RESEARCH ARTICLE

INDONESIAN JOURNAL OF CANCER

Factor Associated with Mortality of Hospitalized Cancer Patients with COVID-19 Infection in Indonesia National Cancer Center

Sri Agustini Kurniawati [1*], ***Noorwati Sutandyo*** [1], ***Hilman Tadjoedin*** [1], ***Jaka Pradipta*** [2], ***Ratu Ralna Ismuha*** [3], ***Citra Dovina Khaira*** [3], ***Kresna Dharma Suryana*** [1], ***Erwin Budi*** [4]

[1] Department of Hematology and Medical Oncology, Dharmais Cancer Hospital - National Cancer Center, Jakarta, Indonesia
[2] Department of Pulmonology, Dharmais Cancer Hospital - National Cancer Center, Jakarta, Indonesia
[3] Department of Pharmacy, Dharmais Cancer Hospital - National Cancer Center, Jakarta, Indonesia
[4] Department of General Practice, Dharmais Hospital National Cancer Center, Jakarta, Indonesia

ARTICLE INFO

Received : 28 May 2023
Reviewed : 26 July 2023
Accepted : 20 May 2024

Keywords:
cancer, COVID-19, DM, D-dimer, mortality, risk factors

*Corresponding author:
Sri Agustini Kurniawati
Department of Hematology and Medical Oncology, Dharmais Cancer Hospital - National Cancer Center, Jakarta, Indonesia
sriagustinikurniawati@gmail.com

ABSTRACT

Background: Cancer patients with COVID-19 are at risk of developing severe complications and outcomes due to immunosuppressive and inflammatory states. This study aims to provide insight into risk factors associated with mortality in this population.

Methods: A retrospective cohort study was conducted at Dharmais National Cancer Center, Jakarta, Indonesia, from May 2020 to July 2021. Data were collected through electronic medical records using the consecutive sampling technique. The numerical and categorical data were then tested statistically.

Results: The results showed 180 cancer patients with COVID-19 were hospitalized at Dharmais National Cancer Center. Among the patients, 114 patients survived, and 66 patients deceased. Across all risk factors analyzed to mortality, patients with Diabetes Mellitus (OR 0.41;0.22-0.77, p-value <0.05) and high level of D-dimer (OR 2.00;1.06-3.79, P-value <0.05) have a higher risk in mortality. The Results showed that survived patients have lower D-dimer levels (2010 ng/L) and deceased patients have higher D-dimer levels (3264 ng/L) with P-value <0.05.

Conclusion: High D-dimer levels and diabetes are risk factors significantly associated with mortality in hospitalized cancer patients with COVID-19 Infection.

INTRODUCTION

Since its appearance in December 2019 in Wuhan City, the coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has spread rapidly around the world and caused a pandemic [1]. The ongoing COVID-19 pandemic has profoundly affected the global population, particularly exacerbating the vulnerabilities of cancer patients. Individuals with cancer are considered a vulnerable population as they are generally older, immunocompromised, and present with various other health issues. Despite numerous studies and reviews, the impact of COVID-19 on cancer patients still presents varying results. Research suggests that individuals with cancer diagnoses face a significantly higher risk of severe outcomes from COVID-19 compared to the general population. For instance, the risk of death within 30 days of a COVID-19 diagnosis in people with cancer ranges from 13% to 33%, which is markedly higher than the 0.5% to 2% mortality rate observed in the broader population. This disparity is attributed to factors such as the inability to self-care, active and progressing cancer, recent chemotherapy, and the presence of comorbidities like lung conditions, kidney disease, or diabetes [2,3].

