

Postoperative delirium in patients undergoing surgery for bone metastases

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Abstract

Postoperative delirium (PD), characterized by acute onset of global impairment in consciousness and cognition, is a common complication following major surgeries and is often associated with adverse outcomes. Because of the multiple comorbidities of the patient along with extensive nature of the surgery, patients undergoing surgery for bone metastases may be prone to developing PD. However, no study exists regarding PD in patients who undergo surgery for bone metastases.

Two hundred seventy six patients with mean age of 64 years (range, 16–94) who underwent surgery for bone metastases were reviewed. The diagnosis of PD was made by the psychiatrist, according to fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. Possible perioperative clinic-pathologic factors that may be associated with the development of PD were investigated.

Among the 276 patients, 9% (n=25) developed PD. On multivariate logistic regression analysis, history of psychiatric disorders (odds ratio [OR]=9.63; 95% confidence interval [CI] 1.78–21.74, $P=.004$), high preoperative serum C-reactive protein (CRP) level (OR=1.17; 95% CI 1.06–1.29, $P=.001$), low preoperative serum albumin level (OR=0.13; 95% CI 0.03–0.48, $P=0.002$), and high dose of opioid analgesics received in the immediate postoperative period (OR=1.05; 95% CI 1.01–1.07, $P=.001$) were independently associated with the development of PD. Patients with PD had lower survival (log rank, $P=.001$) than patients without PD.

Incidence of PD is considerable in patients undergoing surgery for bone metastases. History of psychiatric disorders, preoperative serum albumin and CRP levels, and the dose of postoperative opioid analgesics are associated with the development of PD.

Abbreviations: ALT = alanine aminotransferase, ASA = American Society of Anesthesiologists, AST = aspartate aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, CRP = C-reactive protein, ICU = intensive care unit, MME = morphine milligram equivalent dose, PD = postoperative delirium.

Keywords: bone metastases, delirium, postoperative, risk factors

1. Introduction

Bone is the third most common site of cancer metastasis after the lung and the liver.^[1] It is estimated that 1 of every 5 patients with cancer will develop symptomatic bone metastasis, which considerably reduces the quality of life of the patient. Impending

fractures or pathological fractures by bone metastases often requires surgery to relieve pain and restore function.^[2]

Postoperative delirium (PD) is characterized by acute onset of change in cognitive capacity, altered perception, and inappropriate behavior during the postoperative period.^[3] PD is frequently associated with higher morbidity, prolonged hospital stays, and increased mortality. Thus, identifying the incidence and risk factors of PD would be helpful in the prevention and treatment of PD.^[4–8]

The incidence of PD varies depending upon the type of surgery performed.^[8] The reported incidence rate in elective orthopedic procedures are 13% to 61% and 50% in surgical patients with cancer.^[9–13] The risk factors of PD vary, with advancing age, cognitive impairment, severity of illness, increased number of comorbidities, increased functional dependency, being commonly reported risk factors of PD.^[5,14] Because of the presence of these risk factors, patients who undergo surgery for bone metastases may be prone to developing PD. To our knowledge, no study has been published regarding PD in surgery for bone metastases. Our aim was to report the incidence of PD in patients undergoing surgery for bone metastases; factors associated with development of PD, and survival of patients with PD.

2. Materials and methods

2.1. Study design and study population

A retrospective review of our prospectively collected institutional database was performed and identified 324 patients who

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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underwent surgery for bone metastasis to the extremities or pelvis between January 2014 and July 2017. The institutional review board of the hospital approved this study (IRB No. H-1803–043–923, dated: March 13, 2018). For analytical purpose, the following patients were excluded from the study: patients who underwent other surgical procedures along with the surgery for skeletal metastasis ($n=11$), patients who were operated for skeletal metastases at multiple sites at the same setting ($n=12$), patients with signs of psychiatric abnormalities or poor cognitive function prior to the procedure ($n=4$), patients with insufficient data ($n=8$), and patients with <3 months of follow-up after surgery ($n=13$). The remaining patients ($n=276$) were included in the study.

