

Risk factors for delirium among patients with advanced cancer in palliative care: a multicenter, patient-based registry cohort in South Korea

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Abstract. – OBJECTIVE: Previous studies have comprehensively investigated the prevalence and various potential risk factors for delirium among patients with advanced cancer admitted to the acute palliative care unit (APCU). Our objective was to evaluate the comprehensive association between delirium and various risk factors among patients with advanced cancer in an acute palliative care setting using a patient-based multicenter registry cohort.

PATIENTS AND METHODS: We performed a multicenter, patient-based registry cohort study collected in South Korea between January 1, 2019, and December 31, 2020. Delirium was identified using a medical record review based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

RESULTS: In total, 2,124 eligible patients with advanced cancer in the APCU met the inclusion criteria. There were 127 out of 2,124 patients (prevalence, 6.0%; 95% CI, 5.0 to 7.1) with delirium during admission. Delirium in patients with advanced cancer was associated with age >70 years (OR, 1.793; 95% CI, 1.246 to 2.581), male sex (OR, 1.675; 95% CI, 1.131 to 2.479), no chemotherapy during hospitalization (OR, 2.019; 95% CI, 1.236 to 3.298), hearing impairment (OR, 3.566; 95% CI, 1.176 to 10.810), underweight (OR, 1.826; 95% CI, 1.067 to 3.124), current use of opioid medication (OR, 1.942; 95% CI, 1.264 to 2.982), previous history of delirium (OR, 12.497;

95% CI, 6.920 to 22.568), and mental illness (OR, 2.333; 95% CI, 1.251 to 4.352).

CONCLUSIONS: In a large-scale multicenter patient-based registry cohort, delirium was associated with old age, male sex, no chemotherapy during hospitalization, hearing impairment, underweight, current use of opioid medication, and a history of delirium and mental illness. Our findings suggest physicians should pay attention to delirium in patients with advanced cancer admitted to the APCU with the above risk factors.

Key Words:

Delirium, Cancer, Palliative care, Chemotherapy.

Introduction

Delirium is one of the most common neuropsychiatric problems encountered in patients with advanced cancer¹. It is associated with an increased risk of length of hospital stay, higher mortality and morbidity, higher healthcare costs² and significant psychosocial distress for patients, family members, and healthcare professionals³. Especially in the palliative care setting, its prevalence is reported to be up to 42 to 88%⁴. However, few studies have comprehensively investi-

gated the prevalence and various potential risk factors of delirium among patients with advanced cancer admitted to the acute palliative care unit (APCU)⁵⁻⁷. Although there is no effective preventive intervention for delirium in hospital settings⁸, physicians can attenuate modifiable and preventive factors for delirium in the APCU setting, such as exercise and preventive intervention, including family support^{9,10}.

The hypothesis of this study is that various risk factors can affect delirium and its severity in patients with advanced cancer in the APCU. Therefore, our objective was to evaluate the comprehensive association between delirium and various risk factors among patients with advanced cancer in an acute palliative care setting using a patient-based multicenter registry cohort.

Patients and Methods

Data Source

We conducted a multicenter patient-based registry cohort collected by Seoul National University Bundang Hospital, Yonsei University Severance Hospital, CHA University Bundang Medical Center, and Seoul National University Hospital, South Korea, between January 1, 2019, and December 31, 2020. The protocol was approved by the institutional review boards of the four centers (CHA University, CHAMC 2021-03-054-002; Seoul National University, H-2103-028-1201; Seoul National University Bundang Hospital, B-2104/681-405; and Yonsei University, 4-2021-0323). The institutional review board of the four centers approved this study and waived the requirement for informed consent because only anonymized data were examined.

Our data set consisted of general information (age, sex, data on chemotherapy during hospitalization, if the patient lived with family and received medical aid, education level, use of glasses or hearing aids, and history of alcohol consumption and smoking), clinical risk factors (obesity, blood pressure, and body temperature), and a history of diseases (delirium, cardiovascular disease, diabetes mellitus, respiratory disease, liver disease, mental illness, and head injury). Our data set has the following strengths: (1) patients admitted for supportive care during treatment and patients who discontinued treatment were included; (2) data were collected from four academic cancer centers; and (3) data were collected by oncology trained medical personnel.

