Association of Opioid Use in the Week Before Death Among Patients With Advanced Lung Cancer Having Sepsis

Hey-ran Choi, MD, PhD[1], In-Ae Song, MD, PhD[2], and Tak Kyu Oh, MD[2] 🆔

Abstract

Opioid use can induce immunosuppression; however, it is unclear whether opioid use increases infections in patients with advanced cancers. This study assessed the association between opioid use in the week before death and mortality among patients with advanced lung cancer having sepsis. Data on opioid usage in the week before death, general information, and clinical information of the patients were collected retrospectively. The primary outcome was the association between opioid use in the week before death and mortality after sepsis. The study included 980 patients who died of advanced lung cancer between January 2003 and June 2017 (sepsis related: 413, unrelated to sepsis: 567). The average morphine equivalent daily dose in the final week was higher in the sepsis group (313.5 ± 510.5 mg) than in the nonsepsis group (125.2 ± 246.9 mg, $P < .001$). A significant association was found between the average morphine equivalent daily dose in the final week and mortality due to sepsis (odds ratio: 1.02, 95% confidence interval: 1.01-1.02, $P < .001$). This was especially evident when the dose was increased by 10 mg in the final week. Furthermore, older age, male sex, and a lower body mass index were associated with an increased risk of mortality after developing sepsis. Opioid use in the week before death may be associated with mortality for patients with advanced lung cancer having sepsis.

Introduction

Lung cancer is a major global health issue and one of the deadliest types of cancer.[1] Lung cancers are often diagnosed at an advanced stage and therefore require appropriate palliative care.[2,3] The key purpose of palliative care for patients with advanced cancer is to provide appropriate pain control and, consequently, an improved quality of life.[4] Opioids are often used for this purpose[5] and are prescribed by clinicians in accordance with World Health Organization guidelines.[6]

However, recent reports about the effects of opioids on the immune system suggest that they may have negative impacts on the long-term outcomes of patients with cancer.[7] Specifically, the immune suppression caused by opioid use may increase infection rates,[8,9] especially for patients with advanced cancer who are often already immunocompromised due to chemotherapy or malnutrition.[10] A previous study

suggested a possible association between the excessive use of opioids and shortened survival times for patients with advanced non-small cell lung cancer (NSCLC).[11] A more recent study reported that the increased use of opioids results in increased infection rates in patients with advanced cancer.[12] Because patients with advanced lung cancer are often exposed to

[1] Department of Anesthesiology and Pain Medicine, Inje University Seoul Paik Hospital, Seoul, Korea
[2] Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Corresponding Author:
Tak Kyu Oh, Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 166, Gumi-ro, Bundang-gu, Seongnam 15632, Korea.
Email: airohtak@hotmail.com

infections and consequent sepsis,[13] further studies on this topic are needed.

To our knowledge, no studies have assessed the association between the occurrence of sepsis in patients with advanced lung cancer and the amount of opioid use; thus, our study aimed to assess this association. We hypothesized that patients with terminal stage advanced lung cancer who died due to sepsis were associated with higher quantities of opioid consumption compared to patients who died of other causes.

Materials and Methods

This retrospective observational study was approved by the institutional review board (approval number: B-1707/408-104). Because this was a retrospective review of patient medical records, the requirement for informed consent was waived. The study used the medical records of all adult patients (≥ 19 years of age) who were diagnosed with advanced lung cancer and died while hospitalized at the single tertiary academic hospital between January 2007 and June 2017. Advanced lung cancer was defined as a primary lung cancer that was found to be inoperable at the time of diagnosis. Small-cell lung cancer (SCLC) was defined as an extensive stage cancer at the time of diagnosis, whereas NSCLC was defined as a stage IIIB or IV cancer. Lung cancer staging was conducted according to the 7th edition of the American Joint Committee on Cancer guidelines.[14] Exclusion criteria for patient selection were as follows: inaccurate information on opioid usage in the final week before death, palliative surgery performed in the week before death, or the occurrence of other primary cancers between the time of diagnosis and death. The study center was a 1360-bed tertiary care hospital as of July 2017. All medical records have been managed and stored electronically since 2003.