2.2. Diagnosis of PD

PD was diagnosed by the psychiatrists according to the criteria in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), published by the American Psychiatric Association.^[15] Patients' medical records were systematically assessed by 2 authors (SH and IH) for key words used as diagnostic procedures in past study, such as "delirious," "agitated," "confused," and "disoriented."^[16] A diagnosis of delirium was made when an agreement was reached between the 2 authors. If the patient showed apparent clinical signs of PD, psychiatric consultation was actively sought and treated.

2.3. Statistical analysis

Demographic and clinicopathological data (preoperative, perioperative, and postoperative) were compared between patients with PD and without PD. Continuous variables were presented as mean with range and were compared using the independent-samples t test. Categorical variables were presented as frequencies with percentage using the Pearson chi-squared test. Factors found to have a statistically significant association with the development of PD ($P < .05$) were included in a multivariate logistic regression analyses. Actuarial survival curves were constructed using the Kaplan–Meier method and the differences between survival curves were evaluated by the log rank test. Statistical analyses were performed using the SPSS software (Version 23.0; IBM Co., Armonk, NY).

3. Results

3.1. Factors associated with development of PD

Possible factors associated with development of PD were investigated^[3,14,17,18]: demographics and preoperative factors (Table 1), perioperative factors (Table 2), and postoperative factors (Table 3). Preoperative factors included age, sex, body mass index (BMI), history of medical disease, history of psychiatric disorders, history of smoking (an estimated smoking of >10 cigarettes per day for at least the past 3 years), alcohol consumption (an estimated weekly ethanol consumption of ≥ 200 mL), and prolonged opioid use (>90 morphine milligram equivalent dose [MME] per day for at least ≥ 3 months), primary cancer type, time from cancer diagnosis to bone metastasis, presence of visceral metastases and presence of solitary metastases, preoperative blood tests (hemoglobin, total protein, sodium, potassium, calcium, blood urea nitrogen [BUN], creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST], C-reactive protein [CRP], and total bilirubin),

American Society of Anesthesiologists (ASA) physical status classification, and neo-adjuvant therapy. Perioperative factors included tumor location, surgical procedure, length of operation time, type of anesthesia performed, length of anesthesia time, length of assisted ventilation and blood loss. Postoperative factors included morphine milligram equivalent dose of the opioids administered during the first 5 postoperative days,^[19] duration of mechanical ventilation after surgery, length of intensive care unit (ICU) stay, length of hospital stay, time to ambulation from the surgery, postoperative complications, and mortality.

3.2. Demographics, description of study population

For patient demographics, 182 patients were men (66%) and the mean age was 65 years (range, 16–94). The most common primary cancers in the study group were lung cancer ($n=48$, 17%), renal cell carcinoma ($n=47$, 17%), hepatocellular carcinoma ($n=43$, 16%), and breast cancer ($n=35$, 13%). The femur ($n=155$, 56%) and humerus ($n=54$, 20%) were the most common bones operated on. At the time of surgery, 169 patients (61%) had visceral metastases and 215 patients (78%) presented with multiple bone metastases at the time of surgery. En-bloc resection of the tumor was performed in 84 patients (30.4%) and curettage in 188 patients (68.1%). For reconstruction, osteosynthetic devices were predominantly used after curettage and endoprosthetic reconstruction after en-bloc excision. The most common reconstruction methods used were intramedullary nails ($n=106$, 38.4%), bipolar hemiarthroplasty of the hip ($n=36$, 13%), and megaprotheses ($n=35$, 12.6%). Mean duration of the surgery was 192 (± 98) minutes with an average intraoperative blood loss of 1274 (± 1511) mL. The mean follow-up of the entire cohort was 12 months (range, 1–48). The mean follow-up of survivors was 16 months (range, 3–48).