Moreover, cancer patients often present with other high-risk conditions for severe COVID-19, such as chronic obstructive pulmonary disease (COPD), heart disease, and obesity. Approximately 56% of cancer survivors have at least one such condition, amplifying their susceptibility to the virus.2 In addition to weakened immune systems and are already prone to clotting due to their disease or treatment, face an even greater risk of severe COVID-19 and associated coagulation issues. Research

also suggested that receipts of recent cytotoxic chemotherapy were associated with higher COVID-19 severity, and specific cancer therapies were associated with high 30-day mortality in cancer patients. However, it is noteworthy that certain cancer treatments, including some immunotherapies and targeted therapies, may not be associated with a higher risk of COVID-19 severity, and may offer a degree of protection, particularly after vaccination [4]. Moreover, evidence showed that a significant percentage of patients experienced clotting complications, some of which were fatal. It is now better understood that an aggressive inflammatory response and endothelial damage, among other mechanisms, can worsen the risk of clotting in COVID-19 patients, leading to conditions like deep vein thrombosis and pulmonary embolism [5]. These effects hence put this population at as much as 3.5 times higher risk of requiring mechanical ventilation and intensive care than the general population [6]. In addition, the incidence of thromboembolism contributes to morbidity and mortality, which can interfere with cancer therapy, as cancer-associated thrombosis (CAT) is the second leading cause of death in cancer patients [7].

This study aims to provide an overview of the clinical characteristics and outcomes of cancer patients infected by COVID-19. We aim to identify risk factors for mortality in this vulnerable population, thereby contributing to better management strategies and improved healthcare protocols. The intent is not just to add to the growing body of literature documenting the increased risk that cancer patients infected with COVID-19 must face, but also to offer a localized insight into the situation in Indonesia. Consequently, the result of this study is hoped to contribute to the global understanding of the pandemic's impact on cancer care. Moreover, by highlighting specific risk factors, the study could guide prioritization in treatment and protective measures for cancer survivors [8].

METHODS

This is a retrospective cohort study conducted at the Dharmais National Cancer Center, Jakarta, Indonesia, from May 2020 to July 2021. Data were collected from electronic medical records using the consecutive sampling technique. The sample criteria were that patients had been diagnosed with cancer and confirmed to have COVID-19. The exclusion criteria were patients who were not hospitalized and could not be assessed in terms of the severity of COVID-19. A total of 180 cancer patients with COVID-19 who met the inclusion criteria were included in the study**.** The patient's demographic data collected were age, gender, type of cancer, comorbidities (diabetes mellitus and kidney disease), severity of COVID-19 infection, and hospitalization length. The diagnosis of cancer was made by histopathological examination. COVID-19 infection was established based on confirmation of SARS-Cov-2 through quantitative RT-PCR (Real Time-Polymerase Chain Reaction) nasopharyngeal swab results. Based on WHO guidelines 2020, the severity of COVID-19 infection is divided into Non-severe (mild/moderate), severe, and critically ill [9]. In Indonesia, according to Indonesia Guidelines for treating COVID-19 2020, the severity of COVID-19 is divided into asymptomatic, mild, moderate, severe, and critical [10]. In this study, the study population was taken from hospitalized patients, which included patients with moderate, severe, and critical levels of COVID-19. Blood tests performed at the clinical pathology laboratory of Dharmais National Cancer Hospital were for D-dimer, hemoglobin, leukocytes, platelets, albumin, interleukin-6 (IL-6), and c-reactive protein (CRP). The blood test data collected were initial tests performed when the patients were admitted to the hospital. Laboratory examinations were performed at the Clinical Pathology Laboratory of Dharmais National Cancer Hospital. The types of anticoagulants and antivirals administered to patients were obtained from electronic medical records.

The medical record data were collected using Ms. Excel and analyzed using the SPSS Statistics 29.0 program. Before the statistical testing, the data were tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The statistical test performed for the study was the Mann-Whitney test for abnormal data distribution. The statistical output is meaningful if the P-value is <0.05.

