A Comprehensive Analysis of 5-Year Outcomes in Patients With Cancer Admitted to Intensive Care Units

Yoonki Hong

Kangwon National University <https://orcid.org/0000-0002-1607-6777>

Woo Jin Kim

Kangwon National University

Ji Young Hong

Chuncheon Sacred Heart Hospital

Yun-Jeong Jeong

Dongguk University Ilsan Hospital

Jinkyong Park (✉ pjk3318@gmail.com)

Dongguk University Ilsan Hospital <https://orcid.org/0000-0002-8833-9062>

Research

Keywords: Cancer, Intensive care unit (ICU), Mortality, Hematologic malignancies, Lung cancer, Solid cancer

Posted Date: November 23rd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-111858/v1>

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Version of Record: A version of this preprint was published at Tuberculosis and Respiratory Diseases on January 20th, 2022. See the published version at <https://doi.org/10.4046/trd.2021.0106>.

Abstract

Background

Until recently, studies on long-term outcomes of critically ill patients with cancer have been mainly restricted to specific subgroups of patients. The aim of this study was to evaluate the long-term (5 years) clinical outcomes of patients who received intensive care unit (ICU) treatment using the Korean nationwide data.

Methods

All patients aged >18 years with ICU admission, according to the claims data from the Health Insurance Review and Assessment Service from January 2008 to December 2010, were enrolled. The enrolled patients were followed up until December 2015. We analyzed clinical outcomes, including mortality after admission to the ICU. Critically ill patients were categorized into four subgroups: patients without cancer; with solid cancer except lung; with lung cancer; and with hematologic malignancies.

Results

Among all critically ill patients admitted to the ICU ($n = 323,765$), the proportion of patients with cancer continued to increase from 21.5% in 2008 to 27.8% in 2010. Critically ill patients with cancer showed higher ICU mortality (18.6%) than those without cancer (13.2%, $p < 0.001$). There was no difference in ICU mortality at day 28 among patients without cancer (14.5%) and those with cancer which was not lung cancer or hematologic malignancies (14.3%, $p = 0.28$). Hazard ratios for the ICU mortality at 5 years were: 1.90 (95% confidence interval [CI]: 1.87–1.94) for lung cancer; 1.44 (95% CI: 1.43–1.46) for other solid cancers; and 3.05 (95% CI: 2.95–3.16) for hematologic malignancies, versus patients without cancer.

Conclusion

The results of this study suggest that, in the short term, the outcomes of critically ill patients with cancer were not significantly different from those of general patients, except for cases with lung cancer and hematologic malignancies. However, the long-term survival rate of patients with cancer was significantly worse than that of general critically ill patients.

Background

The incidence rate of cancer is increasing as the elderly population increases. The National Institutes of Health (Bethesda, MD, USA)¹ estimates that approximately 15,760,939 individuals have cancer in the United States of America. The Korea Central Cancer Registry² reported that one in 10 elderly individuals aged >65 years had cancer. Early detection of cancer and advances in treatment options are increasing the overall cancer survival rates³. Nevertheless, as the number of patients with cancer increases, so does

the number of patients requiring admission to the intensive care unit (ICU)⁴. Taccone et al. reported that one in seven critically ill patients admitted to the general ICU in Europe was a patient with cancer⁵.

Numerous recent studies⁶⁻⁸ reported a decrease in mortality despite an increased number of patients admitted to the ICU, as well as increased severity or comorbidities. There are more studies showing that ICU admission helps patients after receiving urgent chemotherapy or undergoing hematopoietic stem cell transplantation, in whom many adverse outcomes were previously recorded⁹⁻¹¹. This is because considerable effort has been focused on providing early critical care to select patients with cancer^{12,13}. However, most of these studies assessed relatively short-term outcomes. This approach is characterized by numerous limitations in terms of clarifying the criteria for treatment continuation or appropriate ICU utilization, as well as precise indications for ICU admission¹⁴. Further investigation of long-term outcomes is warranted to reduce the uncertainty in critically ill patients.

The aim of this study was to investigate the long-term outcomes depending on the type of cancer. A population-based cohort study compared the 5-year mortality rates of critically ill patients with and without cancer to investigate differences in the long-term outcome of each type of cancer.

