Demography and Outcome of Cancer Patients with COVID-19: A Retrospective Cohort Study in Dharmais National Cancer Center Indonesia

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Introduction: Cancer patients have an increased risk of morbidity and mortality due COVID-19 partly due to their immunocompromised status. We aimed to investigate the associations of clinicopathological factors and survival outcomes in cancer patients with COVID-19.

Methods: This was a retrospective cohort study comprised of cancer patients treated in Dharmais National Cancer Center, Indonesia. Main inclusion criteria were pathologically confirmed malignancy with positive results of RTPCR COVID-19 tests.

Results: A total of 16,511 visitors had visited and registered for RTPCR test in Dharmais National Cancer Center from May 2020 to January 2021. Logistic regression showed that male gender (p-value = 0.019; OR = 1.732), haematological type of malignancy (p-value <0.001; OR = 3.073), patients not underwent cancer therapy (p-value = 0.008; OR = 0.485), low RTPCR Ct values (p-value = <0.001; OR = 3.340), poor performance status (p-value = <0.001; OR = 8,194), and disease severity (p-value = <0.001; OR = 5.448) were associated with mortality.

Conclusion: Overall mortality rate in Dharmais cancer patients (25%) was higher than other cancer patients treated in other hospitals in Asia. Moreover, the mortality rate was similar across all age groups. Poor survival in young age might be explained by the fact that median age of cancer patients was 46 years old. In addition to male gender, cancer patients with low Ct values and having delayed cancer treatment were vulnerable groups of having poor outcomes when diagnosed with COVID-19. Long-term follow-up is required to examine the survival rate in cancer patients with COVID-19.

Introduction

Currently, the world is struggling with a global pandemic of coronavirus disease 2019 (COVID-19). World Health Organization (WHO) stated it as a pandemic on March 11, 2020 [1]. Globally, there were 190,671,330 confirmed cases of COVID-19, including 4,098,758 deaths, reported to WHO on July 21, 2021 [2]. During this period, Indonesia had recorded more than 1 million positive cases and 76,200 death cases [3].

While worldwide preventive measures have been ongoing, number of new cases continue to rise and pose persisting threat to all populations, including cancer patients. Patients with cancer had a high risk of contracting severe COVID-19 and with a poorer prognosis than those without cancer [4].

During the pandemic, cancer patients are caught as a unique group with an increased risk of contracting COVID-19 partly due to their immunocompromised condition [4]. Their weakened immunity is resulting from many factors including the malignancy burden and ongoing treatment such as surgery, chemotherapy, radiotherapy, or even due to patients undergoing transplant and use of immunosuppressants [5]. This pandemic has created dilemmas and unpredictable impacts on cancer management which include diagnostic work-ups, treatment schedules, and follow-up visits. The isolation of patients infected with COVID-19 has caused losing valuable clinic visits. New patients could miss an early diagnosis which may lead to worse prognosis. In addition, patients with advanced cancer may have to postpone treatments risking disease progression [6].

Low-and middle-income countries (LMIC) with ailing healthcare systems are more vulnerable to contain the pandemic, especially in efforts to manage cancer patients. Dharmais National Cancer Center in Indonesia has deployed strict mitigation system in order to minimize exposure of viral transmission to healthcare providers and patients to and to optimize cancer management [7]. Our current study analyzed associations of clinical characteristics and outcomes of cancer patients with COVID-19 in Dharmais.

Materials and Methods

Study design and participants

This was a retrospective cohort study to estimate demographic and clinical factors associated with outcome of cancer patients with COVID-19 in National Cancer Center, Indonesia. COVID-19 incidents were obtained from SARS-CoV-2 reverse transcribed polymerase chain reaction (RTPCR) test records of patients registered in medical database of Dharmais Cancer Hospital between May 01, 2020 to January 31, 2021. Based on Indonesia's national COVID-19 management guidelines [8], Dharmais conducted confirmatory SARS-CoV-2 RTPCR test on nasopharyngeal and/or oropharyngeal swabs specimens in the laboratory. Cancer patients were discharged or proceeded to cancer treatment after demonstrating negative test results of two consecutive RTPCR tests, or being declared free of COVID-19 by pulmonologist-in- charge.