Definition of Sepsis in Patients With Advanced Lung Cancer

To define sepsis at the time of death for patients with lung cancer, we used the standards obtained from 2 previously conducted studies[12,15]: (1) a positive blood culture test in the week before death; (2) an abnormally high white blood cell count, neutrophil/granulocyte ratio, C-reactive protein level, and procalcitonin level in the week before death; and (3) a Sepsis-related Organ Failure Assessment (SOFA) score of ≥ 2. Patients who exhibited either the first or second criterion concurrently with the third criterion were considered to have sepsis. The selection of patients with sepsis was based on this definition and was verified by the 2 main investigators of this study, who are certified intensivists.

Measurements

We collected data on each patient's sex, age, body mass index (BMI, kg/m^2), histology of cancer (SCLC or NSCLC), year of death, presence of distant metastasis, history of chemotherapy/radiotherapy, history of smoking, cause of death, and the average morphine equivalent daily dose (MEDD, mg) in the final week before death. Distant metastasis only included metastases of the bones or major organs. Cause of death was categorized as sepsis, respiratory failure without sepsis, cardiologic, neurologic, or others (eg, unclear, gastrointestinal bleeding, acute kidney injury, endocrinologic). The infection source was further categorized as respiratory, digestive, genitourinary, unknown, or others (eg, skin, wound, cardiac, brain, spinal cord, brain). To calculate the average MEDD in the final week, the total opioid usage in the 7 days preceding and including the date of death was accurately measured. Using a standard conversion ratio, the sum of these values was divided by 7 to calculate the average MEDD for the final week[16] (Appendix A).

Outcomes

The primary outcome of this study was the potential association between sepsis as a cause of death in patients with terminal stage advanced lung cancer and opioid usage (based on the average MEDD for the week before death). The secondary outcome was the clinical factors associated with the occurrence of sepsis in patients with terminal stage advanced lung cancer.

Statistical Methods

The patients were grouped into quartiles based on opioid usage. The χ^2 test was used to estimate possible demographic differences in the categorical data for each group. Analysis of variance was also used to find differences in the demographic data between the groups of continuous data, along with the Scheffe test. Similarly, a χ^2 test and t test were used to compare the groups with sepsis at the time of death and those without sepsis.

Finally, univariable and multivariable logistic regression analysis was performed to determine whether opioid usage was independently associated with sepsis at the time of death. All covariates (age, BMI, histology of cancer, distant metastasis, receipt of chemotherapy or radiotherapy, history of smoking, and year of death) were included in the multivariable model for adjustment. Our main independent variable, the average MEDD in the last week, was included in 2 different multivariable models as a continuous variable and as a categorical variable in quartile to avoid multicollinearity in the models. Hosmer-Lemeshow test was used to confirm goodness of fit of the 2 multivariable models. The results of the multivariable model were presented as odds ratio (OR) with 95% confidence interval (CI). Additionally, the restricted cubic spline was used to present the log odds of development of sepsis according to average MEDD for the final week. R software (version 3.6.0; R Foundation, Vienna, Austria) was used for all analyses, and $P < .05$ was considered to be statistically significant.

Results

A total of 1085 Asian adult patients with advanced lung cancer died while hospitalized at the institution between January 2007

Table 1. Baseline Characteristics of Patients With Advanced Lung Cancer for Average MEDD in Last Week by Quartiles.[a]

