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Original Article

Risk Predictors for Mortality in Inpatients with Cancer and Coronavirus Disease 2019 during the Omicron Wave

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Abstract

Background: Patients with cancer are a high-risk population in the coronavirus disease 2019 (COVID-19) pandemic. We analyzed the characteristics and risk factors for mortality in hospitalized patients with cancer and laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the Omicron wave. **Materials and Methods:** We conducted a retrospective, single-center, cohort study of 206 patients with cancer and SARS-CoV-2 infection in southern Taiwan. Clinical characteristics, laboratory data, and cancer characteristics were compared between survivors and nonsurvivors. Risk factors for mortality were identified by univariable and multivariable logistic regression models. **Results:** The median patient age was 69.5 years. Male preponderance was noted (65%). Comorbidities were present in 186 (90%) cases. A total of 113 (54%) patients had active cancer. Metastatic disease accounted for 78 (38%) cases, of whom 19 (9%) had lung metastasis. Sixty-four (31%) patients had active and progressing cancer status. The overall inhospital mortality rate was 17.4%. Univariate logistic regression revealed the following factors to be significantly associated with a higher risk of inhospital mortality among the patients with cancer and COVID-19: nosocomial COVID-19 infection ($P = 0.037$), lung metastasis ($P = 0.005$), received anticancer therapy in the preceding 3 months ($P = 0.083$), active and progressing cancer ($P = 0.008$), and quick Sequential Organ Function Assessment (qSOFA) score ≥2 ($P < 0.001$). However, only nosocomial infection ($P = 0.021$) and qSOFA score ≥2 ($P < 0.001$) were independent predictors of inhospital mortality in the multivariate logistic regression analysis. **Conclusion:** Cancer patients are a population vulnerable to the Omicron variant with higher mortality rate, especially those with nosocomial COVID-19 infection and those with a qSOFA score of ≥2 immediately after confirmation of COVID-19 infection. Thus, the rapid recognition of high-risk groups and nosocomial infection control are critical to prevent COVID-19 in patients with cancer.

Keywords: Cancer, coronavirus disease 2019, hospital acquired, mortality, nosocomial, the Omicron variant

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Introduction

In late 2019, a novel beta-coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China. This virus had high transmission and mutation rates and led to multiple outbreaks worldwide, eventually resulting in a pandemic. At the time of writing, more than 750 million cases and more than 6.5 million deaths due to coronavirus disease 2019 (COVID-19) have been reported.[1]

Patients with cancer are particularly vulnerable to COVID-19 because their immune systems may be fragile owing to either the cancer itself or anticancer treatment. Moreover, such patients may have other risk factors – such as advanced age, multiple comorbidities, smoking history, or obesity – any of which might increase the severity of COVID-19.[2] However, discrepancies in risk factor prediction have been reported for severe COVID-19-related outcomes in patients with cancer.[3-6]

Owing to appropriate border controls, mandatory quarantine, and epidemic prevention measures, Taiwan did not face a community-level outbreak of COVID-19 until May 2021 that outbreak then continued through 2022. On April 8, 2022, the Taiwanese government replaced its zero COVID-19 policy with the "new Taiwanese model." Till January 2023, Taiwan had 9 million confirmed cases of COVID-19 and as many as 15,000 deaths,[7] with the dominant strain being the Omicron variant.[8] The Omicron variant has high transmissibility but causes a milder disease than the other variants. However, the true pathogenicity of COVID-19 in patients with cancer remains questionable,[9] and few studies have investigated this issue.

This retrospective study is the first conducted in Taiwan to analyze the characteristics and risk factors for mortality in hospitalized patients with cancer and laboratory-confirmed SARS-CoV-2 infection during the Omicron wave.

Materials and Methods

Study design and participants

In this single-center, retrospective cohort study, we enrolled patients with solid or hematologic cancer and SARS-CoV-2 infection who were hospitalized in a medical center in Taiwan between January 1 and September 30, 2022. Based on a preprint study,[8] the dominant variants of SARS-CoV-2 infection were BA.1 and BA.2.3.7 during this period.