The population in this study were all patients who were treated in and registered at the Dharmais Cancer Hospital. The eligibility criteria were (1) patients with confirmed cancer diagnosis by pathologists or other supporting results in medical records and (2) had positive SARS-CoV-2 RTPCR-positive tests. Patients with suspected or absent of malignancy were excluded.

Data collection and variables

Data were extracted from hospital medical record of RTPCR test results. All patients with RTPCR-positive test results were taken and then evaluated by pathologists to confirm cancer diagnosis. Subsequently, patient demographics (age and gender), clinical characteristics, cancer management, clinical history of COVID-19 treatment, and outcomes were collected. The clinical characteristics included type of malignancy, symptoms, comorbidity, performance status, RTPCR Cycle Threshold Value (Ct value), and disease severity. We categorized cancer treatment status into treatment naïve and previously treated patients and type of cancer management (diagnostic biopsy, evaluation, stabilized clinical condition, as well as having targeted therapy, chemotherapy, surgery, radiotherapy, chemoradiation, and others). Lastly, clinical outcome indicated the number of patients who survived or died. Death cases were patients who died of any cause within 30 days of

confirmed COVID-19 diagnosis.

Symptoms and comorbidities were collected from patient self-questionnaires. We used The Eastern Cooperative Oncology Group (ECOG) score to measure performance status cancer patients with COVID-19. The ECOG score was ran from 0 to 5, with 0 denoting perfect health and 5 death [9].

This study distinguished in-patients and out-patients to determine the differences in demographic and clinical characteristics of patients between these groups. In-patients indicated that the patient was infected with COVID-19 while undergoing treatment in the hospital wards. On the other hand, outpatients were all patients who had any symptoms of COVID-19, confirmed by RTPCR who were about to undergo any cancer management modalities. Cancer therapy was divided into two categories i.e. having chemotherapy or no chemotherapy. Surgery, radiotherapy, diagnostics, and treatment for stabilized clinical conditions were included in the non-chemotherapy category.

We also measured COVID-19 disease severity. The Ministry of Health Indonesia classified the disease severity of COVID-19 into four groups, namely asymptomatic or mild, moderate, severe, and critical conditions. Mild symptom is a condition without evidence of viral pneumonia or without hypoxia. Symptoms include fever, cough, fatigue, anorexia, shortness of breath, myalgia. Other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, smell (anosmia), or loss of taste (ageusia) [10].

Moderate symptoms in adolescent or adult patients included pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia including $SpO_2 > 93\%$ with room air. In children, it showed symptoms of non-severe pneumonia (coughing or difficulty breathing, rapid breathing, and/or chest wall traction) and no signs of severe pneumonia [10].

In adolescent or adult patients, severe symptoms showed the symptoms of pneumonia (fever, cough, shortness of breath, rapid breathing) and/or respiratory rate > 30 bpm, severe respiratory distress, or $SpO_2 < 93\%$ in room air. Lastly, critical symptoms comprised of Acute Respiratory Distress Syndrome (ARDS), sepsis, and septic shock [10].

There were two types of PCR assay available at our hospital, namely open system and closed system PCR. Open system PCR in our hospital is using QIAsymphony DSP Virus/Pathogen mini kit (Qiagen, Germany) for extraction reagent kit, LightMix Modular SARS-CoV-2 (COVID-19) (Roche, Germany) for amplification reagent kit, and Rotor Gene Q (Qiagen, Germany) for real time PCR cycler. Target genes for this open system PCR were E and RdRp gene as target genes with CT cut off point 36 and 41 respectively. We used two type of closed system PCR, that are Abbott Real Time SARS-CoV-2 assay (Abbott, USA) and GeneXpert (Cepheid, USA). Abbott Real Time SARS-CoV-2 assay was real time assay performed on Abbott m2000 system for extraction (m2000sp) and amplification (m2000rt). The Abbott assay used RdRP and N genes as target genes with CT cut off point 31.6. GeneXpert used the E and N2 gene targets with CT cut off point 45 each. We used Abbott PCR assay as the main PCR assay. GeneXpert is used for cases requiring fast result (within 2 hours) such as deteriorating patients who require ICU, patients who need immediate medical intervention, or post mortem COVID-19 status determination.