RESULTS

A total of 180 cancer patients diagnosed with COVID-19 between May 2020 and July 2021 who met the set criteria for inclusion were included in the study. The demographic and clinical features of the patients are detailed in **Table 1**. The cohort predominantly consisted of females, at 109 (60.6%), with a total mean age of 50.02 (a minimum age of 19 and a maximum age of 81). The most common type of cancer suffered by the patients was solid cancer, with 145 (80.6%) cases, followed by hematological cancer, at 35 (19.4%). The three most common solid cancers were breast cancer (22.2%), lung cancer (11.6%), and cervical cancer (8.8%), while the three most common hematological cancers were acute myeloid leukemia (4.4%), non-Hodgkin's lymphoma (3.8%), and acute lymphocytic leukemia (2.7%). Among all patients, 32 patients (17.8%) were diagnosed with comorbid diabetes mellitus and 39 (21.7%) with comorbid kidney disease. The average hospitalization length was 10.41 days, with the shortest stay being one day and the longest 51 days. A total of 65 patients (36,1%) had been treated for moderate COVID-19 infection, followed by 90 (50%) with severe COVID-19 infection and 25 (13.9%) with critical COVID-19

P-ISSN: 1978-3744 E-ISSN: 2355-6811

Table 1. Clinical characteristics of hospitalized cancer patients with COVID-19 infection

Variable	Total	
	n	%
Sex		
Female	109	60.6
Male	71	39.4
Age		
Median (Min; Max)	51 (19; 81)	
≤50	87	48.3
>50	93	51.7
Cancer Type		
Solid	145	80.6
Breast Cancer	40	22.2
Lung Cancer	21	11.6
Cervical Cancer	16	8.8
Other	68	37.7
Hematology	35	19.4
Acute Myeloid Leukemia	8	4.4
Non-Hodgkin's Lymphoma	7	3.8
Acute Lymphocytic Leukemia	5	2.7
Other	15	8.3
Comorbidity		
DM	32	17.8
Kidney Diseases	39	21.7
Hospitalization length for COVID-19		
Mean (SD)	10.41 (8.63)	
Median (Min; Max)	8 (1; 51)	
≤8 days	94	52.2
>8 days	86	47.8
The severity of infection by COVID-19		
Moderate	65	36.1
Severe	90	50.0
Critical	25	13.9
Antivirus administration		
Yes	131	72.8
No	49	27.2
Anticoagulants administration		
Yes	126	70.0
No	54	30.0
D-dimer (n=180)		
Median (Min; Max)	2520 (270; 159200)	
≤2500 ng/L	90	50.0
>2500 ng/L	90	50.0
Thrombocyte (n=160)		
Median (Min; Max)	228 (11; 692)	
≤150 uL	58	36.3
>150 uL	102	63.8
Hemoglobin (n=161)		
Median (Min; Max)	10.60 (4.20; 15.60)	
≥12 mg/dL	44	27.3
<12 mg/dL	117	72.7
Leucocyte (n=159)		
Median (Min; Max)	11.92 (0.86; 407.00)	
≤10000	65	40.9
>10000	94	59.1
Albumin (n=124)		
Median (Min; Max)	02.90 (1.60; 4.40)	
<3.2 g/dl	80	64.5
≥3.2 g/dL	44	35.5
C-reactive protein (n=124)		
Median (Min; Max)	42.26 (1; 410.85)	
>5 mg/dL	109	87.9
≤5 mg/dL	15	12.1
Interleukin-6 (n=24)		
Median (Min; Max)	1 (0; 1)	
>4 pg/dL	0	0
≤4 pg/dL	24	100.0

infection. For the treatment, 131 (72.8%) patients received antivirus medication and 126 (70%) patients received anticoagulant medication.

In terms of blood test result, it needs to be noted that not all patients included in the study were provided with complete blood test, with D-dimer as the only blood test result available for all cohorts. The values of each blood test component were stratified based on either median data, or cutoff limits that are used as standard reference in Dharmais Cancer Hospital Jakarta. The median values of hemoglobin (n=161) and leucocyte (n=159) were 10.6 g/dl and 11.92/mL, respectively. Most hemoglobin levels were low, with 117 patients (72.7%) at <12 mg/dL. The median value of platelet (n=160) was 228,000/µL, consisting of a minimum value of 11,000/µL and a maximum of 692,000/µL, with 58 patients (36.3%) having thrombocytopenia. The median value of D-dimer (n=180) was 2520 ng/L, with a minimum of 270 ng/L and a maximum of 159,200 ng/L, and was evenly distributed for patients with value >2500 ng/L and ≤2500 ng/L. The median values of CRP (n=124) and IL-6 (n=27) were 42.25 mg/L and 12.13 pg/mL, respectively, consisting predominantly of high CRP (>5 mg/dL) with a total of 109 patients (87.9%).