SARS-CoV-2 was identified based on positive real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR) tests from nasal or pharyngeal specimens obtained from patients suspected of having COVID-19 in an emergency department or on a ward. The institutional review board of hospital approved this study (Number: 11111-007, date: 2022-10-13). Informed consent was waived by the IRB.

Data collection and outcomes

The patients' clinical characteristics, oncological conditions, laboratory data, vaccine status, and clinical outcomes were obtained from the hospital's electronic medical records. At the emergency department, the laboratory data were obtained if clinically indicated. At the ward, the laboratory data were obtained after COVID-19 infection was confirmed. The quick Sequential Organ Function Assessment (qSOFA) score was calculated immediately after confirmation of the COVID-19 infection. These characteristics were compared between survivors and nonsurvivors.

The primary outcome was the inhospital mortality rate, and the secondary outcomes were risk factors for mortality in patients with cancer and COVID-19.

Definitions

We defined "full vaccination" status as having received at least two doses of vaccines approved by Taiwan's National Health Insurance Administration. Nosocomial COVID-19 infection was defined as an RT-PCR diagnosis made >7 days after admission or emergency department arrival based on the National Health Service National Service Scotland and Public Health Scotland (UK).[10] The qSOFA scoring system was used to identify patients outside intensive care units with suspected infection who were at a high risk of inhospital mortality; according to this model, 1 point each was assigned to a Glasgow Coma Scale score of ≤13, systolic blood pressure of ≤100 mmHg, and respiratory rate of ≥22/min (total score: 0–3).[11] The severity of COVID-19 infection was categorized into mild, moderate, severe, and critical disease based on the COVID-19 Treatment Guidelines of NIH.[12]

Statistical analysis

IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp was used for all statistical analyses. Continuous variables were evaluated using the Kolmogorov–Smirnov test of normality and are presented as median values (interquartile ranges). Categorical variables are presented as percentages or absolute values. The Mann-Whitney *U*-test and Chi-squared test were used for between-group comparisons. A logistic regression model was built to explore the potential risk factors for inhospital mortality among patients with cancer and COVID-19. Variables with $P < 0.1$ in the univariate analysis were included in the multivariate analysis, and $P < 0.05$ was set as statistically significant. Laboratory data were not chosen for the logistic regression model because such data are easily influenced by multiple factors. All tests were two-sided with <5% Type I error. Between-group differences were considered significant at $P < 0.05$.

Results

Clinical characteristics and mortality

We enrolled 206 patients with cancer who had a positive RT-PCR test for SARS-CoV-2. The most recently hospitalized patient was discharged on December 5, 2022. The enrolled patients' clinical demographic features are summarized in Table 1.

The median patient age was 69.5 years (range: 60–79.25 years), and male preponderance was noted (65%). Of the patients, 25.5% and 8.8% were former and current smokers, respectively. Moreover, 186 (90%) patients had at least one comorbidity, with the most common being cardiovascular disease (37%; including coronary artery disease, hypertension, and heart failure) and type 2 diabetes mellitus (27%).

Of the patients, 20% had hospital-acquired infection, and 80% had community-acquired infection. In addition, 53.4% were not fully vaccinated, and 46.6% were fully vaccinated or had also received a booster dose. The severity of COVID-19 was mild in 41% of the patients, moderate in 35%, severe in 17%, and critical in 7%. The qSOFA scores immediately after diagnosis were ≤1 in 86.4% of the patients and ≥2 in the remaining 13.6%. The median length of hospital stay was 13 days (interquartile range: 8–23 days). Thirty-six patients died during the follow-up period (nonsurvivors), and the overall inhospital mortality rate was 17.4%. Figure 1 shows the proportion of disease severity based on qSOFA score and COVID-19 clinical severity index between those with hospital-acquired infection and those with community-acquired infection.