Study Population

Our potential participants were patients admitted to the APCU in four centers between January 1, 2019, and December 31, 2020. In total, 2,136 patients met eligibility criteria. Of the 2,136 patients, we excluded those with (1) hospital stay >3 months (excluding n=5), (2) transfer to other departments (excluding n=6), and (3) terminal delirium (excluding n=3). Terminal delirium was defined as delirium that occurred within 2 weeks of death. The final sample included 2,124 patients admitted to the APCU.

Main Outcomes

Delirium was identified using a review of medical records based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. A well-trained physician and academic nurse performed this detailed review. We did not use the code for the 10th revision of the International Classification of Diseases (ICD-10) because it could not guarantee reliability. Furthermore, all potential symptoms, signs, and associated medications were recorded, and at least two specialists (BDK and YJK) were reviewed. In case of disagreement, an additional specialist took the vote (SHY).

Exposure

Data on age, sex, chemotherapy during hospitalization, living with family, medical aid recipients, education level, visual impairment (wearing glasses), hearing impairment (using hearing aids), alcohol consumption, and smoking history were obtained from medical chart reviews. A well-trained nurse measured body mass index, blood pressure, and body temperature¹¹. A history of diseases (delirium, cardiovascular disease, diabetes mellitus, respiratory diseases, liver diseases, mental illness, and head injury) was obtained from a medical chart review and the appropriate ICD-10 codes: respiratory diseases that included chronic obstructive pulmonary disease, asthma, bronchiectasis, and interstitial lung disease; liver diseases that included viral hepatitis, alcoholic liver disease, and liver cirrhosis, mental illness, and head injury^{11,12}.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and SAS (version 9.4; SAS Institute, Cary, North Carolina, USA). Data were analyzed using multinomial and binomial logistic regression models and calculated of odds ratios (OR) with 95% confidence

intervals (CI)^{13,14}. Regression models were adjusted for age (<50, 50-59, 60-69, and ≥ 70 years), sex, cancer treatment (categorical value), living together (categorical value), medical aid recipients (categorical value), education level (high school graduate or under, university graduate or higher and unknown), visual impairment (categorical value), hearing impairment (categorical value), alcohol consumption (non-drinker, 1 to 3 times a week and ≥ 4 times a week), smoking (non-smoker, ex-smoker, and current smoker), obesity (underweight, normal weight, overweight and obese)¹⁵, blood pressure (categorical value), body temperature (categorical value), history of delirium, cardiovascular disease, diabetes mellitus, respiratory diseases, liver diseases, mental illness, and head injury (categorical value). A two-sided p -value < 0.05 was considered statistically significant^{16,17}.

Patient and Public Involvement

None of the patients participated directly in designing the research question or conducting the investigation. No patients were asked for advice on the interpretation or writing of the results. However, we planned to involve patients or the relevant patient community in the dissemination of the study findings.

Results

The characteristics of the 2,124 eligible patients admitted to the ACPU in the four centers are summarized in Table I. There were 127/2,124 (prevalence, 6.0%; 95% CI, 5.0 to 7.1) patients with delirium during admission.

The mean age of the delirium group was 68.7 ± 10.6 . The proportion of men was higher in the delirium group than in the non-delirium group (70.1% vs. 57.4%). The delirium group had fewer patients who underwent chemotherapy during hospitalization than the non-delirium group (15.8% vs. 28.8%). Recipients of medical aid showed higher prevalence of delirium than the non-aided group (7.1% vs. 4.3%). There was no significant difference in education level between the two groups. In the delirium group, the frequency of hearing impairment was higher than that of the non-delirium group (3.2% vs. 0.9%). A higher proportion of patients found in the delirium group (10.2% vs. 4.9%) consumed alcohol ≥ 4 times a week. The proportion of smokers was higher in the delirium group (69.2% vs. 58.3%). In the delirium group, the proportion of obese pa-

tients was lower (8.7% vs. 17.1%), and the proportion of underweight was higher (24.4% vs. 21.5%).

