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COVID-19 Mortality and Severity in Cancer Patients and Cancer Survivors

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ABSTRACT

Background: We aimed to investigate mortality, severity, and risk of hospitalization in coronavirus disease 2019 (COVID-19) patients with cancer.

Methods: Data of all patients aged 40–79 years from the Korean Disease Control and Prevention Agency-COVID19-National Health Insurance Service who were diagnosed with COVID-19 between January 1, 2020 and March 31, 2022, in Korea were included. After 1:1 propensity score matching, 397,050 patients with cancer and 397,050 patients without cancer were enrolled in the main analysis. A cancer survivor was defined as a patient who had survived 5 or more years since the diagnosis of cancer. Multiple logistic regression analysis was performed to compare the risk of COVID-19 according to the diagnosis of cancer and time since diagnosis.

Results: Cancer, old age, male sex, incomplete vaccination against COVID-19, lower economic status, and a higher Charlson comorbidity index were associated with an increased risk of hospitalization, hospitalization with severe state, and death. Compared to patients without cancer, the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for hospitalization, hospitalization with severe state, and death in patients with cancer were 1.09 (1.08–1.11), 1.17 (1.11–1.24), and 1.94 (1.84–2.05), respectively. Compared to patients without cancer, the ORs (95% CIs) for hospitalization in cancer survivors, patients with cancer diagnosed 2–5 years, 1–2 years, and < 1 year ago were 0.96 (0.94–0.98), 1.10 (1.07–1.13), 1.30 (1.25–1.34), and 1.82 (1.77–1.87), respectively; the ORs (95% CIs) for hospitalization for severe disease among these patients were 0.90 (0.85–0.97), 1.22 (1.12–1.32), 1.60 (1.43–1.79), and 2.29 (2.09–2.50), respectively.

Conclusion: The risks of death, severe state, and hospitalization due to COVID-19 were higher in patients with cancer than in those without; the more recent the diagnosis, the higher the aforementioned risks. Cancer survivors had a lower risk of hospitalization and hospitalization with severe disease than those without cancer.

Keywords: COVID-19; Cancer; Cancer Survivors; Mortality; Severity



Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Park JM, Lee JY. Data curation: Lee JR. Formal analysis: Lee JR. Investigation: Park JM, Koo HY. Methodology: Park JM, Koo HY. Project administration: Lee H, Lee JY. Resources: Lee H. Software: Lee JR. Supervision: Lee H, Lee JY. Validation: Lee JR. Visualization: Lee JY. Writing - original draft: Park JM. Writing - review & editing: Koo HY, Lee H, Lee JY.

INTRODUCTION

We have been experiencing the coronavirus disease 2019 (COVID-19) pandemic ever since 2020, and patients with cancer have been affected by this disease. Because of the continuation of the pandemic, understanding clinical outcomes in patients with cancer concomitant with COVID-19 has become important from a public health perspective.

Patients with cancer were found to be a vulnerable population during the COVID-19 pandemic. Compared to the general population, they were reportedly admitted to the hospital more often and had more severe manifestations and higher mortality.¹⁻³ Patients with cancer often experience immunosuppression due to their underlying illness, treatment-related side effects, and poor nutrition.⁴⁻⁶ Thus, they are at an increased risk of being admitted to an intensive care unit, developing severe complications, or even dving. Although previous studies suggest that patients with cancer and COVID-19 are more likely to have adverse outcomes, most of these studies are limited by small samples that only comprised patients with cancer currently undergoing treatment.¹⁻³ Moreover, few studies have investigated the outcomes of COVID-19 in patients who were diagnosed with cancer 5 years ago. Cancer survivors, commonly defined as individuals who survived for longer than 5 years, have completed their acute cancer treatment and have unique healthcare needs that are different from those in patients recently diagnosed with cancer.⁷⁻¹⁰ Their care is focused on health promotion and disease prevention for other conditions as well as monitoring for cancer recurrence.^{7,11-13} We hypothesized that cancer survivors would have a better prognosis after COVID-19 than patients with cancer diagnosed less than 5 years ago. Therefore, this study aimed to compare and examine the risk of hospitalization, hospitalized patients due to severe state, and death due to COVID-19 not only in patients with and without cancer using propensity score matching but also according to the time since cancer diagnosis, including those of cancer survivors.