3.3. Incidence of PD

In all, 9.1% (25/276) of the patients were diagnosed with PD. The mean time from surgery to the diagnosis of PD was 2.1 days (range, 1–9) and 92% (23/25) of the patients were diagnosed within postoperative 5 days. All 25 patients were relieved of PD, with the mean duration of the PD of 4.2 (range, 1–7).

3.4. Factors associated with PD

3.4.1. Comparison of characteristics between patients with and without PD. Patients with PD were more likely to be diabetic ($P=.002$) and to have a history of chronic opioid intake of >90 MME per day for at least 3 months ($P < .001$). Patients with PD were more likely to have had history of psychiatric disorders ($P < .001$) such as delirium ($n=3$), depression ($n=2$), and bipolar disorder ($n=2$). Patients with PD had higher ASA grade, with 64% ($n=16$) having ASA grades of 3 or 4 ($P=.009$). For the preoperative laboratory examinations, patients with PD had lower levels of albumin ($P < .001$), hemoglobin ($P=.005$) and uric acid ($P=.016$), and significantly higher level of CRP ($P < .001$). Among the intraoperative characteristics, patients with PD had more blood loss than patients without PD (2113 ± 2361 vs 1189 ± 1377 mL, $P=.003$). Patients with PD were more likely to be remain intubated after the surgery ($P=.037$) and to have received higher MME postoperatively ($P \leq .001$) than patients without PD. Postoperative complications were more frequent in patients with PD than in patients without PD (56% vs

Table 1
Demographics and preoperative characteristics of patients with and without postoperative delirium.

Characteristics	All patients (n=276)	Without PD (n=251)	With PD (n=25)	P value
Age, y	64.49 (±12.68)	64.16 (±12.93)	67.76 (±9.41)	.177
BMI, kg/m ²	23.03 (±6.11)	23.06 (±6.33)	22.81 (±3.22)	.849
Gender				.820
Male	182 (65.9%)	165 (65.7%)	17 (68.0%)	
Female	94 (34.1%)	86 (34.3%)	8 (32.0%)	
History of				
Diabetes mellitus	78 (28.3%)	64 (25.5%)	14 (56.0%)	.001*
Hypertension	138 (50%)	121 (48.2%)	17 (68.0%)	.059
Psychiatric disorders	21 (7.6%)	14 (5.6%)	7 (28.0%)	<.001*
Neurological disorders	34 (12.3%)	29 (11.6%)	5 (20.0%)	.220
Smoking ^a	42 (15.2%)	37 (14.7%)	5 (20.0%)	.485
Alcohol consumption ^b	68 (24.6%)	59 (23.5%)	9 (36.0%)	.167
Chronic opioid intake ^c	20 (7.2%)	12 (4.8%)	8 (32.0%)	<.001*
Chemotherapy	186 (67.4%)	165 (65.7%)	21 (84.0%)	.063
Radiotherapy	56 (20.3%)	48 (19.1%)	8 (32.0%)	.127
Previous surgery				.515
Not done	57 (20.7%)	54 (21.5%)	3 (12.0%)	
Done	219 (79.3%)	197 (78.5%)	22 (88.0%)	
Interval between bone metastases diagnosis and surgery, wks	25.53 (±55.60)	23.51 (±48.35)	45.84 (±103.00)	.055
Blood investigations				
Serum creatinine, mg/dL	0.87 (±0.50)	0.89 (±0.51)	0.72 (±0.42)	.114
Serum uric acid, mg/dL	4.93 (±1.75)	5.04 (±1.78)	4.14 (±1.28)	.016*
Serum bilirubin, mg/dL	0.81 (±0.69)	0.78 (±0.59)	1.07 (±1.13)	.051
Serum albumin, g/dL	3.51 (±0.72)	3.61 (±0.68)	2.84 (±0.64)	<.001*
Serum alkaline phosphatase, IU/L	126.86 (±89.51)	128.59 (±93.59)	114.68 (±52.17)	.468
Serum cholesterol, mg/dL	167.64 (±46.27)	167.24 (±43.97)	170.44 (±60.96)	.748
ESR, mm/h	45.00 (±37.00)	43.12 (±32.10)	57.50 (±38.73)	.059
CRP, mg/dL	4.05 (±5.53)	3.26 (±4.81)	9.66 (±7.01)	<.001*
Serum hemoglobin, g/dL	11.75 (±1.92)	11.89 (±1.93)	10.75 (±1.55)	.005*
Serum WBC count, ×10 ³ /μL	8.67 (±7.25)	8.77 (±7.61)	7.98 (±3.93)	.610
Others				
Multiple bone metastases	215 (77.9%)	192 (76.5%)	23 (92.0%)	.075
Metastasis to other organs	169 (61.2%)	153 (61.2%)	16 (64.0%)	.784
Preoperative embolization	53 (19.2%)	45 (17.9%)	8 (32.0%)	.088
ASA grade				.007*
1 or 2	168 (60.9%)	159 (63.3%)	9 (36.0%)	
3 or 4	107 (38.8%)	91 (36.2%)	16 (64.0%)	