In the bivariate analysis, significant associations were observed in patients with diabetes mellitus (DM), which

P-ISSN: 1978-3744 E-ISSN: 2355-6811

constituted 17.8% of the cohort, with OR 2.67 (95% CI: 1.23–5.83) and a p-value of 0.01, suggesting a statistically significant association with the outcomes studied. A significant association was also found in patients with thrombocytopenia, with OR 2.08 (95% CI: 1.05–4.16) and a p-value of 0.037. Furthermore, a higher risk was also seen in patients with elevated D-dimer levels (>2500 ng/L), with an OR of 2.57 (95% CI: 1.37–4.81) and a p-value of 0.003.

The multivariate analysis refined these findings, where DM maintained its significance with an OR of 2.51 (95% CI: 1.09–5.75) and a p-value of 0.029. In addition, D-dimer levels of >2500 µL were associated with the outcomes, showing an OR of 2.42 (95% CI: 1.22–4.82) and a p-value of 0.012, indicating a protective effect against the adverse outcomes (**Table 2**).

DISCUSSION

During the COVID-19 pandemic, patients with cancer are recognized as a particularly vulnerable group in the population. Cancer treatments—be it surgery, chemotherapy, or radiotherapy—tend to leave patients more susceptible to secondary infections and severe complications due to the treatments' immunosuppressive effects, as well as increasing the tendency for blood clots, and often requiring patients to be put in special treatment rooms. Consequently, treating cancer presents numerous hurdles, not least because of the potential harm to healthy cells and the adverse effects associated with therapy. Evidence suggests that cancer patients are at a higher risk of contracting COVID-19 and may experience more severe effects upon infection [6,11,12]. A study by Yang et al. [11] found that cancer patients with COVID-19 have a higher risk of developing severe disease outcomes. Specifically, during the initial outbreak In Wuhan, China, a small yet significant percentage (1-2%) had a concurrent cancer diagnosis. This statistic is particularly relevant to our study, which was conducted in a national cancer center hospital in Indonesia.

Our study encompasses a total of 180 patients, with the majority being female. The most prevalent type of cancer among these patients was solid cancers, which accounted for a total of 145 patients (80.6%), with breast cancer as the most common subtype. This aligns with global patterns as breast cancer is often the most frequently occurring solid tumor. Meanwhile, hematological cancer was less common, accounting for only 35 patients (19.4%), with acute myeloid leukemia (AML) as the most common subtype. These findings are consistent with several similar study reports. Yang et al. [11] also reported that solid cancer, particularly breast cancer, was the most common among cancer patients with COVID-19. Sorouri et al. [12] study also found a similar trend, with solid cancer being more predominant than hematological cancer. However, the most common solid cancers found in their study were gastrointestinal cancer followed by breast and lung cancer, while the most common hematological cancer was ALL followed by AML and CML. These variations could be due to geographical and lifestyle differences among the populations studied.