METHODS

Data source

This study used the Korean Disease Control and Prevention Agency-COVID19-National Health Insurance Service (K-COV-N) cohort. The National Health Insurance Service (NHIS), a mandatory health insurance claim run by the government of South Korea, covers nearly the entire South Korean population (> 97%).¹⁴ All healthcare providers are required to submit all treatment data to the NHIS for insurance reimbursement. The Korea Disease Control and Prevention Agency (KDCA) has clinical information on COVID-19-positive patients, as well as vaccination information for the Korean population. The K-COV-N cohort has claims and COVID-19-related data for almost all Koreans obtained by converging data from the NHIS and KDCA. Diagnostic codes were standardized following the 7th version of the Korean Classification of Diseases, a modified version of the 10th edition of the International Classification of Diseases.

In Korea, KDCA manages data on quarantine, test results, confirmation, and vaccination status related to COVID-19. NHIS has information on tests, type of treatment, hospitalization and its duration, and medical expenses that require reimbursement. To promote COVID-19 research, KDCA and NHIS merged both databases and provided access to researchers who had their research projects approved.

All the data used in this study are publicly available. However, all the data used in this study will be made publicly available on the NHIS and KDCA (https://www.nhis.or.kr/nhis/index.do and https://www.kdca.go.kr/). The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No crucial aspects of the study have been omitted, and all discrepancies from the study as planned have been explained.

Data collection

Patients aged 40-79 years who were diagnosed with COVID-19 between January 1, 2020, and March 31, 2022, were included. A total of 397,050 patients with cancer and 3,460,985 patients without cancer were included. After 1:1 propensity score matching, 397,050 patients with cancer and 397,050 patients without cancer were enrolled in the main analysis. A cancer diagnosis was defined as a C code in the International Classification of Diseases 10th Revision (ICD-10), and the day wherein the C code was first entered as the date of diagnosis. Cases with cancer recurrence and those with multiple primary or secondary cancers were excluded. Time since cancer diagnosis was defined as the period from the date of cancer diagnosis to the date of COVID-19 diagnosis. Cancer types were stratified into solid cancers (C00-C80 and C97-C99) and hematologic cancers (C81-C96). A cancer survivor was defined as a patient who had survived ≥ 5 years since the diagnosis of cancer.⁷⁻¹⁰ COVID-19 vaccination was classified as complete if two or more doses were administered, regardless of the type of vaccination, or if one or more doses were received in the case of Janssen, and incomplete if less than one dose was received. Then, we extracted data on age, sex, insurance premiums, Charlson comorbidity index (CCI), hospitalization, severity, and death. For patients with cancer, we further extracted the time since cancer diagnosis and cancer type. We classified household income levels based on health insurance premiums because health insurance premiums are set in proportion to income. The CCI was calculated based on ICD-10 codes from 2019 as a weighted sum of comorbidities, and the CCI was calculated by excluding cancer in patients with cancer.¹⁵ We classified severity as ambulatory state, hospitalization with mild state, or hospitalization with severe state using the COVID-19 severity scale by the World Health Organization.¹⁶ Hospitalization with mild state included no oxygen therapy or oxygen delivered using mask or nasal prongs. Hospitalization with severe state included non-invasive ventilation, high-flow oxygen, intubation and mechanical ventilation, as well as ventilation combined with additional organ support such as dialysis and extracorporeal membrane oxygenation.^{16,17} The scale indicates the clinical severity of the disease and can be used during any infectious disease epidemic^{16,17}; we conducted a previous study using this classification.18

Statistical analysis

First, we analyzed the characteristics of patients with COVID-19 with and without cancer before and after propensity score matching by frequency and percentage. Then, propensity score matching analysis was performed to minimize the probability of selection bias between patients with and without cancer. The propensity score was then generated using multiple logistic regression models, including age, sex, vaccination against COVID-19, and household income. We used the nearest available matching (1:1) method to estimate the propensity score using a caliper of 0.25. Balance was assessed by a standardized mean difference of < 0.1 after matching.

Statistical differences in the severity of COVID-19 between patients with and without cancer were evaluated using the chi-square test.

The odds ratios (ORs) and confidence intervals (CIs) for hospitalization, hospitalization with severe state, and death due to COVID-19 were calculated using multiple logistic regression analyses after adjusting for confounding factors, including group (patients with cancer and without cancer), age, sex, vaccination against COVID-19, household income, and CCI. All the analyses were performed using SAS Enterprise Guide version 8.2 (SAS Institute, Cary, NC, USA) and R version 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement

The Institutional Review Board of the Seoul National University Bundang Hospital approved this study (approval number: X-2207-768-901) and was conducted in accordance with the Declaration of Helsinki. The requirement to obtain informed consent from participants was waived as this was an observational study with an anonymized dataset.