Compared with the survivors, the nonsurvivors were older and had a higher prevalence of nosocomial COVID-19 infection, more severe COVID-19, a higher qSOFA score, and a longer length of hospital stay. Of these factors, nosocomial COVID-19 infection ($P = 0.034$) and qSOFA score ($P < 0.001$) were significantly different. However, no significant differences were observed in age, sex distribution, or comorbidities.

Oncological characteristics

Information regarding the oncological status of the patients is summarized in Table 2. The type of cancer was solid tumor in 96% of the patients and hematological malignancy in 4%. Colorectal cancer was the most frequent type (13%), followed by lung cancer (12%) and then head-and-neck cancer (10%). Seventy-eight patients (36%) had stage IV cancer, and 19 (9%) had lung metastasis. A total of 113 (54%) patients had active cancer, and 93 (45%) had received anticancer therapy in the preceding 3 months; the most common treatment type was chemotherapy (25%).

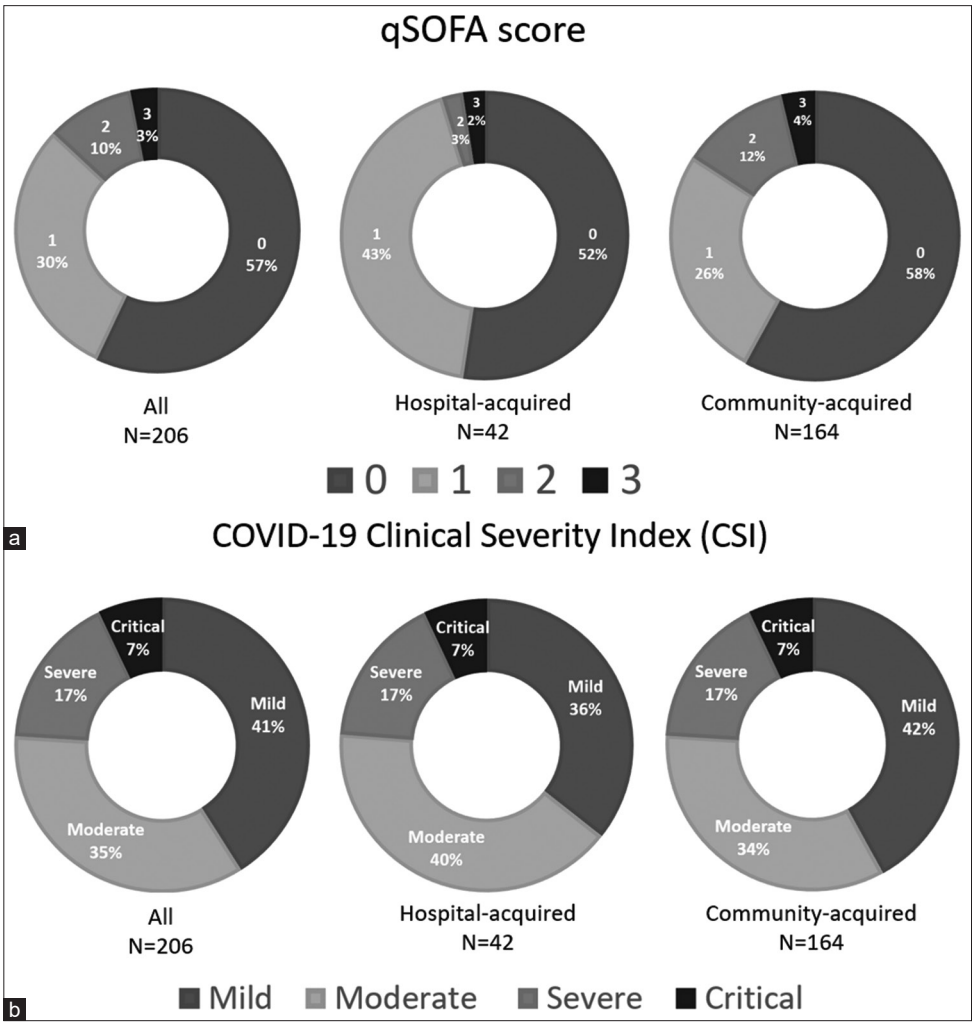

Figure 1: Proportion of disease severity based on different parameters between hospital-acquired infection and community-acquired infections (a) quick Sequential Organ Function Assessment score (b) coronavirus disease 2019 clinical severity index