Variable	Average MEDD in Last Week				
	Q1 < 30, n = 232	30 ≤ Q2 < 60, n = 202	60 ≤ Q3 < 165, n = 291	165 < Q4, n = 255	P Value
Sex: male	170 (73.3)	148 (73.3)	210 (72.2)	194 (76.1)	.768
Age, years	70.1 (10.9)	68.1 (11.5)	65.5 (10.8)	66.5 (10.8)	<.001
Body mass index, kg/m^2	21.3 (3.6)	21.3 (3.8)	21.7 (3.4)	21.4 (3.6)	.294
Histology of cancer					
NSCLC	186 (80.2)	154 (76.2)	230 (79.0)	199 (78.0)	
SCLC	46 (19.8)	48 (23.8)	61 (21.0)	56 (22.0)	
Distant metastasis (bone or major organ)	43 (18.5)	62 (30.7)	89 (30.6)	64 (25.1)	.007
Chemotherapy	19 (8.2)	43 (21.3)	66 (22.7)	58 (22.7)	<.001
Radiotherapy	94 (40.5)	87 (43.1)	151 (51.9)	137 (53.7)	.006
History of smoking	205 (88.4)	174 (86.1)	251 (86.3)	228 (89.4)	.622
Cause of death					<.001
Sepsis	102 (44.0)	62 (30.7)	98 (33.7)	150 (58.8)	
Respiratory failure without sepsis	103 (44.4)	122 (60.4)	168 (57.7)	94 (36.9)	
Cardiovascular disease	5 (2.2)	3 (1.5)	6 (2.1)	3 (1.2)	
Neurologic disease	13 (5.6)	7 (3.5)	5 (1.7)	3 (1.2)	
Others[b]	9 (3.9)	8 (4.0)	14 (4.8)	5 (2.0)	
Year of death					.011
2007-2010	90 (38.8)	52 (25.7)	89 (30.6)	70 (27.5)	
2011-2014	81 (34.9)	73 (36.1)	108 (37.1)	113 (44.3)	
2015-2017	61 (26.3)	77 (38.1)	94 (32.3)	72 (28.2)	

Abbreviations: MEDD, morphine equivalent daily dose; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer.
[a]Presented as mean with standard deviation or number with percentage.
[b]Others: Unclear, gastrointestinal bleeding, acute kidney injury, endocrinologic disease.

and June 2017. The following patients were excluded from the study: 24 patients who had an additional primary cancer at the time of death, 12 patients who died within a week after a palliative operation, and 69 patients who had inaccurate records on opioid usage in the final week before death. In all, 980 patients were included in our analysis. Of these patients, 413 died of sepsis and 567 died of other causes.

Baseline Characteristics by Average MEDD in the Final Week

Table 1 shows the baseline patient characteristics by average MEDD in the final week of life by quartiles. The proportions of deaths due to sepsis were significantly different between the quartiles of opioid usage: quartile 1 (<30 mg): 44.0% (102/232); quartile 2 (30-60 mg): 30.7% (62/202); quartile 3 (60-165 mg): 33.7% (98/291); and quartile 4 (>165 mg): 58.8% (150/255; $P < .001$). In addition, age ($P < .001$), presence of distant metastasis ($P = .007$), history of chemotherapy ($P < .001$), history of radiotherapy ($P = .006$), and the cause of death ($P < .001$) were significantly different between the quartiles. Figure 1A and B are restricted cubic splines that show the relationship between average MEDD in the final week and the log odds of death caused by sepsis and death caused by sepsis due to respiratory infection, respectively. The log odds of mortality from sepsis and from sepsis caused by respiratory infection tended to increase with increased average MEDDs in the final week of life.

Baseline Characteristics by Sepsis Diagnosis

Table 2 shows the differences between patients who died of sepsis and patients who died of other causes. Patients who died of sepsis had significantly higher average MEDDs in the final week of life compared with patients who died of other causes (sepsis: 313.5 ± 510.5 mg vs nonsepsis: 125.2 ± 246.9; $P < .001$). In addition, the proportion of males (sepsis: 78.7% vs nonsepsis: 70.0%; $P = .003$) and age (sepsis: 69.7 ± 9.9 years vs nonsepsis: 65.7 ± 11.7 years; $P < .001$) were also significantly higher among patients who died of sepsis. Body mass index was significantly lower in the sepsis group (sepsis: 21.0 ± 3.6 kg/m^2 vs nonsepsis: 21.7 ± 3.5 kg/m^2; $P = .003$), as was the proportion of patients with distant metastases (sepsis: 22.8% vs nonsepsis: 28.9%; $P = .031$). Respiratory infection was the most common infection type (91.3%).