RESULTS

Table 1 presents the characteristics of patients with COVID-19 with and without cancer before and after propensity score matching. Comparing the standardized mean difference between individual covariates, including age, sex, vaccination against COVID-19, and household income, those with cancer and controls showed a good covariate balance (standardized mean difference < 0.1). Of the total matched groups, men accounted for 42.4% and 44.6% in the cancer and control groups, respectively. The proportions of vaccinations for COVID-19

Table 1. Characteristics of COVID-19 patients with and without cancer in Korea before and after propensity score matching

Characteristics	Before prop	Before propensity score matching			After propensity score matching		
	Patients with cancer	Patients without cancer	SMD	Patients with cancer	Patients without cancer	SMD	
	(n = 397,050)	(n = 3,460,985)		(n = 397,050)	(n = 397,050)		
Age (yr)			0.46			0.023	
40-49	71,099 (17.9)	1,180,495 (34.1)		71,099 (17.9)	69,752 (17.6)		
50-59	107,031 (27.0)	1,041,792 (30.1)		107,031 (27.0)	107,745 (27.1)		
60-69	132,758 (33.4)	860,530 (24.9)		132,758 (33.4)	136,115 (34.3)		
70-79	86,162 (21.7)	378,168 (10.9)		86,162 (21.7)	83,438 (21.0)		
Sex			0.027			0.048	
Female	229,638 (57.8)	1,955,213 (56.5)		229,638 (57.8)	220,147 (55.4)		
Male	167,412 (42.2)	1,505,772 (43.5)		167,412 (42.2)	176,903 (44.6)		
Household income			0.035			0.082	
High	190,924 (48.1)	1,612,171 (46.6)		190,924 (48.1)	174,647 (44.0)		
Middle	105,328 (26.5)	967,101 (27.9)		105,328 (26.5)	113,201 (28.5)		
Low	100,798 (25.4)	881,713 (25.5)		100,798 (25.4)	109,202 (27.5)		
Charlson comorbidity Index			0.299			0.155	
0-1	225,507 (56.8)	2,441,499 (70.5)		225,507 (56.8)	254,788 (64.2)		
2	78,195 (19.7)	530,291 (15.32)		78,195 (19.7)	68,554 (17.3)		
≥ 3	93,348 (23.5)	489,195 (14.13)		93,348 (23.5)	73,708 (18.5)		
Vaccination for COVID-19			0.085			0.004	
Complete	371,059 (93.5)	3,303,477 (95.4)		371,059 (93.5)	370,315 (93.3)		
Incomplete	25,991 (6.5)	157,508 (4.5)		25,991 (6.5)	26,735 (6.7)		
Time since cancer diagnosis							
≥ 5 yr	232,735 (58.6)			232,735 (58.6)			
2–5 yr	91,082 (22.9)			91,082 (22.9)			
1–2 yr	32,899 (8.3)			32,899 (8.3)			
< 1 yr	40,334 (10.2)			40,334 (10.2)			
Cancer type							
Solid	385,680 (97.1)			385,680 (97.1)			
Hematologic	11,723 (2.9)			11,723 (2.9)			

Data are presented as number (%).

COVID-19 = coronavirus disease 2019, SMD = standardized mean difference.

completion were 93.5% in the cancer group and 93.3% in the control group. Moreover, 58.6%, 22.9%, 8.3%, and 10.2% of the patients with cancer were diagnosed \geq 5 years, 2–5 years, 1–2 years, and < 1 year from the time of cancer diagnosis, respectively. In patients with cancer, the proportions of solid and hematologic cancers were 97.1% and 2.9%, respectively.

Table 2 shows the severity of COVID-19 among patients with and without cancer. Among those with cancer, 11.1% were hospitalized and 1.0% died, whereas among those without cancer, 10.2% were hospitalized and 0.5% died. Patients with cancer had significantly higher hospitalization and death rates than those without cancer (P < 0.001).