Table 1: Clinical characteristics of 206 hospitalized patients with cancer and COVID-19 infection

	All (*n*=206), *n* (%)	Survivor (*n*=170), *n* (%)	Nonsurvivor (*n*=36), *n* (%)	*P*
Age	69.5 (60–79.25)	69 (60–80)	74 (60.25–79)	0.165
Sex				
Female	72 (35)	60 (35.3)	12 (33.3)	0.823
Male	134 (65)	110 (64.7)	24 (66.7)	
Smoking				
Never smoked	134 (65.7)	110 (65.5)	24 (66.7)	0.732
Current smoker	18 (8.8)	16 (9.5)	2 (5.6)	
Former	52 (25.5)	42 (25)	10 (27.8)	
BMI	21.99 (19.87–24.97)	22.05 (19.87–24.97)	21.45 (19.7–24.28)	0.539
Source of COVID-19 infection				
Nosocomial transmission	42 (20)	30 (17.6)	12 (33.3)	0.034
Community infection	164 (80)	140 (82.4)	24 (66.7)	
Comorbidity				
Cardiovascular disease	95 (46)	79 (46)	16 (44)	0.825
Chronic lung disease	23 (11)	17 (10)	6 (17)	0.249
Diabetes	68 (33)	59 (35)	9 (25)	0.261
Cerebrovascular disease	36 (18)	29 (17)	7 (19)	0.732
Chronic kidney disease	32 (16)	24 (14)	8 (22)	0.223
Vaccine dose				
≤1 (not fully vaccinated)	110 (53.4)	86 (50.6)	24 (66.7)	0.079
≥2 (fully vaccinated or booster)	96 (46.6)	84 (49.4)	12 (33.3)	
COVID severity				
Mild	84 (41)	79 (47)	5 (14)	
Moderate	72 (35)	60 (35)	12 (33)	
Severe	35 (17)	26 (15)	9 (25)	
Critical	15 (7)	5 (3)	10 (28)	
The qSOFA score				
≤1	178 (86.4)	155 (91.2)	23 (63.9)	<0.001
≥2	28 (13.6)	15 (8.8)	13 (36.1)	
Length of stay	13 (8–23)	11 (7–21)	22 (8–32)	

qSOFA: Quick Sequential Organ Function Assessment, BMI: Body mass index

Compared with the survivors, the nonsurvivors had a higher prevalence of lung metastasis, progressive disease, and anticancer treatment in the preceding 3 months. Lung metastasis ($P = 0.003$) and progressive disease ($P = 0.007$) were significantly different between the two groups; however, no significant effect on mortality was noted in the patients who had received anticancer therapy in the preceding 3 months.

Laboratory characteristics

As shown in Table 3, there were significant differences between the nonsurvivors and survivors in many laboratory characteristics, including a lower lymphocyte count, lower lymphocyte-to-C-reactive protein (CRP) ratio, higher lactate dehydrogenase level, higher CRP level, higher D-dimer level, higher ferritin level, higher procalcitonin level, and lower albumin level (all $P < 0.05$).

