits (MoCA = 26-31), 183 (33.3%) had mild cognitive impairment (MoCA 21-25), and 235 had an MoCA below 21 points (28.5%) missing data). When the MoCA was below 26 points, or delirium or the 2-CAM state was present (n = 510), the IQCODE was applied to patient caregivers. The IQCODE was assessed in 340 (66.7%) of 510 subjects (Table 1). The IQCODE was not available in 170 subjects (33.3%) because we were not able to reach their caregivers.

The highest prevalence of delirium was observed in the ICUs and the neurosurgery department (Figure 1). In contrast to patients without full delirium, the patients with delirium were characterized by older age, higher ISAR, a higher percentage of polypharmacy, a higher percentage of frail patients, and a longer time to perform the chair rising test (Table 1).

Predictors of Delirium

A generalized linear model showed that preexisting cognitive restrictions according to the IQCODE, present cognitive restrictions according to the MoCA, and restricted mobility (chair rising test in seconds or not able to rise) predict the presence of delirium. Among the hospital-acquired factors, an electrolyte imbalance, the number of medications per day, any fixation/physical restraints, and the presence of a urinary catheter predicted the presence of delirium (Table 2). The relative risk factors for delirium and the 2-CAM state for predisposing factors and hospital-acquired factors are listed in Table 3. Among the predisposing factors, restricted mobility, cognitive deficits, higher age, and

Figure 1. Point prevalence (%) of delirium and the 2-CAM state by the clinical department. ENT, eyes, nose, throat; ICU, intensive care unit.

| Predisposing risk factors | Odds ratio | 95% confidence limits |
|---------------------------|------------|----------------------|
| IQCODE, pointsa | 0.35 | 0.11-1.11 |
| MoCA, pointsa | 0.79 | 0.71-0.88 |
| Chair rising test, s| 1.01 | 0.98-1.04 |

| Hospital-acquired risk factors | Odds ratio | 95% confidence limits |
|-----------------------------|------------|----------------------|
| Electrolyte imbalance, no/yes | 1.10 | 0.56-2.16 |
| No. of medicationsa | 1.13 | 1.05-1.21 |
| Fixation/Physical restraints, no/yes | 4.59 | 2.27-9.30 |
| Urinary catheter, no/yes | 2.81 | 1.42-5.56 |

| Backward selection | Odds ratio | 95% confidence limits |
|-------------------|------------|----------------------|
| Predisposing risk factors | Odds ratio | 95% confidence limits |
| IQCODE, pointsa | 0.35 | 0.11-1.11 |
| MoCA, pointsa | 0.79 | 0.71-0.88 |
| Chair rising test, s | 1.01 | 0.98-1.04 |

| Forward selection | Odds ratio | 95% confidence limits |
|-------------------|------------|----------------------|
| Predisposing risk factors | Odds ratio | 95% confidence limits |
| Age, ya | 1.07 | 0.99-1.16 |
| IQCODE, pointsa | 0.26 | 0.07-0.94 |
| MoCA, pointsa | 0.78 | 0.70-0.87 |
| Chair rising test[s]| 1.01 | 0.98-1.04 |

| Hospital-acquired risk factors | Odds ratio | 95% confidence limits |
|-----------------------------|------------|----------------------|
| Surgery, no/yes | 0.76 | 0.38-1.50 |
| Infection, no/yes | 1.52 | 0.70-3.29 |
| Stay on ICU, no/yes | 1.00 | 0.42-2.34 |
| Ward change, no/yes | 0.72 | 0.32-1.59 |
| Electrolyte imbalance, no/yes | 0.98 | 0.49-1.98 |
| No. of medicationsa | 1.11 | 1.03-1.21 |
| Fixation/Physical restraints, no/yes | 0.21 | 0.10-0.46 |
| Urinary catheter, no/yes | 0.33 | 0.16-0.69 |

Abbreviations: CAM, Confusion Assessment Method; ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MoCA, Montreal Cognitive Assessment.