Figure 2 shows the average MEDD before and after the diagnosis of sepsis in patients with advanced lung cancer. The average MEDD before sepsis diagnosis was lower than the average MEDD after the diagnosis of sepsis (MEDD before sepsis: 105.3 ± 148.2 mg vs MEDD after sepsis: 223.5 ± 148.2 mg; $P < .01$).

Logistic Regression Analysis for the Occurrence of Sepsis

Table 3 shows the results of uni- and multivariable logistic regression analyses for death due to sepsis in patients with advanced lung cancer. A significant association was observed between the 10 mg increase of average MEDD in the final week of life and death from sepsis (OR: 1.02, 95% CI:
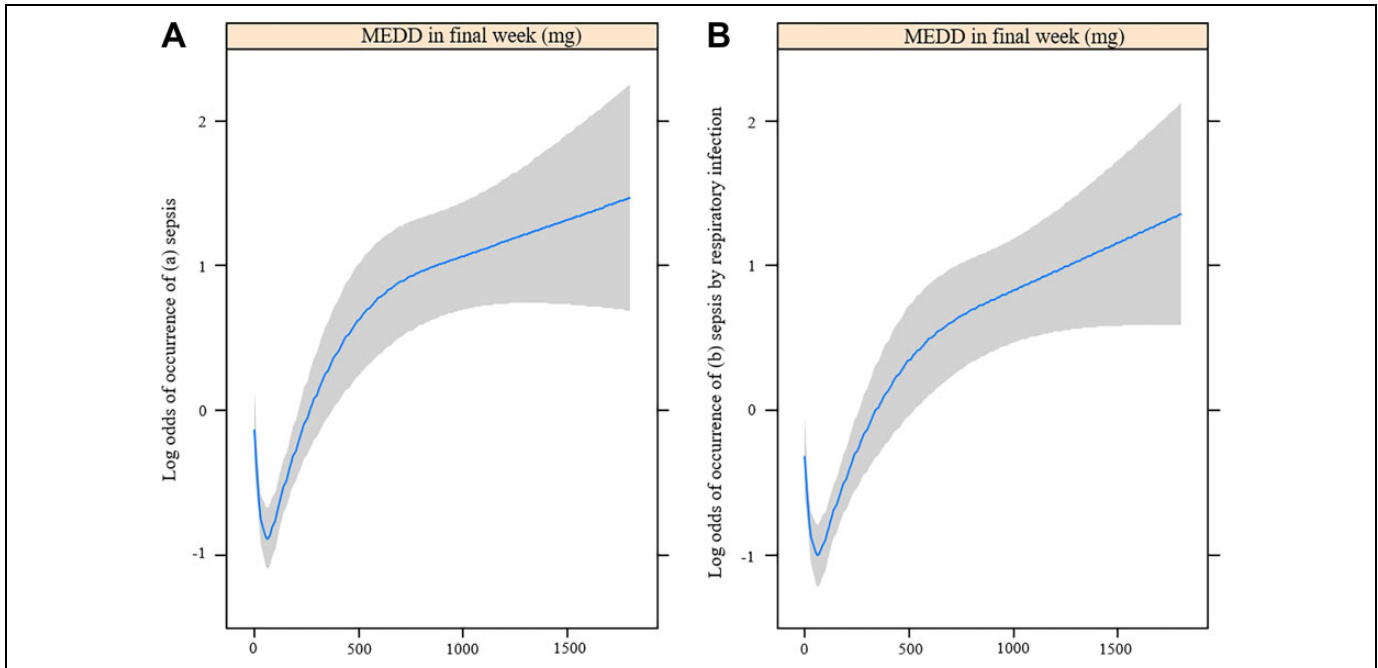
Figure 1. Restricted cubic spline showing opioid dosages for the occurrence of (A) sepsis and (B) sepsis by respiratory infection in patients with lung cancer. MEDD indicates morphine equivalent daily dose (mg).