Logistic regression analysis

The results of logistic regression analysis for mortality are shown in Table 4. Univariate logistic regression revealed that the following factors were significantly associated with a higher risk of inhospital mortality among the patients with cancer and COVID-19: nosocomial COVID-19 infection ($P = 0.037$), lung metastasis ($P = 0.005$), received anticancer therapy in the preceding 3 months ($P = 0.083$), active and progressing cancer ($P = 0.008$), and qSOFA score ≥2 ($P < 0.001$). However, only nosocomial COVID-19 infection ($P = 0.021$) and qSOFA score ≥2 ($P < 0.001$) were independent predictors of inhospital mortality in the multivariate logistic regression analysis.

With changes in the mainstream strains of SARS-CoV-2, the Omicron variant has been found to have a shorter incubation period,[13] potentially rendering the old definition of nosocomial infection outdated. However, our results showed that nosocomial COVID-19 infection, with a changed definition of an RT-PCR diagnosis made >5 days after admission or emergency department arrival, remained a strong predictor factor for inpatient mortality [Supplementary Table 1].

Discussion

This study is the first conducted in Taiwan to focus on patients with both cancer and COVID-19 during the Omicron variant wave in 2022. Our findings indicated an overall inhospital mortality rate of 17.4%.

Table 2: Oncological characteristics of 206 hospitalized patients with cancer and COVID-19 infection

	All (*n*=207)*, *n* (%)	Survivor (*n*=170), *n* (%)	Nonsurvivor (*n*=37), *n* (%)	*P*
Cancer type				
Solid tumor	198 (96)	164 (96)	34 (92)	
Colorectal	26 (13)	22 (13)	4 (11)	
Lung	25 (12)	22 (13)	3 (8)	
Head and neck	21 (10)	18 (11)	3 (8)	
TCC	19 (9)	13 (8)	6 (16)	
Prostate	17 (8)	14 (8)	3 (8)	
HCC	17 (8)	13 (8)	4 (11)	
Breast	11 (5)	9 (5)	2 (5)	
Biliary	7 (3)	5 (3)	2 (5)	
GYN	7 (3)	5 (3)	2 (5)	
Hematological malignancy	9 (4)	6 (4)	3 (8)	
Lymphoma	7 (3)	5 (3)	2 (5)	
Leukemia	2 (1)	1 (1)	1 (3)	
Tumor stage				
Curative (stage I–III)	106 (52)	91 (54)	15 (42)	0.196
Noncurative (stage IV)	78 (38)	61 (36)	17 (47)	0.203
Unsuitable for stage or missing	22 (11)	18 (11)	4 (11)	
With lung metastasis	19 (9)	11 (6)	8 (22)	0.003
Cancer status				
Remission	80 (39)	69 (41)	11 (31)	
Active and respond	24 (12)	19 (11)	5 (14)	
Active and stable	25 (12)	24 (14)	1 (3)	
Active and progressing	64 (31)	46 (27)	18 (50)	0.007
Unknown	13 (6)	12 (7)	1 (3)	
Timing of anticancer treatment				
Never treat	15 (7)	13 (8)	2 (6)	
<3 months	93 (45)	72 (42)	21 (58)	0.08
>3 months	87 (42)	76 (45)	11 (31)	0.118
Unknown	11 (5)	9 (5)	2 (6)	
Recent cancer treatment type				
None	99 (48)	85 (50)	14 (39)	
Chemotherapy	52 (25)	40 (24)	12 (33)	0.219
Immunotherapy	1 (0)	1 (0)	0	
Target therapy	25 (12)	19 (11)	6 (17)	
Endocrine therapy	11 (5)	9 (5)	2 (6)	
Locoregional therapy	3 (1)	2 (1)	1 (3)	
Others	18 (9)	14 (8)	3 (8)	
Unknown	6 (3)	7 (4)	0	

*One patient with double cancer of 206 hospitalized patients with cancer and COVID-19 infection