*aEffects of continuous variables are assessed as one-unit offsets from the mean.
polypharmacy had the highest relative risk for delirium. The presence of a urinary catheter, mechanical ventilation, and staying in the ICU were the strongest hospital-acquired risk factors for delirium (Table 3).

### Outcomes after Delirium and the 2-CAM State

After 6 months of follow-up, the EQ-5D index indicated a worse health-related quality of life for patients with delirium (.50; SD = .36) or the 2-CAM state (.49; SD = .37) compared with patients without delirium (.64; SD = .33). In particular, the EQ-5D health dimensions of mobility, self-care, usual activities, and anxiety/depression scored worse in patients with delirium and the 2-CAM state (Supplementary Figure S2). The mean KPS after 6 months for patients with delirium was 35 (SD = 35; range = 0-100) and for patients with 2-CAM was 38 (SD = 34; range = 0-90). This means that patients are “severely disabled, and hospital admission is indicated” (30 points), or “disabled and require special care and assistance” (40 points). In contrast, patients without delirium had a better mean KPS of 64 (SD = 34; range = 0-100) (70 = cares for self but unable to perform normal activity or to do active work; 60 = requires occasional assistance but is able to care for most of their personal needs).

The 6-, 12-, 18-, and 36-month mortality rates of patients with delirium (37.7%, 44.3%, 51.0%, and 58.4%, respectively) and the 2-CAM state (36.1%, 41.8%, 41.8%, and 50.5%, respectively) were comparable, but they were higher than those in patients without delirium (15.0%, 21.7%, 26.0%, and 29.9%, respectively) and higher than the sex- and age-matched 12-month mortality rate of the German population (4.01%; Figure 2). The fitted Cox proportional hazards regression revealed the effects of age, presence of cancer, surgery, and stay in the ICU interactions with ward changes. In the final model, we observed an increase in all-cause mortality after delirium (adjusted HR = 2.2; 95% CI = 1.4-3.4) and the 2-CAM state (adjusted HR = 1.8; 95% CI = 1.2-2.7).

### Table 3. Risk Factors for Delirium and the 2-CAM State

| Risk factor                              | Relative risk 2-CAM state (95% CI) | Relative risk delirium (95% CI) |
|------------------------------------------|------------------------------------|---------------------------------|
| **Predisposing risk factors**            |                                    |                                 |
| Restricted mobility (chair rising test >15 s) | 7.9 (3.2-19)                      | 14.9 (3.7-61)                   |
| Age ≥ 70 y                               | 2.3 (1.3-3.9)                      | 4.5 (2.1-9.6)                   |
| ISAR >1                                  | 3.2 (1.9-5.4)                      | 4.1 (1.9-8.7)                   |
| Preexisting need of care                | 2.8 (1.8-4.3)                      | 3.4 (1.9-5.9)                   |
| Preexisting cognitive restrictions (IQCODE >3.44) | 4.7 (2.9-7.5)                      | 2.4 (1.4-4.2)                   |
| Present cognitive restriction (MoCA <26)  | 8.2 (2.0-33)                       | b                               |
| Presence of neurologic or psychiatric disorder | 2.3 (1.5-3.5)                      | 2.4 (1.5-3.8)                   |
| Prefrailty or frailty (SOF frailty index >1) | 3.1 (2.0-4.8)                      | 1.7 (1.0-2.8)                   |
| Sensory restrictions                    | .3 (2.7)                           | .5 (1-1.8)                      |
| Presence of cancer                      | .7 (4-1.1)                         | .6 (4-1.1)                      |
| **Hospital-acquired or trigger risk factors** |                                    |                                 |
| Polypharmacy (≥6 medications)           | 2.9 (1.4-5.9)                      | 4 (1.6-9.8)                     |
| Presence of a urinary catheter          | 3.6 (2.4-5.5)                      | 7.2 (4.7-11)                    |
| Mechanical ventilation                  | 3.2 (1.5-6.9)                      | 6.5 (4.3-9.8)                   |
| Stay on ICU                              | 3.0 (2.0-4.5)                      | 4.8 (3.1-7.5)                   |
| Infectiona                              | 2.8 (1.9-4.3)                      | 3.7 (2.4-5.8)                   |
| Ward change                             | 1.9 (1.3-2.9)                      | 2.9 (1.8-4.8)                   |
| Fixation                                 | 5.4 (3.6-8.0)                      | 10.0 (6.1-17)                   |
| Electrolyte imbalance (Na⁺, K⁺)         | 2.1 (1.3-3.4)                      | 2.4 (1.4-4.0)                   |
| Surgery                                  | 1.0 (1.6-5.1)                      | 1.9 (1.2-2.9)                   |