Methods

Data source

This was a retrospective observational cohort study using the claims data from the Health Insurance Review and Assessment Service (HIRA) between January 1, 2007 and December 31, 2015. In Korea, all individuals are covered by the National Health Insurance or Medical Aid Program. The claims data discloses information regarding patients' diagnoses, treatments, procedures, surgical history, and use of prescription drugs.

Patients

The study population included all patients aged >18 years who were examined by chest computed tomography for any reasons from January 2007 to December 2012. Enrolled patients were followed up until March 31, 2016. We identified the first ICU admissions with codes of ICU services (modified version of the International Classification of Diseases 10th revision [ICD-10] codes AJ001-AJ590900). Patients with ICU admission were divided into two groups based on the presence or absence of cancer since January 2008. The exclusion criteria were: 1) patients aged >100 years; 2) ICU admission prior to the diagnosis of cancer; and 3) any claims related to cancer prior to January 2008. Cancer was categorized into lung cancer (code C34 of the ICD 10th revision), hematologic malignancy (codes C81–C86, C88, and C90–C95 of the ICD 10th revision), and other solid cancers.

Comorbidities and concomitant medical therapy

Comorbidities were recognized if the claims data existed 6 months before the index of admission to the ICU. Comorbidity diagnoses were reached using the ICD-10 codes. Concomitant medical therapy was defined by the procedure code of the Korean National Health Insurance or Korean drug and anatomical therapeutic chemical codes.

Ethics

This study was approved by the HIRA. Ethical approval for this study was exempted by the Kangwon National University Hospital Institutional Review Board (B-2018-02-002) because the authors only accessed de-identified, previously collected data.

Statistical analysis

The study endpoint was all-cause mortality in the ICU. Variables are presented as numbers (percentages) or means (standard deviations). Between-group comparisons were performed using χ^2 tests for categorical data and Student's t-tests for continuous data. We used Cox proportional hazards regression to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for in-hospital mortality associated with patient characteristics. The value obtained by subtracting the cancer-related score from the Charlson Comorbidity Index (CCI) system was used to avoid overcorrection of cancer disease. Probabilities <0.05 were considered statistically significant. All analyses were performed using R v3.4.4 (with the packages of survival and ggplot2 function in R to obtain an appropriate updated citation).

Results

During the study period, 323,765 patients were admitted to the ICU at least once. Of all critically ill patients admitted to the ICU, the proportion of patients with cancer continued to increase from 21.5% in 2008 to 27.8% in 2010. Critically ill patients with cancer showed significant male predominance (67.5%, $p < 0.001$) and higher CCI (5.5 ± 3.1 vs. 2.2 ± 2.0 , $p < 0.001$) compared with patients without cancer (Table 1). The length of stay in the ICU was significantly longer for patients with cancer than those without cancer (18.2 ± 14.5 vs. 15.4 ± 14.2 days, respectively; $p < 0.001$). Patients with cancer in the ICU received less support by mechanical ventilator (29.8% vs. 33.2%, respectively; $p < 0.001$). Critically ill patients with cancer showed higher ICU mortality than those without cancer (18.6% vs. 13.2%, respectively; $p < 0.001$). Following admission to the ICU, the mortality rate of patients with cancer was 18.1%, 26.2%, 42.7%, and 55.3% at 28 days, 60 days, 1 year, and 3 years, respectively (Fig. 1). There was no difference in ICU mortality at day 28 among patients without cancer and those with cancer which was not lung cancer and hematologic malignancies (14.5% vs. 14.3%, respectively; $p = 0.28$); however, the difference was statistically significant thereafter. After adjusting for age, sex, year of admission to the ICU, and use of life support system (such as ventilator, continuous renal replacement therapy, vasopressor), the HR of ICU mortality in all patients with cancer at 5 years was 1.56 (95% CI: 1.53–1.59) versus those without cancer. However, there was no significant difference in the HR of ICU mortality for patients with cancer which was

not lung cancer or hematologic malignancies versus those without cancer (HR: 1.00; 95% CI: 0.998–1.016) (Fig. 2).