During the study period, 1543 patients were admitted to a COVID-19 ward, of whom 156 died. The overall inhospital mortality rate of patients without cancer caused by COVID-19 was 9% (120/1337), which is lower than that of our cohort. This outcome may have resulted from an impaired immune system due to the cancer itself (e.g., bone marrow invasion) or anticancer treatment (chemotherapy or target therapy). These findings are consistent with those of previous studies.[14-16] Dai *et al*. conducted a multicenter study including 105 patients with both COVID-19 and cancer and 536 age-matched patients with COVID-19 but not cancer. Multivariate logistic regression revealed that compared with those without cancer, the patients with cancer had an odds ratio of 2.17 for death.[14] A single-center study by Liang *et al*. reported inhospital mortality rates of 21.1% in patients with cancer and COVID-19 and 7.7% in those without cancer.[15] In addition, Abuhelwa *et al*. reported an 11% inhospital mortality rate in COVID-19-infected patients without cancer compared to 17.58% in those with cancer.

In our study, multivariate logistic regression analysis revealed that nosocomial COVID-19 infection and a qSOFA score of ≥2 were independent risk factors for inhospital mortality. Few studies have focused on the predictors of mortality during the Omicron wave among inpatients with cancer.

In our cohort, 42 patients (20%) had nosocomial COVID-19 transmission, which was an independent risk factor, and the

Table 3: Laboratory characteristics

	All ($n=206$), *n* (%)	Survivor ($n=170$), *n* (%)	Nonsurvivor ($n=36$), *n* (%)	*P*
Lymphocyte count	739.7 (488–1209)	766.6 (525–1245)	564.5 (325–1010)	0.024
NLR	6.42 (3.42–12.46)	6.19 (3.39–12.51)	7.99 (3.17–12.55)	0.05
LCR	24.21 (8.04–71.95)	29.47 (9.33–76.43)	9.65 (3.68–37.68)	<0.001
LDH (U/L)	233 (197–302)	224 (194–290)	314 (257–569)	<0.001
ESR (mm/h)	39 (18–59)	37 (19–59)	44 (12.5–60.5)	0.689
CRP (mg/L)	32.2 (11–85)	27.55 (10–73.6)	72.6 (34.05–161.65)	0.002
D-dimer (ng/mL)	1504.3 (683.5–3906.2)	1392.25 (641.2–3397.5)	4977 (1913.45–11,661.1)	<0.001
Creatine kinase (U/L)	69 (40–149)	68.5 (41.75–150)	69 (33–148)	0.762
Procalcitonin (ng/mL)	0.14 (0.05–0.61)	0.11 (0.05–0.43)	0.84 (0.17–2.14)	<0.001
Ferritin	473.8 (220.4–1150.7)	370.48 (169.31–843.34)	1663.35 (870.02–4210.09)	<0.001
Albumin	3.3 (2.9–3.7)	3.4 (3.0–3.7)	2.6 (2.4–3.2)	<0.001

CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, LCR: Lymphocyte-to-CRP ratio, LDH: Lactate dehydrogenase, ESR: Erythrocyte sedimentation rate

Table 4: Logistic regression of patients' clinical and oncologic characteristics

Patient characteristics	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age >65	1.372 (0.633–2.976)	0.423	1.36 (0.524–3.529)	0.528
Sex, male	0.917 (0.428–1.962)	0.823	0.636 (0.259–1.564)	0.324
Nosocomial COVID-19 infection	2.333 (1.051–5.179)	0.037	3.104 (1.187–8.118)	0.021
With lung metastasis	4.13 (1.526–11.174)	0.005	3.111 (0.928–10.426)	0.066
Anticancer treatment <3 m	1.906 (0.919–3.951)	0.083	2.389 (0.939–6.075)	0.067
Active and progressing cancer status	2.696 (1.292–5.626)	0.008	1.499 (0.598–3.757)	0.388
qSOFA ≥2	5.841 (2.466–13.833)	<0.001	11.733 (3.877–35.511)	<0.001
Vaccine complete injection	0.512 (0.241–1.090)	0.082	0.428 (0.179–1.023)	0.056

qSOFA: Quick Sequential Organ Function Assessment, OR: Odds ratio, CI: Confidence interval