The medical history was also different between the delirium and non-delirium groups. In particular, history of delirium was higher in the delirium group (20.47% vs. 1.75%). Additionally, history of mental illness was higher in the delirium group (13.4% vs. 5.6%). The history of cardiovascular disease, diabetes mellitus, respiratory disease, liver disease, and head injury was slightly higher in the delirium group.

In Table II, delirium in patients with advanced cancer was associated with age > 70 years (OR, 1.793; 95% CI, 1.246 to 2.581), male sex (OR, 1.675; 95% CI, 1.131 to 2.479), no chemotherapy during hospitalization (OR, 2.019; 95% CI, 1.236 to 3.298), hearing impairment (OR, 3.566; 95% CI, 1.176 to 10.810), underweight (OR, 1.826; 95% CI, 1.067 to 3.124), and current use of opioid medication (OR, 1.942; 95% CI, 1.264 to 2.982). In Table III, delirium in patients with advanced cancer was associated with history of delirium (OR, 12.497; 95% CI, 6.920 to 22.568) and mental illness (OR, 2.333; 95% CI, 1.251 to 4.352).

Discussion

Key Findings

Using a large-scale multicenter patient-based registry cohort, we investigated the potential risk factors for delirium among patients with advanced cancer. To our knowledge, this is the first large-scale study to investigate potential risk factors for delirium in South Korea. In this multicenter cohort, we found that the incidence of delirium was 6.0% (95% CI, 5.0 to 7.1) in patients with advanced cancer admitted to the APCU in South Korea. Furthermore, delirium was prominently seen in patients with old age, male sex, no chemotherapy during hospitalization, hearing impairment, underweight, and previous history of delirium and mental illness. Our findings suggest physicians should pay attention to delirium in patients with advanced cancer admitted to the APCU with the above risk factors.

Comparison of Previous Studies and Plausible Mechanism

As shown in previous studies^{18,19}, old age was the most prevalent predisposing factor²⁰, which is consistent with our main result. In addition, a history of delirium and hearing impairment are also significant predisposing factors²¹.

Risk factors for delirium

Table I. General characteristics, history of diseases, and symptoms of participants (total n=2,124).