Comparison between patients with solid cancer and hematologic malignancy

Of the 78,736 patients with cancer, except for 10.5% (9,200 patients) with multiple primaries, 5.8% had hematologic malignancies. The proportion of patients with a hematologic malignancy among critically ill patients with cancer increased from 5.4 % in 2008 to 6.6% in 2010. These patients were predominantly female, younger, and had lower CCI versus those with solid cancer (Table 2). Patients with hematologic malignancy stayed longer in the ICU (22.7 ± 17.3 days) than those with solid cancer (18.1 ± 4.3 days). The use of medical support and life support procedures was more frequent in critically ill patients with a hematologic malignancy than those with solid cancer (mechanical ventilators 28.6% vs. 54.5%, $p < 0.01$ or renal replacement therapy 4.8% vs. 22.0%, $p < 0.01$). The ICU mortality was higher in patients with hematologic malignancy than those with solid cancer (43.9% vs. 17.5%, respectively; $p < 0.01$) (Fig. 1). The hazard risk of hematologic malignancies and lung cancer on day 28 was almost the same as that of the general patients in the ICU (Fig. 2). Compared with patients without cancer, the HRs of ICU mortality were 1.49 (95% CI: 1.46–1.52) and 2.37 (95% CI: 2.15–2.28) in patients with solid cancer and hematologic malignancies, respectively.

Comparison within solid cancer: lung cancer versus other solid cancers

Lung cancer accounted for 28.2% of critically ill patients with solid cancer. Patients with lung cancer were predominantly male (72.4% vs. 65.8%, respectively) and older (67.3 ± 10.8 vs. 66.0 ± 12.5 years, respectively) versus those with other solid cancers. Patients with lung cancer were admitted sooner to the ICU following diagnosis than patients with other solid cancers (205.1 ± 409.5 vs. 357.1 ± 571.0 days, respectively; $p < 0.001$). Patients with lung cancer had a shorter length of stay in the ICU (16.1 ± 12.9) than those with other solid cancers (18.8 ± 14.6). In addition, they required more ventilator support than others (31.0% vs. 27.6%, respectively; $p < 0.01$). ICU mortality was higher in patients with lung cancer than those with other solid cancer (25.5% vs. 14.4%, respectively; $p < 0.01$). Compared with patients without cancer, the HRs of 28-day and 5-year survival were 1.93 (95% CI: 1.87–1.99) and 1.90 (95% CI: 1.87–1.94) in patients with lung cancer and 1.07 (95% CI: 1.04–1.10) and 1.44 (95% CI: 1.43–1.46) in patients with other solid cancers, respectively (Fig. 2).

Discussion

This study comprehensively presented the short- and long-term outcomes of critically ill patients over 5 years with relatively representative data. In the short term, the outcomes of critically ill patients with cancer were not significantly different from those of general patients, except for lung cancer and hematologic malignancies. After 60 days, the survival rate of patients with cancer was significantly worse than that of general critically ill patients. Although critical care had a limited effect on the overall course of cancer, it could be beneficial to patients with cancer in terms of overcoming the acute crisis in the ICU.

However, patient selection for ICU admission is necessary for those with lung or hematologic malignancy who require intensive care to overcome an acute crisis.

Between 1987 and 1992, the 5-year survival rate of the Finnish mixed ICU was 59.9%¹⁵. This data revealed that cancer was a powerful factor in determining outcomes as bad as 3.17 of relative risk for death. Our data showed that, although the present study was conducted 10 years later, the 5-year survival rate was lower than that of the Finnish ICU because the proportion of cancer patients more than double and the proportion of people with respiratory failure was more than four times. Moreover, our patients stayed 16.2 ± 14.3 days in the ICU. According to Hermans et al.¹⁶, these patients can be termed “prolonged stayers.” In this group of patients the 5-year survival rate was 51.8%. Moreover, there was a difference of 5 years between the studies. The previous research was conducted for 5 years since 2012, while ours was conducted 5 years earlier. In fact, the heterogeneity of patients observed between the studies complicates data comparisons.

Similar to the Finnish data¹⁵, our results demonstrated that critically ill patients with cancer had worse long-term outcomes than those without cancer. However, in our study, the short-term outcomes in the ICU (28 days) for patients with solid cancer (excluding lung cancer) were similar to those of general patients. The hazard risks for mortality within 28 days in patients with lung cancer and hematologic malignancies were similar. After 60 days, a difference in the survival rate and hazard risk for mortality became noticeable between groups in the ICU. The survival rates of patients with other solid cancer (excluding lung cancer) showed a survival pattern closer to that of patients with lung cancer. Between 28 days and 180 days, the survival rate declined rapidly. Three years after admission to the ICU, patients with all types of cancer reached the life expectancy of critically ill patients without cancer. We found that, with the advancement of early cancer diagnosis technology enabling accurate cancer treatment and the development of the ICU, the short-term outcomes of patients with cancer were markedly improved. Nevertheless, the long-term outcomes for five years were 1.56 times higher in critically ill patients with cancer compared to those without cancer.