Table 2. Demographics and Baseline Characteristics According to Sepsis in Patients With Advanced Lung Cancer.[a]

	Patients With Advanced Lung Cancer (n = 980)		
Variable	Sepsis (n = 413)	Nonsepsis (n = 567)	P Value
Sex: male	325 (78.7)	397 (70.0)	.003
Age, years	69.7 (9.9)	65.7 (11.6)	<.001
BMI, kg/m^2	21.0 (3.6)	21.7 (3.5)	.003
MEDD[b] (mg)	313.5 (510.5)	125.2 (246.9)	<.001
Cancer type			.212
NSCLC	332 (80.4)	437 (77.1)	
SCLC	81 (19.6)	130 (22.9)	
Distant metastasis (bone or major organ)	94 (22.8)	164 (28.9)	.031
Chemotherapy	61 (14.8)	125 (22.0)	.004
Radiotherapy	186 (45.0)	283 (49.9)	.131
History of smoking	361 (87.4)	497 (87.7)	.909
Infection source			<.001
Respiratory	377 (91.3)	0 (0.0)	
Digestive	13 (3.1)	7 (1.2)	
Genitourinary	4 (1.0)	0 (0.0)	
Others[c]	6 (1.5)	0 (0.0)	
Unknown	13 (3.1)	0 (0.0)	

Abbreviations: BMI, body mass index; MEDD, morphine equivalent daily dose; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer.
[a]Presented as mean with standard deviation or number with percentage.
[b]MEDD: Average MEDD in last week.
[c]Others: Skin, wound, cardiac, brain, spinal cord, bone.

1.01-1.02, $P < .001$; model 1). As a categorical variable, in the Q4 group, the average MEDD in the final week of life was associated with death from sepsis, compared with that in the Q1 group (Q4, OR: 1.82, 95% CI: 1.62-3.49, $P < .001$; model 2). In addition, age (OR: 1.03, 95% CI: 1.02-1.05, $P < .001$), male sex (OR: 1.48, 95% CI: 1.07-2.05, $P < .001$), and BMI (OR: 0.95, 95% CI: 0.91-0.99; $P = .013$) were also significantly associated with death from sepsis (model 1).

Discussion

Our study shows that patients with terminal stage advanced lung cancer who died of sepsis used higher quantities of opioids compared with patients with terminal stage advanced lung cancer who died of other causes; this result was statistically significant in the multivariate logistic analysis. This finding is in agreement with the results of a study in which the daily increased oral morphine equivalent was associated with a risk of infection in patients with advanced cancer.[12] A unique characteristic of our study is that it only included deaths caused by sepsis in patients with terminal stage advanced cancer. In addition, our study suggests that the risk of death due to sepsis is positively associated with increased age, male sex, and NSCLC cancer type.

This study shows that excessive opioid use by patients with advanced cancer could contribute to the development of sepsis. Because sepsis is common among hospitalized patients with cancer,[17] this finding may have clinical significance.
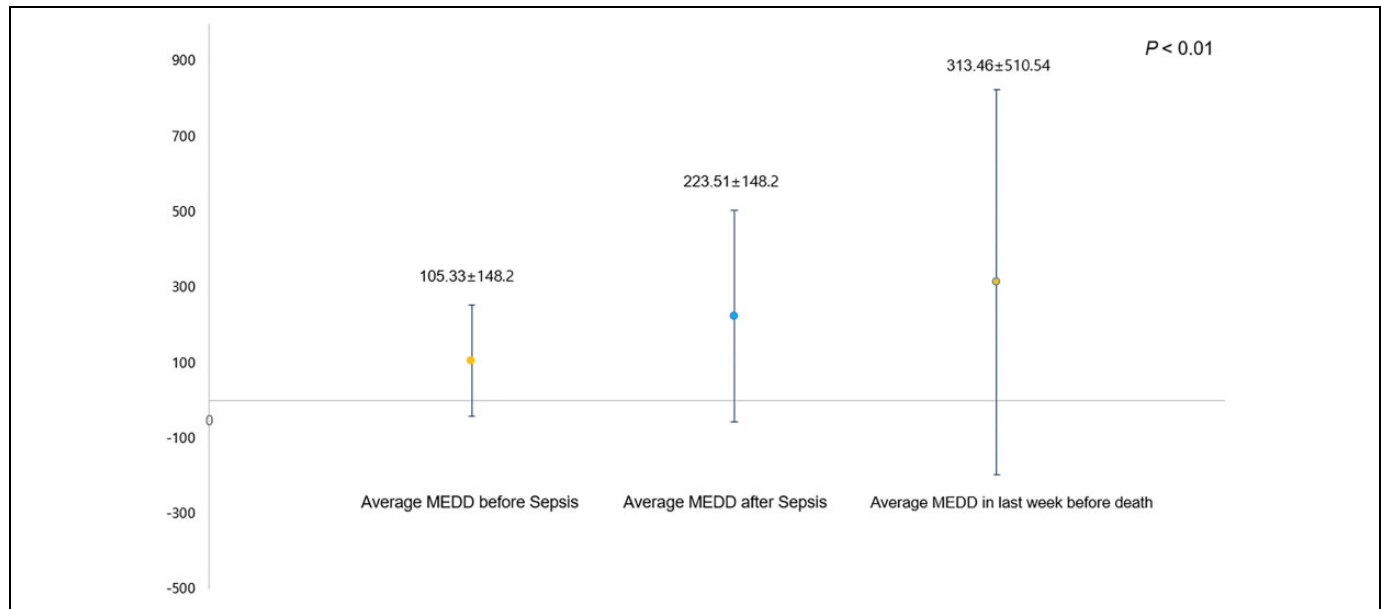
Figure 2. Opioid use before and after sepsis diagnosis in patients with advanced lung cancer. MEDD indicates morphine equivalent daily dose (mg).