Cancer patients with asymptomatic COVID-19 or with only mild symptoms typically manage their illness by self-isolating at home. However, those with moderate, severe, or critical symptoms often require hospitalization [13]. Our study zeroes in on patients hospitalized in the National Cancer Centre, given that cancer patients typically present with additional health challenges as well as comorbidities that demand careful management. Cancer patients with COVID-19 who are hospitalized have a higher severity of COVID-19 infection. One of the key observations in this study is the interplay between hospitalization length, severity of the COVID-19 infection, and existing comorbid conditions. Our study indicates no significant difference in mortality rates between patients hospitalized for ≤8 days and those for >8 days. However, this finding is contrary to Sorouri et al. [12], where the length of hospital stay was correlated with outcomes in COVID-19 patients with cancer, suggesting that shorter hospital stays might be due to rapid health deterioration leading to mortality. It's plausible that the hospitalization length in the context of Indonesia did not drastically affect outcomes due to the difference in medical interventions or other unmeasured factors like patient resilience or hospital resource availability. Our study also suggests that the severity of COVID-19 infection did not show a statistically significant association with mortality based on the multivariate analysis. This finding is interesting since it could indicate that other factors, such as the cancer type or treatment, may play a more substantial role in determining patient outcomes. This idea is supported by other studies where severe infection states have been tied to poorer outcomes for cancer patients [12,14].

Regarding comorbid conditions, our study found that diabetes mellitus (DM) was significantly associated with increased mortality. This is consistent with broader research that highlights DM as a critical factor in COVID-19 severity and mortality, underscoring the heightened vulnerability of patients with this comorbidity [12–14]. The mechanism of cancer development in patients with diabetes remains unclear. However, several pathogeneses have been suggested to play a consequential role in carcinogenesis, among which processes primarily lie in the effect of chronic inflammation resulting from hyperglycemia and obesity. Failure of insulin secretion regulation caused by hyperinsulinemia leads to increasing growth of biological activity of insulin-like growth factor, which has been reported to promote rapid proliferation and metastasis of cancer cells. Furthermore, diabetes increases the

Table 2. Bivariate and multivariate analysis of demographic and clinical characteristics for mortality

Variable	Outcome				Bivariate Analysis		Multivariate Analysis	
	Deceased		Alive		OR (95% CI)	p	OR (95% CI)	p
	n	%	n	%				
Sex								
Female	41	37.6	68	62.4	1.10 (0.59–2.06)	0.74		
Male	25	35.2	46	64.8				
Age								
≤50	35	40.2	52	59.8	1.34 (0.73–2.47)	0.33		
>50	31	33.3	62	66.7				
Cancer Type								
Solid	55	37.9	90	62.1	1.33 (0.61–2.93)	0.47		
Hematology	11	31.4	24	68.6				
Comorbid								
DM	18	56.3	14	43.8	2.67 (1.23–5.83)	0.01	2.51 (1.09–5.75)	0.029
Kidney Disease	17	43.6	22	56.4	1.45 (0.71–2.98)	0.31		
Hospitalization Length for COVID-19								
≤8 days	36	38.3	58	61.7	0.86 (0.47–1.58)	0.63		
>8 days	30	34.9	56	65.1				
The severity of infection of COVID-19								
Moderate	23	35.4	42	64.6				
Severe	30	33.3	60	66.7	1.091 (0.57–2.05)	0.78		
Critical	13	52.0	12	48.0				
Antivirus administration								
Yes	51	38.9	80	61.1	1.44 (0.71–2.91)	0.30		
No	15	30.6	34	69.4				
Anticoagulants administration								
Yes	48	38.1	78	61.9	1.23 (0.63–2.40)	0.54		
No	18	33.3	36	66.7				
D-dimer (n=180)								
≤2500 ng/L	24	26.7	66	73.3	2.57 (1.37–4.81)	0.003	2.42 (1.22–4.82)	0.012
>2500 ng/L	42	46.7	48	53.3				
Thrombocyte (n=160)								
≤150 uL	26	44.8	32	55.2	2.08 (1.05–4.16)	0.03		
>150 uL	29	28.4	73	71.6				
Hemoglobin (n=161)								
≥12 mg/dL	20	45.5	24	54.5	1.87 (0.92–3.82)	0.083		
<12 mg/dL	36	30.8	81	69.2				
Leucocyte (n=159)								
≤10000	20	30.8	45	69.2	1.33 (0.68–2.61)	0.40		
>10000	35	37.2	59	62.8				
Albumin (n=124)								
<3.2 g/dl	33	41.3	47	58.8	0.66 (0.31–1.44)	0.30		
≥3.2 g/dL	14	31.8	30	68.2				
C-reactive protein (n=124)								
>5 mg/dL	46	42.2	63	57.8	2.92 (0.77–10.94)	0.11		
≤5 mg/dL	3	20.0	12	80.0				
Interleukin-6 (n=24)								
>4 pg/dL	0	0	0	0				
≤4 pg/dL	8	33.3	16	66.7				