ASA=American Society of Anaesthesiology, BMI=body mass index, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, PD=postoperative delirium, WBC=white blood cell.

^a An estimated smoking of >10 cigarettes per day for at least the past 3 years.

^b An estimated weekly ethanol consumption of ≥200 mL.

^c >90 MMD per day for at least 3 months or more.

* Indicates statistical significance.

14%, $P=.004$). Patients who developed PD had longer hospital stay ($P<.001$) and were less likely to regain ambulatory status ($P=.003$).

3.4.2. Factors associated with PD. On univariate logistic regression analyses of possible factors associated with the development of PD, history of diabetes mellitus ($P=.002$), history of psychiatric disorders ($P<.001$), history of chronic opioid intake ($P<.001$), ASA grade ($P=.009$), intraoperative blood loss ($P=.008$), increased dose of postoperative opioid analgesics ($P<.001$) and preoperative serum levels of uric acid ($P=.018$), hemoglobin ($P=.006$), albumin ($P<.001$), and CRP ($P<.001$) were significant (Table 4). On multivariate analysis, history of psychiatric disorders (OR=9.63, $P=.004$), high preoperative serum CRP level (OR=1.17, $P=.001$), low preoperative serum albumin level (OR=0.13, $P=.002$), and high dose of opioid analgesics received in the immediate postoperative period (OR=1.05, $P=.001$) were independently associated with the development of PD.

3.5. Survival

Among the 276 patients, 192 (70%) died during the follow-up period. The actuarial survival rate calculated by Kaplan–Meier analysis at 6 months, 1 year, and 2 years was $70.3 \pm 3.2\%$, $58.6 \pm 4.8\%$, and $36.8 \pm 4.1\%$, respectively. 84% of the patients with PD died whereas 68% of the patients without PD died ($P=.012$). On Kaplan–Meier analysis, patients with PD showed significantly worse survival than those without PD ($P=.001$) (Fig. 1). However, the in-hospital mortality rate after the procedure was not different between patients with PD and patients without PD (12% vs 7.5%, $P=.142$).

4. Discussion

PD is a relatively common complication following major surgeries and is often associated with considerable postoperative morbidity.^{15,61} Because of the multiple comorbidities of the patient along with the extensive nature of the surgery, patients undergoing surgery for bone metastases may be prone to

Table 2
Perioperative characteristics of patients with and without postoperative delirium.