Table 3. Univariable and Multivariate Logistic Regression Analysis for Development of Sepsis in Patients With Advanced Lung Cancer.[a]

	Univariable Model		Multivariable Model	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age, years	1.04 (1.02-1.05)	<.001	1.03 (1.02-1.05)	<.001
Male sex (vs female)	1.58 (1.18-2.13)	.002	1.48 (1.07-2.05)	<.001
BMI, kg/m^2	0.95 (0.91-0.98)	.003	0.95 (0.91-0.99)	.013
NSCLC (vs SCLC)	1.22 (0.89-1.67)	.213	1.40 (0.99-1.97)	.058
Distant metastasis	0.72 (0.54-0.97)	.031	0.94 (0.68-1.31)	.718
Chemotherapy	0.61 (0.44-0.86)	.004	0.70 (0.48-1.00)	.049
Radiotherapy	0.82 (0.64-1.06)	.132	0.97 (0.72-1.30)	.835
History of smoking	0.98 (0.67-1.44)	.909	0.77 (0.51-1.17)	.219
Year of death				
2007-2010	1		1	
2011-2014	1.03 (0.76-1.40)	.847	0.85 (0.62-1.19)	.854
2015-2017	0.96 (0.69-1.32)	.789	0.74 (0.51-1.06)	.101
MEDD[b] per 10 mg (model 1)	1.02 (1.01-1.02)	<.001	1.02 (1.01-1.02)	<.001
MEDD[b] in quartile (model 2)				
Q1 < 30	1		1	
30 ≤ Q2 < 60	0.56 (0.38-0.84)	.005	0.68 (0.42-1.05)	.058
60 ≤ Q3 < 165	0.66 (0.46-0.94)	.020	0.87 (0.60-1.27)	.474
165 < Q4	1.82 (1.27-2.61)	.001	2.38 (1.62-3.49)	<.001

Abbreviations: BMI, body mass index; CI, confidence interval; MEDD, morphine equivalent daily dose; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer.
[a]Hosmer-Lemeshow test = χ^2 = 12.17, df = 8 (P = .144) in model 1, χ^2 = 10.78, df = 8 (P = .215) in model 2.
[b]MEDD: Average MEDD in last week.

Furthermore, effective pain control that avoids excessive opioid use is now an important issue in the palliative care of patients with advanced cancer.[18] Therefore, our findings suggest that opioid dosage may affect mortality from sepsis for patients with advanced lung cancer.