Table 3 presents the logistic regression models for severity, including those adjusted for hospitalization, hospitalization with severe state, and mortality. Cancer, older age, male sex, incomplete vaccination against COVID-19, lower household income, and higher CCI were associated with an increased risk of hospitalization, severe hospitalization, and death. Compared to the patients without cancer, ORs (95% CIs) for hospitalization, hospitalization with severe state, and death in the patients with cancer were 1.09 (1.08–1.11), 1.17 (1.11–1.24),

Table 2. Severity of COVID-19 in patients with and without cancer

Characteristics	Patients with cancer (n = 397,050)	Patients without cancer (n = 397,050)	P value
Total number of hospitalization	44,074 (11.1)	40,428 (10.2)	< 0.001
COVID-19 severity			< 0.001
Ambulatory state	352,184 (88.7)	356,303 (89.7)	
Hospitalization with mild state	39,308 (9.9)	37,075 (9.4)	
Hospitalization with severe state	1,543 (0.4)	1,562 (0.4)	
Death	4,015 (1.0)	2,110 (0.5)	

Data are presented as number (%).

P values are obtained by using chi-squared test.

COVID-19 = coronavirus disease 2019.

Table 3. ORs and 95% confidence intervals for hospitalization, hospitalization with sever state, and death
according to cancer diagnosis, age, sex, vaccination against COVID-19, household income, and CCI

(Reference) (1.08-1.11) (Reference) (1.19-1.25)	1 (Reference) 1.17 (1.11-1.24) 1 (Reference)	1 (Reference) 1.94 (1.84–2.05) 1 (Reference)
(1.08-1.11) (Reference)	1.17 (1.11-1.24) 1 (Reference)	1.94 (1.84–2.05)
(Reference)	1 (Reference)	. ,
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(1.19-1.25)		
	1.79 (1.52–2.12)	2.48 (2.07-2.96)
(1.35-1.42)	4.71 (4.06-5.47)	4.89 (4.14-5.77)
(2.20-2.31)	8.97 (7.70-10.39)	14.07 (11.94-16.58)
(Reference)	1 (Reference)	1 (Reference)
(1.30-1.34)	2.11 (1.99-2.23)	2.20 (2.08-2.32)
(Reference)	1 (Reference)	1 (Reference)
(4.47-4.66)	16.09 (15.25-16.99)	16.73 (15.87-17.63)
(Reference)	1 (Reference)	1 (Reference)
(1.12-1.17)	1.06 (1.00-1.14)	1.18 (1.11-1.26)
(1.33-1.38)	1.15 (1.08-1.23)	1.33 (1.25-1.41)
(Reference)	1 (Reference)	1 (Reference)
(1.11-1.16)	1.22 (1.13-1.32)	1.25 (1.16-1.34)
(1.53-1.59)	1.88 (1.76-2.00)	2.03 (1.91-2.15)
	(1.19-1.25) (1.35-1.42) (2.20-2.31) (Reference) (1.30-1.34) (Reference) (4.47-4.66) (Reference) (1.12-1.17) (1.33-1.38) (Reference) (1.11-1.16) (1.53-1.59)	(1.35-1.42) 4.71 (4.06-5.47) (2.20-2.31) 8.97 (7.70-10.39) (Reference) 1 (Reference) (1.30-1.34) 2.11 (1.99-2.23) (Reference) 1 (Reference) (4.47-4.66) 16.09 (15.25-16.99) (Reference) 1 (Reference) (1.12-1.17) 1.06 (1.00-1.14) (1.33-1.38) 1.15 (1.08-1.23) (Reference) 1 (Reference) (1.11-1.16) 1.22 (1.13-1.32)

ORs are adjusted for group, age, sex, vaccination against COVID-19, household income, and CCI. OR = odds ratio, COVID-19 = coronavirus disease 2019, CCI = Charlson Comorbidity Index.

Table 4. Odds ratios and 95% confidence intervals for hospitalization, hospitalization with severe state, an	d
death according to time since cancer diagnosis and cancer type	

Characteristics	Hospitalization	Hospitalization with severe state	Death
Time since cancer diagnosis			
Patients without cancer	1 (Reference)	1 (Reference)	1 (Reference)
≥ 5 yr (cancer survivor)	0.96 (0.94-0.98)	0.90 (0.85-0.97)	1.24 (1.16-1.32)
2–5 yr	1.10 (1.07-1.13)	1.22 (1.12-1.32)	1.90 (1.76-2.06)
1–2 yr	1.30 (1.25-1.34)	1.60 (1.43-1.79)	3.04 (2.76-3.35)
< 1 yr	1.82 (1.77-1.87)	2.29 (2.09-2.50)	4.95 (4.60-5.34)
Cancer type			
Patients without cancer	1 (Reference)	1 (Reference)	1 (Reference)
Solid cancer	1.08 (1.07-1.10)	1.11 (1.06-1.18)	1.85 (1.76-1.95)
Hematologic cancer	1.72 (1.36-1.81)	3.18 (2.78-3.64)	3.85 (3.35-4.42)

and 1.94 (1.84–2.05) after adjusting for age, sex, vaccination against COVID-19, household income, and CCI.