Our study followed up critically ill patients for a long period of 5 years. Of note, a few limitations should be considered when interpreting the data. Firstly, this study used claims data designed for reimbursement purposes. It was not possible to present these data with standard scoring, such as APACHII or SAPS. Alternatively, the condition of organ failure was assessed using medical resources used for organ failure. There was no information on the performance status before admission to the ICU. This study may have included both low-severity patients and futile cases. Although it is difficult to identify accurate predictors for survival in this study, it is important to realistically assess the demand for ICU in a society where the number of patients with cancer increases. This is because, practically, it is difficult for physicians to actually deny admission to the ICU for patients with acute problems¹⁷. Secondly, we enrolled patients admitted to the ICU based on computed tomography examination. Hence, the present study may include relatively limited data on patients with gastrointestinal alone or genitourinary alone problems. However, this may be of little impact to the overall outcomes of patients with solid cancer, considering that the outcomes of ICU care for most solid cancers, except lung cancer, are similar.

Conclusions

The policy of admission to the ICU for patients with cancer remains unclear. This is because most previous studies reported predictors for survival based on short-term outcomes and involved less-representative populations rather than all patients with cancer. Our study of a relatively representative population can assist physicians in developing a comprehensive understanding of the relatively long-term prognosis of 5 years. In the future, more comprehensive research and interdisciplinary discussions are warranted. Communication and collaboration between the ICU team and oncologists and palliative care specialists should pre-describe clearer ICU admission criteria for patients with cancer and assist in making informed decisions.

Abbreviations

CCI; Charlson Comorbidity Index

CIs; confidence intervals

HRs; hazard ratios

HIRA; Health Insurance Review and Assessment Service

ICU; intensive care unit

ICD-10; International Classification of Diseases 10th revision

Declarations

Ethics approval and consent to participate

The study was reviewed by the Institutional Review Board (IRB) of Kangwon National University Hospital (B-2018-02-002) and was exempted because we only accessed de-identified previously collected administrative data.

Consent for publication

Not applicable

Availability of data and materials

We cannot share our data because of administrative data of Korean government

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Research Foundation of Korea Grant funded by Korean Government (NRF 2020R1A2C1011455)

Authors' contributions

YH and JP are responsible for the conception and design. All the authors were responsible for the data acquisition, analysis and interpretation. YH and JP wrote the first draft of the manuscript. All authors read, provided critical revision, and approved the final manuscript.

Acknowledgements

Not applicable

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Tables

Table 1 Characteristics and outcomes of critically ill patients

Characteristic	Total	With cancer	Without cancer	p
	(N = 323765)	(N = 87936)	(N = 235829)	
Female	128471 (39.7%)	28611 (32.5%)	99860 (42.3%)	0.000
Age, years	66.2 ± 14.4	66.0 ± 12.3	66.3 ± 15.1	0.000
Charlson Comorbidity Index	3.1 ± 2.8	5.5 ± 3.1	2.2 ± 2.0	0.000
Overall follow-up, days	1074.7 ± 988.6	843.6 ± 908.9	1160.9 ± 1003.2	0.000
LOS in ICU, days	16.2 ± 14.3	18.2 ± 14.5	15.4 ± 14.2	0.000
Use of mechanical ventilator	104444 (32.3%)	26222 (29.8%)	78222 (33.2%)	0.000
Renal replacement therapy	21261 (6.0%)	4903 (5.6%)	16358 (6.9%)	0.000
CRRT	11974 (3.7%)	3305 (3.8%)	8669 (3.7%)	0.273
Vasopressor	100836 (31.1%)	26996 (30.7%)	73840 (31.3%)	0.001
Overall mortality	176202 (54.4%)	55388 (63.0%)	120814 (51.2%)	0.000
ICU mortality	47459 (14.7%)	16388 (18.6%)	341071 (13.2%)	0.000
ICU mortality at day 28	50069 (15.5%)	15959 (18.1%)	34110 (14.5%)	0.000
ICU mortality at day 60	68747 (21.2%)	23008 (26.2%)	45739 (19.4%)	0.000
ICU mortality at day 90	77585 (24.0%)	26164 (29.8%)	51421 (21.8%)	0.000
ICU mortality at 6 months	92314 (28.5%)	31349 (35.6%)	60965 (25.9%)	0.000
ICU mortality at 1 year	109618 (33.9%)	37526 (42.7%)	72093 (30.6%)	0.000
ICU mortality at 2 years	130656 (40.4%)	44654 (50.8%)	86002 (36.5%)	0.000
ICU mortality at 3 years	145106 (44.8%)	48662 (55.3%)	96444 (40.9%)	0.000
ICU mortality at 5 years	166595 (51.5%)	53585 (60.9%)	113010 (47.9%)	0.000