Because of the effects of opioids on the immune system, we hypothesized that the excessive use of these drugs may be associated with death due to sepsis in patients with advanced lung cancer. The suppression of the immune system through opioid usage and the consequent worsening of long-term oncologic outcomes are important issues, although they are still controversial.[19] Furthermore, it remains unclear how opioids affect the immune system, and the findings pertaining to induced immunosuppression and immunostimulation are

paradoxical.[20,21] However, unlike previously conducted studies, our findings show that the excessive use of opioids is associated (although weakly) with infections in patients with advanced cancer.[12] In general, a patient with advanced cancer is already in an immunocompromised state, and their condition worsens as the cancer progresses to the terminal stage.[10] Based on the results of a previous study, which reported increased rates of opportunistic infections in opioid abusers,[8] we suggest that the excessive use of opioids by immunocompromised patients with advanced cancer can increase infection rates.

A few points should be considered in the interpretation of our study's findings. First, infection and sepsis in the patients may not have been affected by the immune system, but by various other factors. For example, in the case of aspiration pneumonia, mental status and swallowing difficulty are important causative factors.[22] In the case of urinary tract infections, the time taken for Foley catheter insertion inevitably has effects, whereas all nosocomial infections are likely to be affected by the length of the hospitalization period.[23] Furthermore, chemotherapy history and nutritional status should also be considered. Despite the fact that our study could not consider the type and number of chemotherapy agents/treatments administered and the exact assessment of the nutritional status could not be performed, factors such as the history of chemotherapy and BMI had no effects on death due to sepsis in patients with advanced lung cancer. Therefore, considering the drawbacks arising from the retrospective nature of this study, the excessive use of opioids has a significant association, rather than a clear causal relationship, with death due to sepsis in patients with advanced lung cancer. Moreover, the difference in the ORs between the average MEDD in the final week and death caused by sepsis was 1.002, which is extremely close to the value of 1 and further supports our hypotheses.

Another important issue is the appropriateness of the definition of sepsis, considering the characteristics of patients with advanced lung cancer. Infection and sepsis, severe sepsis, and septic shock cannot be easily distinguished, and their definitions change often.[24] We used the standards suggested by Shao et al[12] who defined infection in patients with advanced cancer. Thus, the first step in defining the infection was based on the results of a blood culture test. Then, laboratory test results were considered, including white blood cell counts, neutrophil granulocyte ratios, C-reactive protein levels, and procalcitonin levels. Second, to assess organ dysfunction, SOFA scores were used. Lastly, the systemic inflammatory response syndrome (SIRS) sign was used in parallel. Patients with advanced lung cancer can have symptoms similar to those of SIRS due to the unstable hemodynamic status that results from various reasons other than infection.[25] Therefore, an SIRS assessment in patients with terminal stage advanced lung cancer would have low specificity and was not performed in this study. However, there are no established tools or systems that can effectively judge and define sepsis in patients with lung cancer; therefore, additional studies must be conducted.

This study had a few limitations, including the retrospective design of the experiment. Second, we only accurately assessed opioid use (amount) in the final week before death; the rate of increase in opioid usage, according to disease progression, could not be considered. Third, the changes and developments that the clinics underwent, along with the changes in the physicians, across the 15 years (2003-2017) of the study could not be taken into consideration. Lastly, to calculate the sums of the different types of opioids, conversions needed to be performed; the accuracy of the conversion method we used is still controversial.[26] However, this study's strength lies in the fact that it is the first study to assess the association between opioid usage and death from sepsis in patients with advanced cancer.

In conclusion, our study showed a significant association between the amount of opioids used in the final week before death and death due to sepsis in patients with advanced lung cancer.

Appendix

Appendix A. Equianalgesic Opioid Conversion Table.

Opioid	Administration Route	Dose Equivalent to 10 mg of Oral Morphine (mg)
Morphine	Oral	10
Morphine	Intravenous	3.3
Morphine	Epidural	0.33
Hydromorphone	Oral	2
Fentanyl	Intravenous	0.03
Oxycodone	Oral	7
Codeine	Oral	80
Tramadol	Oral	40

ORCID iD

Tak Kyu Oh, MD https://orcid.org/0000-0002-4027-4423

References

1. Cheng TY, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The International Epidemiology of Lung Cancer: latest

trends, disparities, and tumor characteristics. *J Thorac Oncol*. 2016;11(10):1653-1671.