Table 4 shows ORs for hospitalization, hospitalization with severe state, and death according to time since cancer diagnosis and cancer type. A more recent cancer diagnosis was associated with an increased risk of hospitalization. Cancer survivors were associated with a decreased risk of hospitalization and hospitalized severely. Compared to the patients without cancer, the ORs (95% CIs) for hospitalization in cancer survivors, patients with cancer diagnosed 2-5 years ago, those diagnosed 1-2 years ago, and those diagnosed < 1 year ago were 0.96 (0.94–0.98), 1.10 (1.07–1.13), 1.30 (1.25–1.34), and 1.82 (1.77–1.87), respectively. Moreover, compared to the patients without cancer, the ORs (95% CIs) for hospitalization with severe state in cancer survivors, those with cancer diagnosed 2-5 years ago, 1-2 years ago, and < 1 year ago, were 0.90 (0.85-0.97), 1.22 (1.12-1.32), 1.60 (1.43-1.79), and 2.29 (2.09–2.50), respectively. Hematologic cancer was associated with an increased risk of hospitalization, hospitalization for severe disease, and death. Compared with patients without cancer, the ORs (95% CIs) for hospitalization for solid and hematologic cancer were 1.08 (1.07-1.10) and 1.72 (1.36-1.81), respectively. Additionally, compared to those without cancer, the ORs (95% CIs) for hospitalization with severe state among patients with solid and hematologic cancers were 1.11 (1.06-1.18) and 3.18 (2.78-3.64), respectively. Furthermore, hematologic cancers are associated with an increased risk of death. Compared to patients without cancer, the ORs (95% CIs) for death among those with solid and hematologic cancers were 1.85 (1.76-1.95) and 3.85 (3.35-4.42), respectively.

DISCUSSION

In this real-world, large-scale, nationwide, population-based study, we found that the risk of hospitalization, hospitalization for severe disease, and death due to COVID-19 was higher in patients with cancer than in those without cancer after adjusting for confounding variables. Moreover, a more recent cancer diagnosis was associated with an increased risk of hospitalization, severe hospitalization, and death. Cancer survivors, individuals diagnosed with cancer \geq 5 years ago, had lower rates of hospitalization and hospitalization for severe disease than those without cancer. Furthermore, patients with hematologic cancer have a higher risk of hospitalization, severe disease, and death than those with solid cancers.

Our findings are consistent with the results of previous studies, wherein patients with cancer have a higher rate of hospital admission, severe disease status, and mortality than those

without cancer.¹³ Furthermore, patients with hematologic cancers are more vulnerable to COVID-19 than those with solid cancers.^{19,20} Additionally, our results suggest that among patients with cancer, the risk of hospitalization, severe status, and death differs depending on the time of cancer diagnosis. In particular, cancer survivors had a lower risk of hospitalization and hospitalization for severe disease after COVID-19 compared to those without cancer. Previous studies were limited by small sample sizes, including patients with cancer currently undergoing treatment, and few studies have investigated the outcomes of COVID-19 in cancer survivors. To our knowledge, this is the first large-scale nationwide study to compare and examine the risk of hospitalization, hospitalization with severe state, and death due to COVID-19 not only in patients with and without cancer using propensity score matching but also according to the time since cancer diagnosis, including those of cancer survivors. Thus, our results expand on earlier findings on the clinical outcomes in patients with cancer and COVID-19.