Characteristics	Total (n=2,124)	Delirium group (n=127)	Non-delirium group (n=1,997)
Age (mean, SD)	63.69 (12.18)	68.72 (10.56)	63.37 (12.89)
Age group (years, n, %)			
<50	279 (13.14)	3 (2.36)	276 (13.82)
50-59	449 (21.14)	21 (16.54)	428 (21.43)
60-69	668 (31.45)	41 (32.28)	627 (31.40)
≥70	728 (34.27)	62 (48.82)	666 (33.35)
Sex (n, %)			
Male	1,235 (58.15)	89 (70.08)	1,146 (57.39)
Female	889 (41.85)	38 (29.92)	851 (42.61)
Chemotherapy during hospitalization (n, %)			
No	1,529 (71.99)	107 (84.25)	1,422 (71.21)
Yes	595 (28.01)	20 (15.75)	575 (28.79)
Living with family (n, %)			
No	710 (33.43)	45 (35.43)	665 (33.30)
Yes	1,414 (66.57)	82 (64.57)	1,332 (66.70)
Medical aid recipients (n, %)			
No	2,029 (95.53)	118 (92.91)	1,911 (95.69)
Yes	95 (4.47)	9 (7.09)	86 (4.31)
Education level (n, %)			
High school graduated or under	977 (46.00)	51 (40.16)	926 (46.37)
University graduated or higher	524 (24.67)	26 (20.47)	498 (24.94)
Unknown	623 (29.33)	50 (39.37)	573 (28.69)
Visual impairment (wearing glasses) (n, %)			
No	2,018 (95.01)	122 (96.06)	1,896 (94.94)
Yes	106 (4.99)	5 (3.94)	101 (5.06)
Hearing impairment (using hearing aids) (n, %)			
No	2,103 (99.01)	123 (96.85)	1,980 (99.15)
Yes	21 (0.99)	4 (3.15)	17 (0.85)
Alcohol consumption (n, %)			
Non-drinker	1,781 (83.85)	98 (77.17)	1,683 (84.28)
1-3 times a week	233 (10.97)	16 (12.60)	217 (10.87)
≥4 times a week	110 (5.18)	13 (10.24)	97 (4.86)
Smoking (n, %)			
Non-smoker	1,456 (68.55)	74 (58.27)	1,382 (69.20)
Ex-smoker	617 (29.05)	45 (35.43)	572 (28.64)
Current smoker	51 (2.40)	8 (6.30)	43 (2.15)
Obesity (n, %)†			
Underweight	460 (21.66)	31 (24.41)	429 (21.48)
Normal weight	971 (45.72)	70 (55.12)	901 (45.12)
Overweight	341 (16.05)	15 (11.81)	326 (16.32)
Obese	352 (16.57)	11 (8.66)	341 (17.08)
Blood pressure (n, %)			
SBP ≥140 mmHg or DBP ≥90 mmHg	321 (15.11)	19 (14.96)	302 (15.12)
SBP <140 mmHg and DBP <90 mmHg	1,803 (84.89)	108 (85.04)	1,695 (84.88)
Body temperature (n, %)			
Normal temperature <38°C	2,033 (95.71)	121 (95.28)	1,912 (95.74)
Hyperthermia (≥38°C)	91 (4.28)	6 (4.72)	85 (4.26)
History of delirium (n, %)	61 (2.87)	26 (20.47)	35 (1.75)
History of cardiovascular disease (n, %)	823 (38.75)	62 (48.82)	761 (38.11)
History of diabetes mellitus (n, %)	470 (22.13)	39 (30.71)	431 (21.58)
History of respiratory diseases (n, %)	187 (8.80)	15 (11.81)	172 (8.61)
History of liver diseases (n, %)	138 (6.50)	11 (8.66)	127 (6.36)
History of mental illness (n, %)	128 (6.03)	17 (13.39)	111 (5.56)
History of head injury (n, %)	150 (7.06)	13 (10.24)	137 (6.86)
Current use of opioid medication (n, %)	1,353 (63.70)	97 (76.38)	1,256 (62.89)

DBP, diastolic blood pressure; SD, standard deviation; SBP, systolic blood pressure. †Obesity (body mass index, kg/m²) was categorized as <18.5 kg/m² (underweight), 18.5 to 23 kg/m² (normal), 23 to 25 kg/m² (overweight), and ≥25 kg/m² (obese).

Table II. Odds ratio (95% confidence intervals) for delirium according to general characteristics.