Characteristics	All patients (n=276)	Without PD (n=251)	With PD (n=25)	P value
Diastolic BP, mm Hg	70.04 (±11.18)	70.19 (±11.18)	68.57 (±11.29)	.490
IVF, mL	2763 (±1730)	2707 (±1642)	3328 (±2410)	.087
Surgical time, min	191 (±98)	190 (±100)	207 (±79)	.420
Anesthesia time, min	246 (±72)	244 (±71)	260 (±83)	.313
Blood loss, mL	1273 (±1510)	1189 (±1377)	2113 (±2361)	.003*
Type of anesthesia administered				.535
General	264 (95.6%)	241 (96.0%)	23 (92.0%)	
Spinal	11 (3.9%)	9 (3.6%)	2 (8.0%)	
Regional	1 (0.03%)	1 (0.4%)	0 (0.0%)	
Bone substitutes used				.792
Bone cement	219 (79.3%)	198 (78.9%)	21 (84.0%)	
Bone graft	13 (4.7%)	13 (5.2%)	0 (0.0%)	
Bone cement and bone graft	2 (0.7%)	2 (0.8%)	0 (0.0%)	
None	42 (15.2%)	38 (15.1%)	4 (16.0%)	
Blood transfusion	182 (65.9%)	164 (65.3%)	18 (72.0%)	.503
Tumor removal				.456
Not removed	4 (1.4%)	4 (1.6%)	0 (0.0%)	
Curettage	188 (68.1%)	172 (68.5%)	12 (48.0%)	
Excision	84 (30.4%)	75 (29.8%)	13 (52.0%)	
Reconstruction method				.229
None	48 (17.4%)	44 (17.5%)	4 (16.0%)	
Internal fixation	147 (53.2%)	137 (54.6%)	10 (40.0%)	
Prosthesis	81 (29.3%)	70 (27.9%)	11 (44.0%)	
Patients who remained intubated after the surgery	22 (7.9%)	17 (6.8%)	5 (20.0%)	.037*

BP = blood pressure, IVF = intravenous fluids, PD = postoperative delirium.

* Indicates statistical significance.

developing PD. However, no study exists regarding the incidence and risk factors of PD in patients who undergo surgery for bone metastases. This study showed the incidence of PD as 9%, and identified history of psychiatric disorders, high preoperative serum CRP level, low preoperative serum albumin level, and high dose of opioid analgesics received in the immediate postoperative period as risk factors associated with the development of PD.

The 9% incidence of PD falls within the range of PD following common orthopedic procedures.^[20,21] However, the incidence rate was lower than most of the studies following major surgery for cancer. As the initial assessment was made by the non-psychiatrist medical staff, PD might have been underestimated, especially for hypoactive delirium, which can often be misinterpreted as

fatigue or depression.^[12,22] However, psychiatric consultation was actively sought if the patient showed apparent clinical signs of altered mental status, which may have prevented underestimating PD.

Psychoactive medications like opioid analgesics directly or through neuroactive metabolites can interfere with the normal functioning of thalamic modulatory pathways and can thus cause delirium.^[23,24] Opioid medication has been identified as the single modifiable risk factor for PD and reducing its dose or switching to other analgesics can also reverse the occurrence of delirium, in patients who have developed PD.^[25,26] An opioid dose of >90 mg MME per day increased the risk of developing delirium by 40% (OR = 1.7, 95% CI = 1.37–2.11).^[24,25] Horacek

Table 3
Postoperative characteristics of patients with and without postoperative delirium.

Characteristics	All patients (n=276)	Without PD (n=251)	With PD (n=25)	P value
Postoperative assisted ventilation	31 (11.2%)	26 (10.3%)	5 (20%)	.037*
Total duration of hospital stay, d	19.05 (±12.35)	18.14 (±11.64)	28.28 (±15.43)	<.001*
Patients needing ICU care after surgery	38 (13.7%)	31 (12.3%)	7 (28%)	.007*
Average MME within first 5 POD, mg	74.58 (±34.43)	71.19 (±32.26)	108.64 (±37.65)	<.001*
Average VAS within first 5 POD	3.98 (±1.23)	3.94 (±1.25)	4.32 (±0.96)	.150
Time to start oral diet, d	1.42 (±0.91)	1.36 (±0.90)	2.04 (±0.84)	<.001*
Postoperative transfusion within POD5	120 (43.5%)	106 (42.2%)	14 (56.0)	.191
Start of ambulation				.003*
By POD 10 or less	187 (67.8%)	179 (71.6%)	8 (32.0%)	
After POD 10	48 (17.4%)	41 (16.4%)	7 (28.0%)	
Not ambulated till discharge	40 (14.5%)	30 (12.0%)	10 (40.0%)	
Postoperative complications	50 (18.1%)	36 (14.3%)	14 (56.0%)	.004*
Mean follow-up duration, wks	48.77 (±55.22)	50.37 (±55.67)	32.37 (±48.51)	.136
Mortality at final follow-up	192 (69.6%)	171 (68.1%)	21 (84.0%)	.012*