With the increase in the number of cancer survivors, comprehensive care for cancer survivors, including lifestyle modification and chronic disease management, has been suggested and implemented in Korea for the last decade.^{12,21,22} Cancer survivors are more likely to have better access to knowledge on health such as cessation or reduction of smoking and drinking, vaccination, and improvements in exercise and nutrition.²² The smoking rate of cancer survivors in Korea is 6.7–9.6%, much lower than in the overall smoking rate in Korea, which is about 20%.^{23,24} Previous studies showed that active smoking was related to increased risk of COVID-19 progression towards severe disease.^{25,26} Furthermore, cancer survivors are considered to be under better hypertension control than the general population because they were more likely to engage in better hypertension management behavior.²⁷ Because higher uncontrolled blood pressure could contribute to a more severe disease course,²⁸ relatively well-controlled chronic diseases such as hypertension may have lowered the risk of hospitalization and hospitalization for severe disease after COVID-19. In addition, according to a study conducted on cancer patients in Korea, cancer survivors were more willing to receive the COVID-19 vaccine than other groups.²⁹

This study also showed that older age, lower economic status, and incomplete vaccination against COVID-19 were associated with an increased risk of hospitalization, severe hospitalization, and death due to COVID-19. These findings are in agreement with those of previous studies,³⁰⁻³³ further confirming the reliability of this study. Although there has been controversy about vaccination against COVID-19, it seems clear that vaccination against COVID-19 has reduced the hospitalization, severe hospitalization, and death due to COVID-19 in Korea.

This study found that patients with hematologic malignancies had a significantly increased risk of hospitalization, severe disease, and death compared with patients with solid cancers, which may be because of the immune dysfunction in this group of patients. Hematologic cancers, including lymphoma and leukemia, can directly affect the immune system. T-cell exhaustion and senescence are the main features associated with immune dysfunction in hematologic cancers.³⁴ Since the recruitment of immune cell populations could play a key role in COVID-19 recovery, dysregulation of the immune response in patients with hematologic diseases could be a mechanism underlying this finding.^{34,35}

Moreover, we found that men had a significantly increased risk of hospitalization, severe disease, and death than women, which was frequently the case in various other studies.^{20,36} Possible mechanisms associated with this relationship include Type II Transmembrane

Serine Protease (TMPRSS2) and Angiotensin-Converting Enzyme 2 (ACE2). COVID-19 infectivity depends on its entry via the binding of its viral spike (S) protein to the ACE2 receptor and on the S protein priming by TMPRSS2, which is upregulated by androgens.^{37,38}

This study had some limitations. First, since it is based on an insurance claims database (NHIS database), which provides limited information on patients and does not include all medical records, information on clinical manifestations of COVID-19 and the course of cancer treatment was not available. Second, because this was a retrospective observational study based on the claims database, several possible biases exist, including selection and coding biases, and it is possible that residual confounders remain. Insurance reimbursement policies may influence the coding practice of medical institutions. Moreover, according to the type of medical institute, there may be differences in coding practice. Nevertheless, regardless of the limitations of the claims database, since COVID-19 is an infectious disease monitored by the government and all the affected patients have been identified, there is expected to be little omission in coding, testing, or treatment methods. Third, we were unable to analyze the effect of immunosuppressant treatment on the outcomes of patients with cancer and COVID-19 because this information was not collected. Fourth, we compared solid cancer and hematologic cancer, but we did not analyze each cancer type separately; hence, it was difficult to identify the differences between cancer types. Lastly, we did not analyze the data according to the type of vaccine administered. Further research is needed on the mortality, severity, and risk of hospitalization of COVID-19 patients with cancers according to the type of vaccine and the number of doses administered.

Despite these potential limitations, we believe that our findings have clinical implications for public health strategies in that it confirms the risk by examining the results according to the period after the cancer diagnosis, including cancer survivors, rather than simply comparing cancer patients to normal individuals. Thus, we conducted a large population-based study using real-world data from nearly the entire South Korean population. Moreover, to minimize confounding factors, age, sex, household income, CCI, and vaccination against COVID-19 were matched using the propensity score and adjusted for in multiple logistic regression analyses.

In conclusion, in this real-world, large-scale, nationwide population-based study, the risk of hospitalization, hospitalization for severe disease, and death due to COVID-19 was higher in patients with cancer than in those without cancer. Moreover, a more recent cancer diagnosis was associated with an increased risk of hospitalization, hospitalization with severe state, and death. Cancer survivors were associated with a decrease in hospitalization and hospitalization for severe state. Patients with cancer and COVID-19 require special attention, especially those recently diagnosed with cancer because they represent a vulnerable population with a higher case fatality rate than those without cancer.

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- The KDCA is the Korea Disease Control and Prevention Agency, Republic of Korea.
- The NHIS is the National Health Insurance Service, Republic of Korea.