CRRT: continuous renal replacement therapy; ICU: intensive care unit; LOS: length of stay

Table 2 Characteristics and outcomes of critically ill patients according to cancer type, except for multiple primaries

	Solid cancer		Hematologic malignancies	p
Characteristic	Lung cancer	Other solid cancers		
	(N = 20902)	(N = 53282)	(N = 4552)	
Female	5770 (27.6%)	18247 (34.2%)	1879 (41.3%)	0.000
Age, years	67.3 ± 10.8	66.0 ± 12.5	60.4 ± 15.3	0.000
Charlson Comorbidity Index	5.5 ± 3.1	5.5 ± 3.1	4.3 ± 2.6	0.000
Interval from diagnosis to ICU	205.1 ± 409.5	357.1 ± 571.0	320.7 ± 514.4	0.000
Overall follow-up	796.2 ± 946.9	887 ± 896.4	383.1 ± 693.2	0.000
LOS in ICU	16.1 ± 12.9	18.8 ± 14.7	22.7±17.3	0.000
Use of mechanical ventilator	6490 (31.0%)	14715 (27.6%)	2483 (54.5%)	0.000
Renal replacement therapy	660 (3.2%)	2878 (5.4%)	1002 (22.0%)	0.000
CRRT	450 (2.2%)	1793 (3.4%)	792 (17.4%)	0.273
Vasopressor	6017 (28.8%)	15799 (29.7%)	2693 (59.2%)	0.001
Overall mortality	13976 (66.9%)	31831 (59.7%)	3736 (82.1%)	0.000
ICU mortality	5322 (25.5%)	7676 (14.4%)	1997 (43.9%)	0.000
ICU mortality at day 28	5291 (25.3%)	7609 (14.3%)	1638 (36.0%)	0.000
ICU mortality at day 60	7363 (35.2%)	11136 (20.9%)	2454 (53.9%)	0.000
ICU mortality at day 90	8145 (39.0%)	12928 (24.3%)	2722 (59.8%)	0.000
ICU mortality at 6 months	9347 (44.7%)	16053 (30.3%)	3051 (67.0%)	0.000
ICU mortality at 1 year	10551 (50.5%)	20125 (37.8%)	3311 (72.7%)	0.000
ICU mortality at 2 years	11796 (56.4%)	24951 (46.8%)	3522 (77.4%)	0.000

ICU mortality at 3 years	12548 (60.0%)	27599 (51.8%)	3602 (79.1%)	0.000
ICU mortality at 5 years	13568 (64.9%)	30710 (57.6%)	3699 (81.3%)	0.000

CRRT: continuous renal replacement therapy; ICU: intensive care unit; LOS: length of stay

Figures

Figure 1

Kaplan-Meier curves of risk for all-cause death in A) ICU and at B) 5 years of each group compared with that of critically ill patients without cancer.

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Kaplan-Meier curves of risk for all-cause death in A) ICU and at B) 5 years of each group compared with that of critically ill patients without cancer.

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Kaplan-Meier curves of risk for all-cause death in A) ICU and at B) 5 years of each group compared with that of critically ill patients without cancer.

Figure 2

Cox regression proportional hazard model analysis of all cause mortality. comparison of critically ill patients without cancer. Adjusted hazard ratios (solid circles) and 95% CIs (horizontal lines) for death. Hazard ratios are adjusted for age, sex, year of admission to the ICU, and use of life support system (such as ventilator, continuous renal replacement therapy, vasopressor).

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Cox regression proportional hazard model analysis of all cause mortality. comparison of critically ill patients without cancer. Adjusted hazard ratios (solid circles) and 95% CIs (horizontal lines) for death. Hazard ratios are adjusted for age, sex, year of admission to the ICU, and use of life support system (such as ventilator, continuous renal replacement therapy, vasopressor).

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