P-ISSN: 1978-3744 E-ISSN: 2355-6811

production of oxidative stress leading to DNA damage, which increases the risk of cancer development. In addition, the hyperglycemic state is disruptive to the mechanism of repair in damaged cells [15]**.** A study by Ranc et al. [16] suggested that there's an increased mortality rate among cancer patients using oral hypoglycemic agents (OHAs) or insulin that reflects the greater comorbidity at cancer diagnosis and thus poorer survival outcomes. Other studies such as those by Kulscar et al. [17] have demonstrated that SARS-CoV and MERS-CoV infections caused prolonged airway inflammation, immune system disruption, and changes in the expression of inflammatory markers in diabetic models. These findings are particularly alarming for cancer patients, whose immune system and chronic could be major factors driving poor outcomes upon COVID-19 infection.

Notably, hospitalization is linked to a greater intensity of COVID-19 symptoms in these patients. One of the common complications in severe COVID-19 cases is the cytokine storm, marked by a surge in pro-inflammatory cytokines such as IL-6, which can escalate to respiratory failure and, consequently, death. The intricate balance of the immune response in cancer patients, which can swing between suppression and hyperactivation due to the malignancy or its treatment, also plays a role in the increased susceptibility to SARS-CoV-2 infection [18,19]. In our study, we found that patients with solid cancers have a higher death percentage compared to hematological cancers, which possibly reflects the greater proportion of solid tumor cases in the patient population. However, several studies reported contrasting results. Yang et al. [11] reported a 41% mortality rate for hematological cancers, which surpasses the 17% associated with solid tumors, while several multicenter studies reported [20,21,22] that patients with hematological cancers exhibit a higher mortality rate attributed to COVID-19 compared to those with solid cancers. This observation is likely due to acute respiratory distress syndrome and coagulopathy, which are more prevalent in patients with hematological cancers. Furthermore, the administration of myelosuppressive therapy in these patients also plays a role, on top of an already immunocompromised state of their underlying condition. Research by Lee et al. [23] demonstrated that hospitalization and mortality rates are higher for hematological cancers compared to other tumor types. On that account, it should be taken into consideration that discrepancies between our study and others may result from varying cancer characteristics and conditions within the Indonesian population as opposed to other countries.

Examining both cancerous and non-cancerous cohorts with COVID-19, studies suggest an equivalent rate of thrombosis. However, the mortality rate is significantly higher in the cancer-affected cohort [22]. The tendency towards hypercoagulation in cancer patients with COVID-19, which is a result of severe inflammation, may see potential improvements in prognosis with timely anticoagulation treatment, highlighting the need for immediate response upon detection of hypercoagulability [24,25]. Coagulation disorders present a critical risk for COVID-19 patients, and within our study cohort, most cancer patients (92.8%) experienced an increase in D-dimer values (>500 ng/L), averaging at 5863 ng/L. Multivariate analysis also showed higher D-dimer (>2500 ng/L) have a significantly higher mortality risk (P-Value <0.05). This is in line with studies that have showed consistent presentation of higher levels inflammation and clotting markers such as IL-6, CRP, D-dimer, and prothrombin in cancer patients compared to non-cancer patients with COVID-19 [26]. Research has also proposed a predictive model incorporating CRP and D-dimer levels as indicators to gauge the gravity of COVID-19 infection. A predictive model study from Indonesia showed that the combined values of CRP 72.65 mg/L and D-dimer 1250 mg/L could be used to determine the severity of COVID-19 infection with moderate accuracy [27]. Although our findings noted an increase in mortality as CRP levels rose (value >5 ng/L), the association wasn't statistically significant. Conversely, a meta-analysis indicated that the value of D-dimer can be used as a prognostic factor for both COVID-19 severity and the likelihood of patient survival [28]. Another study suggested a stratification of D-dimer into different levels (0.5 g/ml, 1 g/ml, and 2 g/ml) to predict COVID-19 mortality [29]. Additionally, a noted variance in D-dimer levels between non-cancer (1011 on average, n=353) and cancer patients (1595 on average, n=45) reinforces the potential benefits of anticoagulant therapy in treating hypercoagulation in cancer patients with COVID-19 [30]. Furthermore, data presented by the Register COVID-19 and Cancer Consortium (CCC19) through a cohort study of patients hospitalized with cancer and COVID-19, history of cancer therapy, active disease, cancer with a high risk of VTE, and ICU admissions demonstrate that patients who have a high risk of developing VTE and PE have a minimal risk after receiving anticoagulant therapy before hospitalization [31].