case fatality rate was 29% (12 patients). Biernat *et al*.[17] reported a case fatality rate of 36.8% in a hematological unit in Poland. In a Canadian hospital database study, Elkrief *et al*. reported a mortality rate of 47% among patients with both cancer and hospital-acquired COVID-19 infection.[18] A Japanese study conducted by Itoh *et al*.[19] reported that an inhospital Omicron outbreak in a head-and-neck cancer ward led to 6 and 3 of 14 nosocomial COVID-19-infected patients developing moderate and severe illness, respectively. Because patients with cancer require frequent admissions for anticancer treatment or cancer-related complications, they may be more vulnerable to nosocomial COVID-19 infection and develop a more severe form of the disease. Moreover, they may become spreaders because of long incubation and viral shedding times.[19] These results highlight the importance of strict measures to prevent nosocomial COVID-19 infection in susceptible patients with cancer.

The SOFA scoring system is used extensively because of its high predictive value for mortality in patients with sepsis.[11] However, it requires laboratory measurements, which may delay the diagnosis. Therefore, a simplified method, namely the qSOFA, was developed; the qSOFA includes only altered mentation, hypotension, and tachypnea to assist physicians in identifying patients at risk.[20] The multivariate analysis in our study revealed that a qSOFA score of ≥2 was an independent risk factor for mortality in patients with both cancer and COVID-19. These results are comparable with those of previous studies.[21] Because of the limited availability of medical equipment and beds during the pandemic, the qSOFA score can help clinicians distinguish people with milder forms of illness from those with more critical forms and thus facilitate medical resource allocation.

Unlike the results of previous studies[4,22,23] involving inpatients with both cancer and COVID-19 during the first wave, our data indicated no significant associations with inhospital mortality among older patients (>65 years), those with recent anticancer therapy exposure, male sex, cancer status, and comorbidities. These results may be multifactorial, as the average age of our group was higher than that in the previous wave and older adults are believed to have more comorbidities. Moreover, nearly half of the inpatients in our cohort were fully vaccinated, and some had even received a booster dose. Although the efficacy of COVID-19 vaccines against the Omicron variant in patients with cancer remains uncertain and was not an independent protective factor in our study, vaccines were shown to play a vital role against morbidity and mortality due to COVID-19 in patients with cancer in OnCovid study during the Omicron B.1.1.529 variant outbreak.[24]

This study has some limitations. First, this was a single-center study with a small sample size; thus, it may have been influenced

by selection bias. Second, some laboratory measurements were lacking, precluding further analysis. Finally, some patients had a do-not-resuscitate or do-not-intubate order, which may have led to the overestimation of inhospital mortality.

Conclusion

The Omicron variant of COVID-19 was found to cause a relatively mild form of the disease, possibly because of the COVID-19 mRNA vaccine, decreased pathogenicity, or antiviral agent use. Cancer patients are a population vulnerable to the Omicron variant with a higher risk of mortality, especially those with nosocomial infection and those with a qSOFA score of ≥2 immediately after confirmation of COVID-19 infection. Thus, the rapid recognition of high-risk groups and nosocomial COVID-19 infection control is critical to prevent COVID-19 in patients with cancer and to decrease their morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Material

Supplementary Table 1: Logistic regression of patients' clinical characteristics (With a changed definition of an RT-PCR diagnosis made >5 days after admission or emergency department arrival)

Nosocomial COVID-19 infection (>5 days)	Survivor (n=170), n (%)		Nonsurvivor (n=36), n (%)	P
Yes	37 (22)		14 (39)	0.031
No	133 (78)		22 (61)	
Patient characteristics	**Univariate**		**Multivariate**	
	OR (95% CI)	P	**OR (95% CI)**	P
Nosocomial COVID-19 infection (>5 days)	2.28	0.033	3.38	0.012

OR: Odds ratio, CI: Confidence interval