Abbreviations: CAM, Confusion Assessment Method; ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; ISAR, Identification of Seniors at Risk questionnaire; MoCA, Montreal Cognitive Assessment; SOF, Study of Osteoporotic Fractures frailty index.

aInfection was defined as body temperature ≥ 38°C or ≤ 36°C or antibiotic therapy during the past 3 days and increased C-reactive protein (≥7.5 mg/L) and leukocytosis (≥11.3 gpt/L).

bBecause none of the patients with delirium or the 2-CAM state had an MoCA >26, the risk factor could not be calculated.

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**Figure 2.** Kaplan-Meier survival curves comparing the time to death for patients with no delirium, the 2-CAM state, delirium, and the German healthy reference.
Sensitivity and Specificity to Detect Delirium in the Daily Routine

Parallel to the standardized assessment, nurses caring for individual patients in the hospital were asked to assess whether delirium was present. In patients without delirium (according to the standardized assessment), the percentage of patients estimated to be without delirium (ie, specificity) was higher in patients in the awake/agitated state than in sedated patients (89% and 77%, respectively). However, the proportion of patients who were correctly identified as having delirium (ie, sensitivity) was lower (25% in sedated and 53% in awake/agitated patients).

DISCUSSION

In our study, delirium was present in 10.8% of the investigated patients. This result is at the lower end of the prevalence rates described in a systematic review that showed the occurrence rate per admission as varying between 11% and 42%.2,17 This disparity can be attributed to the fact that the rates observed in studies using an ongoing assessment of delirium are lower than those obtained in studies using data from routine care.18 Our study supports substantial ward-level variability regarding occurrence rates of delirium with the highest prevalence in the ICU, neurosurgical, and neurologic wards. Variability underlines the limited generalizability of studies focusing on single departments and units. Risk factors for delirium were classified into predisposing and hospital-acquired factors.19

The principal predisposing risk factor identified in both our analysis and previous studies is cognitive impairment.1,4 Therefore, it is not surprising that, according to the IQCODE, a relevant proportion of our patients with delirium had cognitive deficits before admission to the hospital. The second leading predisposing risk factor is advanced age.4,20 However, in our linear model, we found that functional parameters, such as mobility and cognition and not chronological age, are predictive for delirium. This finding is because chronological age does not capture the complex heterogeneity of the health status in older persons.21 Other measures of the individual’s functions and homeostatic reserves are aligned with this observation, such as restricted mobility, poor vision and hearing, and frailty that have also been identified as risk factors of delirium in our study and former studies.2 In addition, patients with neurologic or psychiatric disorders, as well as cancer, are at higher risk for delirium. Cancer and cognitive impairment frequently coexist in older age.

Moreover, the burden of cancer itself and cancer treatment can lead to cognitive impairment and confusion or delirium.22–24 Among precipitating factors for delirium, polypharmacy, anticholinergic drugs, surgery, anesthesia, anemia, and infections are the most commonly reported.2 More relevant is the association between delirium and potentially preventable procedures, such as urinary catheters or ward changes. This finding emphasizes that such interventions and alterations in patients’ surroundings should be avoided.