ICU = intensive care unit, MME = morphine milligram equivalent dose, PD = postoperative delirium, POD = postoperative day, VAS = visual analogue scale score.

* Indicates statistical significance.

Table 4**Multivariate logistic regression analyses of factors associated with postoperative delirium.**

Characteristics	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
History of diabetes mellitus			.002			
No	1.00					
Yes	3.72	1.60–8.60				
History of psychiatric disorders			<.001			.019*
No	1.00			1.00		
Yes	6.58	2.36–18.36		9.63	1.78–21.74	
History of chronic opioid intake			<.001			
No	1.00					
Yes	9.37	3.37–26.01				
Serum uric acid, mg/dL	0.70	0.52–0.94	.018			
Serum albumin, g/dL	0.24	0.12–0.45	<.001	0.13	0.03–0.48	.002*
Serum CRP, mg/dL	1.16	1.08–1.23	<.001	1.17	1.06–1.29	.001*
Serum hemoglobin, g/dL	0.70	0.54–0.90	.006			
ASA grade			.009			
1 or 2	0.32	0.13–0.76				
3 or 4	1.00					
Blood loss, mL	1.00	1.00–1.00	.008			
Remain intubated after surgery			.039			
No	1.00					
Yes	1.47	0.23–9.04				
Postoperative ICU care	1.79	1.10–1.94	.005			
Average MME within first 5 POD, mg	1.02	1.01–1.03	<.001	1.05	1.01–1.07	.001*

ASA = American Society of Anaesthesiology, CRP = C-reactive protein, GA = general anaesthesia, ICU = intensive care unit, MME = morphine milligram equivalent dose, POD = postoperative day.

* Indicates statistical significance on multivariate analysis.

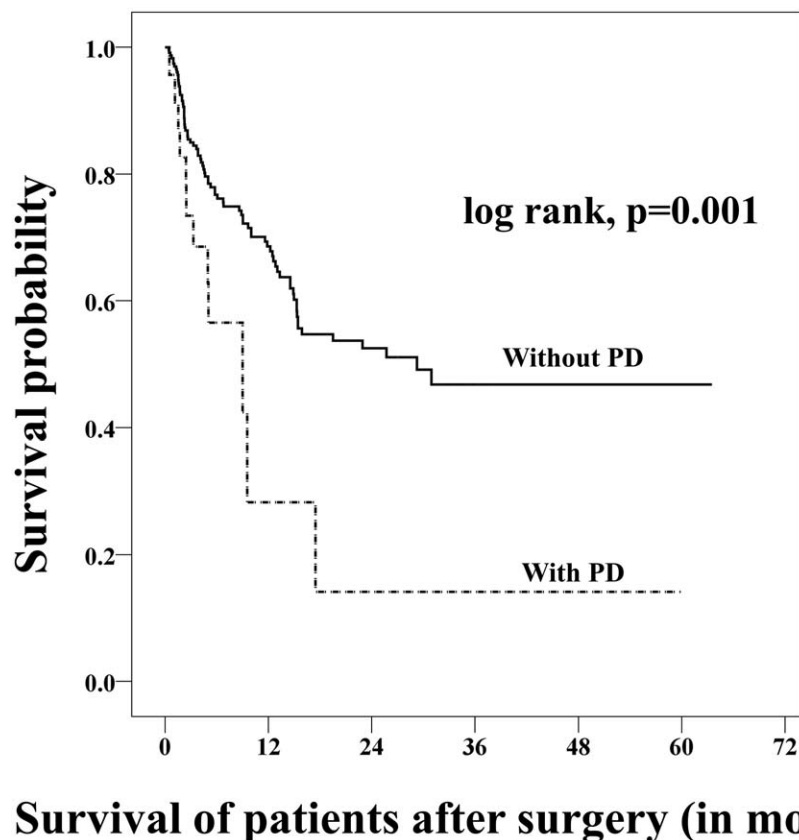


Figure 1. Kaplan–Meier survival curves showing worse postoperative survival in patients with postoperative delirium (PD) than in patients without PD (log rank, $P=0.001$).