Statistical analysis

We used descriptive statistics and bivariate analysis. Median and range (min-max) was evaluated for the continuous variables, while the proportion for the categorical variables used to describe the data. We differentiated the proportion of demographics, clinical characters patients in inpatients and outpatients, and death from any cause within 3 months of observation using crosstabulation and chi-square test. Besides, for continous variables using independent samples t-test. The association independent variables with outcome patient were assessed by logistic regression. All analyses were two-sided and the significance level was set at $p < 0.05$.

Ethical Statement

This study was approved by the Ethical Committee of the Dharmais National Cancer Center (approval No.: 0149/KEPK/X/2020).

Results

A total of 16,511 visitors had visited and registered for RTPCR test in Dharmais National Cancer Center from May 2020 to January 2021 with the results 878 visitors came positive and 15,633 were negative. There were 403 cancer patients with COVID-19 whereby 170 (42.2%) were inpatients and 233 (57.8%) were outpatients. Patient`s demography and clinical characteristics were described, see Table 1.

Variables	Total (%) (N = 403)	Inpatient (%) (N = 170)	Outpatient (%) (N = 233)
Median Age, (min-max) years	46 (5 - 73)	46 (5 - 73)	48 (7 - 77)
Gender			
Male	148 (36.7)	78 (52.7)	70 (47.3)
Female	225 (63.3)	92 (36.1)	163 (63.9)
Type of malignancy			
Solid tumors	339 (84.1)	124 (36.6)	215 (63.4)
Breast cancer	110 (27.3)	30 (27.3)	80 (72.7)
Lung cancer	28 (6.9)	16 (57.1)	12 (42.9)
Nasopharyngeal cancer	22 (5.5)	9 (40.9)	13 (59.1)
Cervical cancer	28 (6.9)	9 (32.1)	19 (67.9)
Colorectal cancer	36 (8.9)	11 (30.6)	25 (69.4)
Others	112 (27.8)	48 (42.9)	64 (57.1)
Hematology	64 (15.9)	46 (71.9)	18 (28.1)
ALL	13 (3.2)	10 (76.9)	3 (23.1)
Lymphoma	22 (5.5)	10 (45.5)	12 (54.5)
AML	18 (4.5)	15 (83.3)	3 (16.7)
Others	14 (3.5)	12 (85.7)	2 (14.3)
Symptoms			
Asymptomatic	180 (44.7)	15 (8.3)	165 (91.7)
Symptomatic	223 (55.3)	155 (69.5)	68 (30.5)
Respiratory	167 (41.4)	115 (68.9)	52 (31.1)
Gastrointestinal (GI)	12 (3.0)	6 (50.0)	6 (50.0)
Respiratory and GI	36 (8.9)	32 (88.9)	4 (11.1)
Others	8 (2.0)	2 (25.0)	6 (75.0)
Comorbidity			
Malignancy alone	319 (79.2)	136 (42.6)	183 (57.4)
Additional comorbidity			
Hypertension	44 (10.9)	18 (40.9)	26 (59.1)
Heart failure	7 (1.7)	4 (57.1)	3 (42.9)
Diabetes	10 (2.5)	4 (40.0)	6 (60.0)
Multiple comorbidity	23 (5.7)	8 (34.8)	15 (65.2)
Ct value (median, min-max)*	17.17 (2.81 – 31.33)	14.38 (2.81-30.95)	18.00 (3.42-31.33)
Therapy status			
Treatment naïve	168 (41.7)	93 (55.4)	75 (44.6)
Previously treated	74 (18.4)	41 (55.4)	33 (44.6)
Ongoing therapy	161 (40.0)	99 (61.5)	62 (38.5)
Cancer management			
Diagnostic biopsy	58 (14.4)	18 (31.0)	40 (69.0)