Identification of risk factors of delirium is essential for the implementation of preventive strategies and the close monitoring of patients. The low sensitivity of the nurses’ assessments in our study underlines that an effective screening for delirium-threatened patients requires training. This is particularly relevant because it was reported that 30% of delirium can be prevented.17 In this context, our study highlights the role of ISAR as a useful screening tool for quantifying predisposing factors for delirium. Although a score of 2 or higher is regarded as predictive for adverse health outcomes, a score of 1 or higher was found to be highly predictive for the development of delirium and the 2-CAM state.

A total of 12% of the subjects in our cohort were categorized into the 2-CAM state. This state was characterized by either an acute change or fluctuation of mental status or inattention with one additional CAM symptom (ie, disorganized thinking or an altered level of consciousness). Whereas delirium is consistently associated with an increased risk of death and institutionalization,25–28 our study reveals that patients who have been in the 2-CAM state have an equal risk of death and an equal decline in health-related quality of life.2,29–31 Given the design of the study, we cannot determine in what kind of phase the patient was assessed or if the 2-CAM state was going to become subsyndromal delirium or full delirium. Nevertheless, we believe this finding is highly relevant for clinical practice because slight acute neuropsychological changes at one time point during the hospital stay are also associated with a poor outcome. Therefore, older patients with one core symptom and one additional feature of delirium, according to the CAM, warrant the same clinical attention as patients with delirium.

This study is not free of limitations. The study was monocentric and restricted to a university hospital that might reduce generalizability. However, the Jena University Hospital is the only hospital in Jena and surrounding regions, and therefore patients with all kinds of diseases and disease severities are treated there. The strength of our study was that the assessment was not restricted to distinct units and provided comprehensive data for nearly all departments of a large university hospital. Moreover, the outcomes of the 2-CAM state and delirium were explored with an adequate length of follow-up, complete follow-up, and objective outcome criteria. With up to 36 months of follow-up, we can provide rare long-term mortality data of delirium.

To our knowledge, this was the first comprehensive prospective analysis of people having some symptoms of delirium at a single observation time point. In terms of long-term outcomes, both delirium and the 2-CAM state were found to be associated with a similar decline in health-related quality of life and increased mortality. Given the high prevalence and relevance of acute neuropsychological changes and the low sensitivity of detection of full delirium, structured screening methods should be implemented in hospitals to identify older adults at risk and to improve long-term outcomes.

ACKNOWLEDGMENTS

Financial Disclosure: None.

Conflict of Interest: The authors have declared no conflicts of interest for this article.

Author Contributions: Hannah M. Zipprich, André Scherag, Anja Kwetkat, Ulrich Wedding, Frank M. Brunkhorst, Otto W. Witte, and Christoph Redecker substantially contributed to the conception and design of this study. Hannah M. Zipprich and Marie-Christine Arends organized

Hannah M. Zipprich and Marie-Christine Arends organized
data acquisition. Hannah M. Zipprich, Ulrike Schumacher, and Tino Prell had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in the interpretation of the data. Tino Prell and Hannah M. Zipprich drafted the manuscript, and all authors revised it critically for important intellectual content. All authors gave final approval of this version to be submitted. Tino Prell is the guarantor.

Sponsor’s Role: Not applicable.

Availability of Data and Materials: The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics, Consent, and Permissions: This study was approved by the local ethics committee of the Jena University Hospital. Participant consent was not required.