REFERENCES

- Costa GJ, de Azevedo CRAS, Júnior JIC, Bergmann A, Thuler LCS. Higher severity and risk of in-hospital mortality for COVID-19 patients with cancer during the year 2020 in Brazil: a countrywide analysis of secondary data. *Cancer* 2021;127(22):4240-8.
 PUBMED | CROSSREF
- de Azambuja E, Brandão M, Wildiers H, Laenen A, Aspeslagh S, Fontaine C, et al. Impact of solid cancer on in-hospital mortality overall and among different subgroups of patients with COVID-19: a nationwide, population-based analysis. *ESMO Open* 2020;5(5):e000947.
- Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21(3):335-7.
 PUBMED | CROSSREF
- 4. Yürekli A, Erbaş O. Cancer and immunosuppression. J Exp Basic Med Sci 2021;2(2):116-21.
- Zhang Y, Rajput A, Jin N, Wang J. Mechanisms of immunosuppression in colorectal cancer. *Cancers (Basel)* 2020;12(12):3850.
 PUBMED | CROSSREF
- Oh SE, Choi MG, Seo JM, An JY, Lee JH, Sohn TS, et al. Prognostic significance of perioperative nutritional parameters in patients with gastric cancer. *Clin Nutr* 2019;38(2):870-6.
 PUBMED | CROSSREF
- Jeong W, Park EC, Nam CM, Park S, Nam JY, Jang SI. Health behavior changes and mortality among South Korean cancer survivors. *Sci Rep* 2022;12(1):16011.
 PUBMED | CROSSREF
- Johnson C, Krakow M, Patel V. Access and Use of Electronic Health Information by Individuals with Cancer: 2017–2018. Washington, D.C., USA: Office of the National Coordinator for Health Information Technology; 2020.
- Marzorati C, Riva S, Pravettoni G. Who is a cancer survivor? A systematic review of published definitions. *J Cancer Educ* 2017;32(2):228-37.
 PUBMED | CROSSREF
- Chopra I, Kamal KM. A systematic review of quality of life instruments in long-term breast cancer survivors. *Health Qual Life Outcomes* 2012;10(1):14.
 PUBMED | CROSSREF
- Lee JW, Yeo Y, Ju HY, Cho HW, Yoo KH, Sung KW, et al. Current status and physicians' perspectives of childhood cancer survivorship in Korea: a nationwide survey of pediatric hematologists/oncologists. *J Korean Med Sci* 2023;38(29):e230.
 PUBMED | CROSSREF
- Lee JE, Shin DW, Lee H, Son KY, Kim WJ, Suh YS, et al. One-year experience managing a cancer survivorship clinic using a shared-care model for gastric cancer survivors in Korea. *J Korean Med Sci* 2016;31(6):859-65.
 PUBMED | CROSSREF
- Bober SL, Recklitis CJ, Campbell EG, Park ER, Kutner JS, Najita JS, et al. Caring for cancer survivors: a survey of primary care physicians. *Cancer* 2009;115(18 Suppl):4409-18.
- Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2017;46(3):799-800.
 PUBMED | CROSSREF
- Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson comorbidity index: ICD-9 update and ICD-10 translation. *Am Health Drug Benefits* 2019;12(4):188-97.
- World Health Organization. COVID-19 therapeutic trial synopsis. https://www.who.int/publications/i/ item/covid-19-therapeutic-trial-synopsis. Updated 2020. Accessed June 23, 2023.
- WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020;20(8):e192-7.
 PUBMED | CROSSREF
- Lee H, Sung HK, Lee D, Choi Y, Lee JY, Lee JY, et al. Comparison of complications after coronavirus disease and seasonal influenza, South Korea. *Emerg Infect Dis* 2022;28(2):347-53.
 PUBMED | CROSSREF
- Başcı S, Ata N, Altuntaş F, Yiğenoğlu TN, Dal MS, Korkmaz S, et al. Patients with hematologic cancers are more vulnerable to COVID-19 compared to patients with solid cancers. *Intern Emerg Med* 2022;17(1):135-9.
 PUBMED | CROSSREF