Routine Evaluation	36 (8.9)	5 (13.9)	31 (86.1)
Stabilized clinical condition	48 (11.9)	45 (93.8)	3 (6.3)
Targeted therapy	1 (0.2)	1 (100.0)	0 (0.0)
Chemotherapy	122 (30.3)	41 (33.6)	81 (66.4)
Surgery	31 (7.7)	21 (67.7)	10 (32.3)
Radiotherapy	35 (8.7)	12 (34.3)	23 (65.7)
Chemoradiation	6 (1.5)	4 (66.7)	2 (33.3)
Others	66 (16.4)	23 (34.8)	43 (65.2)
Performance status (ECOG)			
0	103 (25.6)	10 (9.7)	93 (90.3)
1	138 (34.2)	42 (30.4)	96 (69.6)
2	92 (22.8)	57 (62.0)	35 (38.0)
3	48 (11.9)	41 (85.4)	7 (14.6)
4	22 (5.5)	20 (90.9)	2 (9.1)
COVID-19 disease grade			
Asymptomatic	180 (44.7)	15 (8.3)	165 (91.7)
Mild	69 (17.1)	6 (8.7)	63 (91.3)
Moderate	54 (13.4)	52 (96.3)	2 (3.7)
Severe	96 (23.8)	93 (96.9)	3 (3.1)
Critical	4 (1.0)	4 (100.0)	0 (0.0)
Outcomes			
Survive	302 (74.9)	78 (25.8)	224 (74.2)
Deceased	101 (25.1)	92 (91.1)	9 (8.9)

Table 1. Demography and Clinical Characteristics of Cancer Patients with COVID-19.

*based on Abbott Ct value

The median age was 46 years; 84.1% of the patients had a solid tumor and breast cancer was the most frequent malignancy. Approximately, half of patients had respiratory symptoms of COVID-19 and near one-fifth of patients had other comorbidities besides malignancy.

The median Ct values of RTPCR positive results were 16.98, Table 2. Most patients were not under chemotherapy program (68.5%). 61% of patients had mild to asymptomatic COVID-19, 59% had ECOG performance score 0-1, and 25% of patients died of any cause.

Ct value	n	Ct value Cut off	Mean	Median	Min - Max
Abbott*	365	31.6	16.52	17.17	2.81 – 31.33
GeneXpert	8				
E		45	27.4	26.85	16.20 – 42.80
N2		45	30.1	29.4	18.70 – 38.80
Qiagen	20				
E		36	25.48	27.78	10.90 – 33.47
RdRP		41	28.75	31.37	11.49 – 38.63

Table 2. SARS-CoV-2 RTPCR Ct Values Based on Several Assays.

*frequently-used

Male patients were mostly in-patients while female patients were in outpatients. Haematological cancer especially *Acute myeloid leukemia* (AML) had higher proportions of in-patients care than

solid tumor. Most common symptoms of in-patients COVID-19 cancer patients were respiratory (cough, shortness of breath, fever) and gastrointestinal (nausea, vomiting, and diarrhea). The inpatients disease severity and mortality were also higher than outpatients. Mortality rate in haematological cancer was also higher than solid tumors. Based on type of malignancy, hematological mortality was higher than solid tumors, lung cancer and nasopharyngeal cancer were the highest deaths in solid tumors, AML was the highest mortality in hematology (Figure 1).

Figure 1. Outcome of Cancer Patients with COVID-19. Based on Type of Malignancy, Hematological Mortality was Higher than Solid Tumors (A), Lung Cancer and Nasopharyngeal Cancer were the Highest Deaths in Solid Tumors (B), AML was the Highest Mortality in Hematology (C).

Chemotherapy was the most frequent modality of cancer management (Figure 2).

Figure 2. Cancer Management in COVID-19 Patients. Chemotherapy is the most common cancer management when patients diagnosed with COVID-19.

Logistic regression showed that gender (p-value = 0.019; OR = 1.732, 95% CI OR = 1.095-2.739), type malignancy (p-value = <0.001; OR = 3.073, 95% CI OR = 1.761-5.362), Ct value (p-value = <0.001; OR = 3.340, 95% CI OR = 0.192-0.547), performance status (p-value = <0.001; OR = 8,194, 95% CI OR = 4,669-14,381), and disease severity (p-value = <0.001; OR = 5.448, 95% CI OR = 3,916-7,578) were associated with mortality. We did adjustments in therapy cancer and status performance to confirmed the number of deaths in patients with ECOG score ≤ 2. The results showed that mortality in patients who did not undergo chemotherapy was higher than those having chemotherapy, see Table 3.