REFERENCES

1. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. JAMA. 2017;318(12):1161-1174.
2. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med. 2017;377(15):1456-1466.
3. Klein Khouweng PM, Zaal JJ, Spittoni C, et al. The attributable mortality of delirium in critically ill patients: prospective cohort study. BMJ. 2014;349:g6652.
4. Inouye SK, Westendorp RG, Szczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911-922.
5. Ravi B, Pincus D, Choi S, Jenkinson R, Wasserstein DN, Redelmeier DA. Association of duration of surgery with postoperative delirium among patients receiving hip fracture repair. JAMA Netw Open. 2019;2(2):e190111.
6. Saravanan-Bawar R, Warkentin LM, Rucker D, Carr F, Churchill TA, Khadaroo RG. Incidence and predictors of postoperative delirium in the older acute care surgery population: a prospective study. Can J Surg. 2019;62(1):33-38.
7. Wassenaar A, van den Boogaard M, van Achterberg T, et al. Multinational development and validation of an early prediction model for delirium in ICU patients. Intensive Care Med. 2015;41(6):1048-1056.
8. Young J, Murthy I, Westby M, Akunne A, O'Mahony R, Guideline DG. Diagnosis, prevention, and management of delirium: summary of NICE guidance. BMJ. 2010;341:c3704.
9. Cole MG, Giampi A, Belzile E, Dubuc-Sarrasin M. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. Int J Geriatr Psychiatry. 2013;28(8):771-780.
10. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941-948.
11. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). JAMA. 2001;286(21):2703-2710.
12. Jorm AF. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): a review. Int Psychogeriatr. 2004;16(3):275-293.
13. McCusker J, Bellavance F, Cardin S, Trepapanc S, Verdon J, Ardman O. Detection of older people at increased risk of adverse health outcomes after an emergency visit: the ISAR screening tool. J Am Geriatr Soc. 1999;47(10):1229-1237.
14. Sutton M, Grimmer-Somers K, Jeffries L. Screening tools to identify hospitalised elderly patients at risk of functional decline: a systematic review. Int J Clin Pract. 2008;62(12):1900-1909.
15. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch Intern Med. 2008;168(4):382-389.
16. Bilotta F, Lauretta MP, Borozdina A, Mzikov VM, Rosa G. Postoperative delirium: risk factors, diagnosis and perioperative care. Minerva Anestesiol. 2013;79(9):1066-1076.
17. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35(4):350-364.
18. McCoy TH Jr, Hart KL, Perls RH. Characterizing and predicting rates of delirium across general hospital settings. Gen Hosp Psychiatry. 2017;46:1-6.
19. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA. 1996;275(11):852-857.
20. Elle M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly hospitalized patients. J Gen Intern Med. 1998;13(3):204-212.
21. Bellelli G, Moresco R, Panina-Bordignon P, et al. Is delirium the cognitive harbinger of frailty in older adults? A review about the existing evidence. Front Med (Lausanne). 2017;4:188.
22. Lawlor PG, Bush SH. Delirium in patients with cancer: assessment, impact, mechanisms and management. Nat Rev Clin Oncol. 2015;12(2):77-92.
23. Karuturi M, Wong ML, Hsu T, et al. Understanding cognition in older patients with cancer. J Geriatr Oncol. 2016;7(4):258-269.
24. Snaedal J. Does my older cancer patient have cognitive impairment? J Geriatr Oncol. 2018;9(3):183-185.
25. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753-1762.
26. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med. 2004;32(11):2254-2259.
27. van den Boogaard M, Schoonhoven L, van der Hoeven JG, van Achterberg T, Pickkers P. Incidence and short-term consequences of delirium in critically ill patients: a prospective observational cohort study. Int J Nurs Stud. 2012;49(7):775-783.
28. Fong TG, Jones RN, Marcantonio ER, et al. Adverse outcomes after hospitalization and delirium in persons with Alzheimer disease. Ann Intern Med. 2012;156(12):848-856, W296.
29. Keely DK, Bergmann MA, Murphy KM, Jones RN, Orav EJ, Marcantonio ER. Delirium among newly admitted postacute facility patients: prevalence, symptoms, and severity. J Gerontol A Biol Sci Med Sci. 2003;58(5):M441-M445.
30. Cole M, McCusker J, Dedukuri N, Han L. The prognostic significance of subsyndromal delirium in elderly medical inpatients. J Am Geriatr Soc. 2003;51(6):754-760.
31. Cole MG, McCusker J, Voyer P, et al. Subsyndromal delirium in older long-term care residents: incidence, risk factors, and outcomes. J Am Geriatr Soc. 2011;59(10):1829-1836.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure S1: Flowchart of patients.

Supplementary Figure S2: EQ-5D health dimensions after 6 months. Details for patient flow/study design and long-term changes of health-related quality of life.