Characteristics	OR (95% confidence intervals) for delirium after cancer	
	Crude	Adjusted†
Age		
<70 years	1 (reference)	1 (reference)
≥70 years	1.906 (1.330 to 2.733)	1.793 (1.246 to 2.581)
Sex		
Female	1 (reference)	1 (reference)
Male	1.739 (1.178 to 2.569)	1.675 (1.131 to 2.479)
Chemotherapy during hospitalization		
Yes	1 (reference)	1 (reference)
No	2.163 (1.329 to 3.521)	2.019 (1.236 to 3.298)
Living together		
No	1 (reference)	1 (reference)
Yes	0.910 (0.625 to 1.324)	1.010 (0.663 to 1.540)
Medical aid recipients		
No	1 (reference)	1 (reference)
Yes	1.695 (0.832 to 3.452)	1.680 (0.764 to 3.696)
Education level		
High school graduated or under	1 (reference)	1 (reference)
University graduated or higher	0.948 (0.584 to 1.539)	1.347 (0.794 to 2.286)
Unknown	1.584 (1.058 to 2.372)	2.263 (1.406 to 3.645)
Visual impairment (wearing glasses)		
No	1 (reference)	1 (reference)
Yes	0.770 (0.308 to 1.924)	0.938 (0.362 to 2.428)
Hearing impairment (using hearing aids)		
No	1 (reference)	1 (reference)
Yes	3.788 (1.255 to 11.428)	3.566 (1.176 to 10.810)
Alcohol consumption		
Non-drinker	1 (reference)	1 (reference)
Drinker	1.586 (1.030 to 2.442)	1.237 (0.732 to 2.090)
Smoking		
Non-smoker	1 (reference)	1 (reference)
Ex- or current smoker	1.609 (1.117 to 2.319)	1.240 (0.774 to 1.985)
Obesity		
Overweight or obese	1 (reference)	1 (reference)
Normal weight	0.930 (0.600 to 1.442)	0.928 (0.598 to 1.440)
Underweight	1.854 (1.086 to 3.166)	1.826 (1.067 to 3.124)
Blood pressure		
SBP <140mmHg and DBP <90 mmHg	1 (reference)	1 (reference)
SBP ≥140 mmHg or DBP ≥90 mmHg	0.987 (0.597 to 1.632)	1.322 (0.768 to 2.274)
Body temperature		
Normal temperature (<38°C)	1 (reference)	1 (reference)
High temperature (≥38°C)	1.114 (0.477 to 2.602)	0.830 (0.317 to 2.171)
Current use of opioid medication		
No	1 (reference)	1 (reference)
Yes	1.954 (1.285 to 2.972)	1.942 (1.264 to 2.982)

DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure. †Adjusted for age, sex, cancer treatment, living together, medical aid recipients, education level, visual impairment, hearing impairment, alcohol consumption, smoking, obesity, blood pressure, body temperature, history of delirium before cancer, cardiovascular disease, diabetes mellitus, respiratory diseases, liver diseases, mental illness, head injury, and current use of opioid medication. Numbers in bold indicate significant differences (p -value <0.05).

Table III. Odds ratio (95% confidence intervals) for delirium according to history of diseases.

Characteristics	OR (95% confidence intervals) for delirium after cancer	
	Crude	Adjusted†
History of delirium		
No	1 (reference)	1 (reference)
Yes	14.437 (8.368 to 24.908)	12.497 (6.920 to 22.568)
History of cardiovascular disease		
No	1 (reference)	1 (reference)
Yes	1.549 (1.081 to 2.219)	1.125 (0.732 to 1.731)
History of diabetes mellitus		
No	1 (reference)	1 (reference)
Yes	1.610 (1.088 to 2.383)	1.384 (0.889 to 2.155)
History of respiratory diseases		
No	1 (reference)	1 (reference)
Yes	1.421 (0.811 to 2.491)	1.197 (0.653 to 2.195)
History of liver diseases		
No	1 (reference)	1 (reference)
Yes	1.396 (0.733 to 2.658)	1.366 (0.681 to 2.741)
History of mental illness		
No	1 (reference)	1 (reference)
Yes	2.626 (1.522 to 4.531)	2.333 (1.251 to 4.352)
History of head injury		
No	1 (reference)	1 (reference)
Yes	1.548 (0.850 to 2.819)	0.962 (0.481 to 1.926)

OR, odds ratio. †Adjusted for age, sex, cancer treatment, living together, medical aid recipients, education level, visual impairment, hearing impairment, alcohol consumption, smoking, obesity, blood pressure, body temperature, history of delirium before cancer, cardiovascular disease, diabetes mellitus, respiratory diseases, liver diseases, mental illness, head injury, and current use of opioid medication. Numbers in bold indicate significant differences (p -value <0.05).

In particular, delirium occurred more frequently in men¹⁸, which might be because the more detectable hyperactive form of delirium was more than twice as common in men²².