Variables	Survive (%)	Deceased (%)	Sig	OR	95% CI OR
Age					
< 50	165 (74.7)	56 (25.3)	0.649	0.94	0.721-1.226
50 – 59	79 (74.5)	27 (25.5)			
60 – 69	45 (73.8)	16 (26.2)			
> 70	13 (86.7)	2 (13.3)			
Gender					
Female	201 (78.8)	54 (21.2)	0.019 *	1.732	1.095-2.739
Male	101 (68.2)	47 (31.8)			
Types of malignancy			<0.001 *	3.073	1.761-5.362
Solid tumor	267 (78.8)	72 (21.2)			
Haematology	35 (54.7)	29 (45.3)			
Comorbidity			0.672	1.046	0.850-1.287
No comorbidity	238 (74.6)	81 (25.4)			
Additional comorbidity besides malignancy					
Hypertension	37 (84.1)	7 (15.9)			
Heart failure	3 (42.9)	4 (57.1)			
Diabetes	8 (80.0)	2 (20.0)			
Double comorbidity	16 (69.6)	7 (30.4)			
Therapy status					
Treatment naive	121 (72.0)	47 (28.0)	0.193	0.846	0.659-1.088
Previously treated	55 (74.3)	19 (25.7)			
Ongoing therapy	126 (78.3)	35 (21.7)			
Ct value#					

Abbott (median = 17.17)					
≥ median	159 (86.9)	24 (13.1)	<0.001 *	3.34	1.970-5.664
< median	121 (66.5)	61 (33.5)			
GeneXpert (median = 26.85)					
< median	2 (50.0)	2 (50.0)	0.429	0.5	0.188-1.332
≥ median	0 (0.0)	4 (100.0)			
Qiagen (median = 31.37)					
< median	9 (60.0)	6 (40.0)	0.613	0.375	0.033-4.228
≥ median	4 (80.0)	1 (20.0)			
Performance status					
ECOG ≤ 2	276 (82.9)	57 (17.1)	<0.001 *	8.194	4.669-14.381
ECOG >2	26 (37.1)	44 (62.9)			
ECOG ≤ 2					
not chemotherapy	179 (80.3)	44 (19.7)	0.074	0.545	0.280-1.061
chemotherapy	97 (88.2)	13 (11.8)			
Disease severity					
Asymptomatic	174 (96.7)	6 (3.3)	<0.001 *	5.448	3.916-7.578
Mild	66 (95.7)	3 (4.3)			
Moderate	39 (72.2)	15 (27.8)			
Severe	23 (24.0)	73 (76.0)			
Critical	0 (0.0)	4 (100.0)			

Table 3. Logistic Regression of Cancer Patients with COVID-19 Clinical Outcomes.

#based on Abbott; * Significance < 0.05; OR, Odds Ratio

Discussion

Given the wide range in disease course for COVID-19, the ability to predict which cancer patients are at particularly high risk of deterioration and negative outcomes would be of particular value in the clinical setting. Our study found five risk factors that were significantly associated with mortality in cancer patients with COVID-19, i.e. gender, type malignancy, RTPCR Ct values, performance status, and COVID-19 disease severity. Demographic factors and clinical characteristics are important in predicting mortality.

This study investigated the association of age and gender to mortality in cancer patients with COVID-19. The results showed that age was not significant risk factor of mortality and had been showed by previous studies [11,12]. The median age in cancer patients was lower (46 years old) than the general population (50 years old) in Indonesia [13] and over 50 years old in globally [14,15]. In Asia Pacific (China, Singapura, Korea, and Australia) [16-18], Europe (Italy, Spain, France, and United Kingdom) [19-22], and America (USA and Brazil) [23,24] has a median aged more than 60 years [25]. Our data suggest that vulnerability of cancer patients to high risk of mortality was independent of age.

In our cohort, male cancer patients had higher risk of COVID-19 mortality than female patients. Females and males have differences in their susceptibility and response to viral infections, leading to gender differences in the incidence and severity of the disease [26]. However, and likely in association with differences in the incidence of poor condition, risky and preventive behaviours, or immune systems, male gender was overrepresented among COVID-19 fatalities. This observation was consistent with recent data from China, Spain, and Italy regarding the COVID-19 outbreak

showed that the percentage of males who have died due to the infection was much higher than females [27]. In China, for example, found that the fatality rate among men with the virus was about 65% higher than among women. A study in 177 countries and territories suggested that more consideration should be paid to male patients, particularly those over 65 years old for enhanced clinical management [25].