- Russell B, Moss CL, Shah V, Ko TK, Palmer K, Sylva R, et al. Risk of COVID-19 death in cancer patients: an analysis from Guy's Cancer Centre and King's College Hospital in London. *Br J Cancer* 2021;125(7):939-47.
 PUBMED | CROSSREF
- 21. Shin DW, Sunwoo S, Lee J. Management of cancer survivors in Korea. J Korean Med Assoc 2015;58(3):216-26. CROSSREF
- Yang YS, Kimm H, Jung KJ, Moon S, Lee S, Jee SH. Prediction of cancer survivors' mortality risk in Korea: a 25-year nationwide prospective cohort study. *Epidemiol Health* 2022;44:e2022075.
 PUBMED | CROSSREF
- 23. National Cancer Center. Management of Cancer Survivors. Goyang: National Cancer Center; 2015.
- 24. Trends in the prevalence of current cigarette smoking, 2012–2021. *Public Health Wkly Rep* 2023;16(20):632-3. CROSSREF
- He Y, He Y, Hu Q, Yang S, Li J, Liu Y, et al. Association between smoking and COVID-19 severity: a multicentre retrospective observational study. *Medicine (Baltimore)* 2022;101(29):e29438.
 PUBMED | CROSSREF
- Mohsin FM, Tonmon TT, Nahrin R, Tithy SA, Ame FA, Ara I, et al. Association between smoking and COVID-19 severity: evidence from Bangladesh. *J Multidiscip Healthc* 2021;14:1923-33.
 PUBMED | CROSSREF
- Wook Shin D, Young Kim S, Cho J, Kook Yang H, Cho B, Nam HS, et al. Comparison of hypertension management between cancer survivors and the general public. *Hypertens Res* 2012;35(9):935-9.
 PUBMED | CROSSREF
- Gallo G, Calvez V, Savoia C. Hypertension and COVID-19: current evidence and perspectives. *High Blood Press Cardiovasc Prev* 2022;29(2):115-23.
 PUBMED | CROSSREF
- Chun JY, Kim SI, Park EY, Park SY, Koh SJ, Cha Y, et al. Cancer patients' willingness to take COVID-19 vaccination: a nationwide multicenter survey in Korea. *Cancers (Basel)* 2021;13(15):3883.
 PUBMED | CROSSREF
- Romero Starke K, Reissig D, Petereit-Haack G, Schmauder S, Nienhaus A, Seidler A. The isolated effect of age on the risk of COVID-19 severe outcomes: a systematic review with meta-analysis. *BMJ Glob Health* 2021;6(12):e006434.
 PUBMED | CROSSREF
- Kofahi HM, Swedan SF, Khabour OF, Nimer RM. Predictors of COVID-19 severity and hospitalization: a survey-based study from Jordan. *Inform Med Unlocked* 2022;31:100994.
 PUBMED | CROSSREF
- 32. Arceo-Gomez EO, Campos-Vazquez RM, Esquivel G, Alcaraz E, Martinez LA, Lopez NG. The income gradient in COVID-19 mortality and hospitalisation: an observational study with social security administrative records in Mexico. *Lancet Reg Health Am* 2022;6:100115.
 PUBMED | CROSSREF
- 33. Kim YY, Choe YJ, Kim J, Kim RK, Jang EJ, Lee H, et al. Vaccine effectiveness against severe disease and death for patients with COVID-19 during the delta-dominant and omicron-emerging periods: a K-COVE Study. J Korean Med Sci 2023;38(11):e87. PUBMED | CROSSREF
- 34. Tang L, Wu J, Li CG, Jiang HW, Xu M, Du M, et al. Characterization of immune dysfunction and identification of prognostic immune-related risk factors in acute myeloid leukemia. *Clin Cancer Res* 2020;26(7):1763-72.
 PUBMED | CROSSREF
- 35. Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nat Med* 2020;26(4):453-5.
 PUBMED | CROSSREF
- Pivonello R, Auriemma RS, Pivonello C, Isidori AM, Corona G, Colao A, et al. Sex disparities in COVID-19 severity and outcome: are men weaker or women stronger? *Neuroendocrinology* 2021;111(11):1066-85.
 PUBMED | CROSSREF
- Mjaess G, Karam A, Aoun F, Albisinni S, Roumeguère T. COVID-19 and the male susceptibility: the role of ACE2, TMPRSS2 and the androgen receptor. *Prog Urol* 2020;30(10):484-7.
- Chakravarty D, Nair SS, Hammouda N, Ratnani P, Gharib Y, Wagaskar V, et al. Sex differences in SARS-CoV-2 infection rates and the potential link to prostate cancer. *Commun Biol* 2020;3(1):374.
 PUBMED | CROSSREF