Recently, obesity has been reported to affect the survival rate in some carcinomas as an ‘obesity paradox’²³. Currently reported in postoperative delirium, but not in cancer delirium²⁴, a high body mass index was a protective factor for postoperative delirium. Interestingly, the incidence of cancer delirium is also low in obese patients, which supports the obesity paradox.

Studies of chemotherapeutic drugs and delirium are inconclusive and inconsistent. Although chemotherapeutic drugs that penetrate the blood-brain barrier may be risk factors for delirium²⁵, most epidemiological studies²⁰ have suggested that discontinuation of chemotherapy is associated with an increased risk of delirium during admission in a palliative setting. An epidemiologic study²⁶ suggested discontinuation of chemotherapy may lead to poor general condition, metas-

tasis of primary cancer (including to the brain), cachexia, and emotional instability. Therefore, these results should be interpreted with caution, especially when interpreting the finding that chemotherapy prevents the development of delirium.

Policy Implication

Delirium is a great burden, not only for the patient but also for the family and it becomes a social burden²¹. APCU is a specialized unit for patients who need supportive care during disease treatment, as well as terminally ill patients. Active symptom control can help them receive additional treatment in the future. Therefore, active intervention and prevention efforts are required in patients with high-risk factors²⁷⁻³⁰.

Strengths and Limitations

This study has some limitations. First, we relied on medical record reviews, which may have led to underestimation bias. However, the data sets were obtained from well-trained physicians

and medical specialists through discussion; thus, underestimation bias may be reduced³¹. Second, although we conducted a multicenter study, our findings may not be generalizable nationwide. However, two centers were located in urban areas, and the other two centers in rural areas³². Therefore, we minimized the urban-rural difference by considering the region as much as possible. Third, this was a retrospective cohort study³³. We attempted to minimize this selection bias by collecting data from multiple centers. Despite these limitations, our study is the first large-scale, multicenter, patient-based registry cohort study to investigate the possible risk factors for delirium in South Korea. We also found a novel association between delirium and various risk factors (i.e., old age, male sex, no chemotherapy during hospitalization, hearing impairment, underweight, and history of delirium and mental illness) among patients with advanced cancer in the APCU.

Conclusions

Through a large-scale, multicenter, patient-based registry cohort, we identified various potential risk factors for delirium (i.e., old age, male sex, no chemotherapy during hospitalization, hearing impairment, underweight and history of delirium and mental illness) among patients with advanced cancer in South Korea. Thus, attention should be paid to the occurrence of delirium in patients with these risk factors, and interventions should be considered for early diagnosis and treatment, as well as prevention.

Conflict of Interest

The authors declare no conflicts of interests.

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Authors' Contributions

Dong Keon Yon and Beodeul Kang had full access to all data in the study and took responsibility for the integrity of the data and accuracy of the data analysis. All authors approved the definitive version before submission. Study concept and design: Dong Keon Yon and Beodeul Kang; Acquisition, analysis, or interpretation of data: Dong Keon Yon and Beodeul Kang; Drafting of the manuscript: Dong Keon Yon and Beodeul Kang; Critical revision of the man-

uscript for important intellectual content: Si Won Lee, Eun Hee Jung, Hyeon Jin Kim, Chanyang Min, Shin Hye Yoo, Yu Jung Kim, Sun Young Rha, Dong Keon Yon, and Beodeul Kang; Statistical analysis: Hyeon Jin Kim, Chanyang Min; Study supervision: Dong Keon Yon. Dong Keon Yon supervised the study and is a guarantor of this study. The corresponding author attests that all listed authors meet the authorship criteria, and that no others who meet the criteria have been omitted. Si Won Lee, Eun Hee Jung, and Hyeon Jin Kim contributed equally to this work.

Informed Consent

The institutional review board of the four centers approved this study and waived the requirement for informed consent because only anonymized data were examined.

Ethics Approval

The protocol was approved by the institutional review boards of the four centers (CHA University, CHAMC 2021-03-054-002; Seoul National University, H-2103-028-1201; Seoul National University Bundang Hospital, B-2104/681-405; and Yonsei University, 4-2021-0323).

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