Cancer patients are particularly susceptible to respiratory pathogens and severe pneumonia, because they are at an immunosuppressive state due to malignancy and anticancer therapy. Nearly half of haematology malignancy had high death rates in this study. One of the reasons why outcomes may be worse in patients with haematologic malignancies is that in many cases, immune responses to the virus are less pronounced and highly variable compared with people with other types of cancer, with delayed or negligible seroconversion, prolonged viral shedding, and sustained immune dysregulation [28]. Lower respiratory tract diseases caused by human coronaviruses in patients with haematological malignancies have been associated with high rates of oxygen use and mortality [29]. Solid tumor on the other hand had good prognoses. More than half solid tumor patients survived from COVID-19.

Cancer management such as chemotherapy, surgery, and radiotherapy protocols may suppress immune system, which may lead to worsening of COVID-19 associated morbidity and/or mortality [30]. Furthermore, cancer patients who were being diagnosed with COVID-19 may also risk cancer progression which may jeopardize a chance of survival [31]. However, there was no strong association between status of cancer therapy and mortality within this study cohort.

Cancer therapy can cause a weakened immune system, including chemotherapy. The first objective of using chemotherapy is to kill cancer cells. Chemotherapy can also affect immune cells and thus contribute not only to effective tumor response but also to tumor resistance [32]. Chemotherapy can cause neutropenia (decreased number of neutrophils, a type of white blood cell). This means the body may not be able to fight infection properly. While chemotherapy may affect survival of blood cancer patients with COVID, others studies show that chemotherapy may not imposed additional survival risk [33,34].

Cancer patients with COVID-19 had delayed treatment because they have to be quarantined for approximately 14 days or more. Delayed treatment of cancer can make adverse consequences on outcome. A four-week delay in treatment was associated with an increased risk of death. For surgery, 6-8% increased risk of death for every four-week delay. This effect was even more marked in some radiotherapy and systemic indications, with an increased risk of death of 9% and 13% for definitive head and neck radiotherapy and adjuvant systemic treatment for colorectal cancer, respectively [35]. Therefore, our data may indicate that the increased rate of mortality in patients who did not undergo chemotherapy may die due to malignancy instead of COVID-19. At this stage we could not distinguish the death of COVID-19 or of malignancy. The cycle threshold (Ct) value is the number of cycles of amplification to detect the virus genetic materials. It is an estimate of how much virus was likely in the sample to start with – instead of the actual number of viable virus particles. If the virus is found in a low number of cycles (Ct value under 30), it means that the virus was easier to find in sample and that the sample started out with a large amount of the virus [36]. Clinical knowledge of COVID-19 is constantly evolving, with studies being published at a high rate; however, there is currently only limited data relating to the correlation of viral loads with patient prognoses, such as mortality or disease progression. A study reported on the association between mortality and SARS-CoV-2 Ct value and showed that lower Ct values correlated with increased risk of death, [37] which is consistent with data for previous epidemic-causing coronaviruses [38,39].

Many studies reported on the correlation of Ct values with symptom severity that indicated that lower Ct values were associated with more severe disease. This is consistent with some previous studies of Ct values in other respiratory infections, although other studies do not show correlation [40]. The limitation of our study, we did not perform quantitative measurement of viral particles in laboratory culture and correlate with Ct values.

Lastly, patients with ECOG > 2 had 8 times risk for death. We did an adjustment and the data showed in this category the patients were doing 'not chemotherapy' category and stabilized the clinical condition. In Dharmais Hospital as a tertiary hospital. So, the patients that came to us more likely had poor prognostic. For the patient that came for diagnostic, the moment they got COVID-19, we had to delayed any action or treatment for the cancer. In conclusion, when exposed to COVID-19, cancer patients had higher mortality rate than general population. Gender as demographics factors has association with mortality significantly. Clinical characteristics such as type malignancy, Ct value, performance status, and disease severity were associated with mortality. COVID-19 had a huge impact on cancer treatment and management. Cancer patients with COVID-19 would postpone doctor visits, diagnostic work-up, chemotherapy, and others which can increase the risk of mortality. Further research is required to investigate the others factor of infection COVID-19 such as body mass index (BMI), blood type, smoking history and examine the survival rate in cancer patients with COVID-19.

Acknowledgments

Conflict Of Interest

The authors report no conflict of interest

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