2. Leppert W, Turska A, Majkowicz M, Dziegielewska S, Pankiewicz P, Mess E. Quality of life in patients with advanced lung cancer treated at home and at a palliative care unit. *Am J Hosp Palliat Care*. 2012;29(5):379-387.

3. Yoong J, Park ER, Greer JA, et al. Early palliative care in advanced lung cancer: a qualitative study. *JAMA Intern Med*. 2013;173(4):283-290.

4. Singer PA, Martin DK, Kelner M. Quality end-of-life care: patients' perspectives. *JAMA*. 1999;281(2):163-168.

5. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13(2): e58-68.

6. Azevedo Sao Leao Ferreira K, Kimura M, Jacobsen Teixeira M. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? *Support Care Cancer*. 2006;14(11):1086-1093.

7. Ninkovic J, Roy S. Role of the mu-opioid receptor in opioid modulation of immune function. *Amino Acids*. 2013;45(1):9-24.

8. Roy S, Ninkovic J, Banerjee S, et al. Opioid drug abuse and modulation of immune function: consequences in the susceptibility to opportunistic infections. *J Neuroimmune Pharmacol*. 2011; 6(4):442-465.

9. Oh TK, Jeon JH, Lee JM, et al. Investigation of opioid use and long-term oncologic outcomes for non-small cell lung cancer patients treated with surgery. *PLoS One*. 2017;12(7): e0181672.

10. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an international expert panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008;8(4):287-313.

11. Zylla D, Kuskowski MA, Gupta K, Gupta P. Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer. *Br J Anaesth*. 2014;113(suppl 1):i109-i116.

12. Shao YJ, Liu WS, Guan BQ, et al. Contribution of opiate analgesics to the development of infections in advanced cancer patients. *Clin J Pain*. 2017;33(4):295-299.

13. Radford JA, Ryder WD, Dodwell D, Anderson H, Thatcher N. Predicting septic complications of chemotherapy: an analysis of 382 patients treated for small cell lung cancer without dose reduction after major sepsis. *Eur J Cancer*. 1992;29A(1):81-86.

14. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471-1474.

15. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.

16. Management of cancer pain: adults. Cancer Pain Guideline Panel. Agency for Health Care Policy and Research. *Am Fam Physician*. 1994;49(8):1853-1868.

17. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care*. 2004;8(5): R291-298.

18. Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*. 2017;20(2S): S3-S92.

19. Kim R. Anesthetic technique and cancer recurrence in oncologic surgery: unraveling the puzzle. *Cancer Metastasis Rev*. 2017; 36(1):159-177.

20. Liang X, Liu R, Chen C, Ji F, Li T.Opioid system modulates the immune function: a review. *Transl Perioper Pain Med*. 2016; 1(1):5-13.

21. Plein LM, Rittner HL. Opioids and the immune system—friend or foe. *Br J Pharmacol*. 2018;175(14):2717-2725.

22. Martin BJ, Corlew MM, Wood H, et al. The association of swallowing dysfunction and aspiration pneumonia. *Dysphagia*. 1994; 9(1):1-6.

23. Yu SM, Park KY. Risk factors for nosocomial urinary tract infection in the intensive care unit with a positive urine culture and Foley catheterization [in Korean]. *Taehan Kanho Hakhoe Chi*. 2007;37(7):1149-1158.

24. Sterling SA, Puskarich MA, Glass AF, Guirgis F, Jones AE. The impact of the sepsis-3 septic shock definition on previously defined septic shock patients. *Crit Care Med*. 2017;45(9): 1436-1442.

25. Andrejak C, Terzi N, Thielen S, et al. Admission of advanced lung cancer patients to intensive care unit: a retrospective study of 76 patients. *BMC Cancer*. 2011;11:159.

26. O'Bryant CL, Linnebur SA, Yamashita TE, Kutner JS. Inconsistencies in opioid equianalgesic ratios: clinical and research implications. *J Pain Palliat Care Pharmacother*. 2008;22(4): 282-290.