et al^[27] reported a mean MME consumption 108 (\pm 39.3)mg in 142 consecutive delirious patients admitted to the department of central intensive care unit for surgery, which was similar to our study.

Prior studies have identified depression, preoperative executive dysfunction and cognitive impairment prior to surgery as independent risk factors for PD.^[28–30] Similar to our study, Mollon et al^[31] identified history of depression as an independent risk factor for developing PD in patients operated by total shoulder arthroplasty with an odds ratio of 2.29 (95% CI 1.68–3.1; $P < .001$).

Patients with elevated preoperative serum CRP level had increased risk of developing PD. The association of elevated serum CRP level with PD has been shown in various types of surgeries.^[32,33] Individuals who are predisposed to an heightened inflammatory response when exposed to an acute episode of stress, like surgery, are at an increased risk of developing delirium.^[32] Neuronal and synaptic dysfunction caused by acute peripheral inflammatory stimulation may lead to subsequent neurobehavioral and cognitive symptoms.^[34] CRP has also been labeled as the strongest delirium-related protein on proteomics analyses.^[35] These findings suggest that the assessment of serum CRP, a relatively easy and safe test, might be useful in predicting the development of PD in patients undergoing surgery for bone metastases.

Low serum albumin was an independent factor for PD in this study. As serum albumin functions as primary oxygen radical trapping and antioxidant agent,^[36,37] reduced levels of serum albumin may result in hampered oxidative defense in the central nervous system, contributing to toxic cognitive impairment.^[38] In line with this study, decreased level of albumin was reported in patients who developed PD following spine surgery.^[39]

Development of PD was significantly associated with worse survival in this study. The association of PD with poor survival has been shown in various types of surgeries.^[40–42] The increase in eventual mortality coupled with the lack of increased in-hospital mortality may indicate that the deleterious effects of PD is not attributable to the PD itself. The increased mortality in patients who developed PD may be secondary to the underlying conditions that led to the development of delirium.^[43]

This study had a number of limitations. First, as the analyses were done in retrospective fashion, not all patients in the study were specifically assessed for delirium in the postoperative period. Second, not all patients were screened by a psychiatrist, as cross reference by a psychiatrist was asked for only when the treating doctor felt it was necessary. Many patients especially with hypoactive delirium could have been missed and hence the magnitude of the problem should be overestimated than the reported incidence rate. Third, there was no quantitative preoperative cognitive assessment for operated patients, even though all the patients were screened for cognitive dysfunction before the procedure and such patients were excluded from the study. Lastly, the treatment for the primary cancers and other metastases were not considered.

5. Conclusion

Our study suggests that the incidence of PD is considerable in patients undergoing surgery for bone metastases. History of psychiatric disorders, preoperative serum albumin and CRP levels, and the dose of postoperative opioid analgesics are associated with the development of PD. These results would be

helpful in the prevention and treatment of PD in patients undergoing surgery for bone metastases, although a long-term prospective study with all patients being individually screened for PD in the postoperative period is needed in the future.

Author contributions

SH collected and analyzed the data, wrote the manuscript. HSK supervised the analysis, encouraged in collecting data and manuscript writing. IH designed the model for data collection, verified the analytical methods, proofread the manuscript, formatted the tables, corrected and contributed in the final version of the manuscript, and was in charge of the overall direction and planning. All authors provided critical feedback, helped shape the research and analysis, discussed results and commented on the manuscript.

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