Although anticoagulation is a key strategy in managing the severe state of COVID-19, a higher prevalence of thrombocytopenia, particularly in populations with hematological cancers may pose a challenge to its implementation [11,32]. Our findings using bivariate analysis found that thrombocytopenia is a risk factor associated with mortality in hospitalized cancer patients with COVID-19 (P value <0,05). These findings are consistent with several similar study reports, such as those of Sorouri et al. [12] that found thrombocytopenia as a risk factor for increased mortality rate among cancer patients with COVID-19. Although, it is worth mentioning that platelet data were limited to only 160 patients in

our study sample. The coagulation abnormalities seen with COVID-19 are thought to involve a mix of dysregulation of the coagulation process. The currently available evidence suggests that COVID-19 coagulopathy represents a combination of localized pulmonary platelet consumption, low-grade disseminated intravascular coagulation (DIC), and variably thrombotic microangiopathy. Elevated levels of vWF (von Willebrand Factor) levels and soluble thrombomodulin imply activated or damaged endothelium, as has been seen histologically in autopsy studies. The damaged endothelium would result in the release of ultra-large vWF multimers capable of interacting with platelets, leading to platelet activation, microthrombi, and platelet consumption [33]. The association of DIC with severe state and poor prognosis of COVID-19 patients therefore highlights the need to focus on coagulation dysfunction as part of patient management. Monitoring these coagulation markers may improve the prognosis of COVID-19 inpatients. Furthermore, increasing evidence to support DIC, a devastating systemic disorder is linked with severe COVID-19, prompting considerable concern about multiple organ dysfunction [34].

Anticoagulation is an important modality in preventing hypercoagulation, especially in at-risk populations such as cancer patients, and its administration in hospitalized COVID-19 patients requires consideration of prophylactic anticoagulation unless contraindications are found [25,35]. In our study, a total of 126 (70%) cancer patients with COVID-19 received anticoagulants, while the other 30% did not. However, our analysis indicates that there was no statistically significant decrease in mortality with anticoagulant administration in this cohort. Albeit so, it raises an important consideration given the increased risk of thrombosis in cancer patients, especially with COVID-19. Previous studies have emphasized the critical role of anticoagulants in managing COVID-19 patients, particularly in preventing complications from hypercoagulability [36]**.** The American Society of Hematology recommends that anticoagulation therapy in COVID-19 patients should be considered if platelet values <30–50 x 10^9/L or fibrinogen <1.0 g/L [37]. A similar study shows that cancer patients with COVID-19 have increased thromboembolic events, with poorer outcomes. Patients who receive prophylactic anticoagulation have a lower incidence of thrombosis, and those who receive anticoagulation therapy have a lower platelet count. The study found that mortality, ICU admission rates, intubation, and hospitalization length were higher in COVID-19 patients with cancer, with their average hospitalization being 6 days [38]. In addition to anticoagulant therapy, antiviral therapy is a vital component of COVID-19 management, especially in cancer patients who are at increased risk of thromboembolic events. However, in our study, the administration of antivirals did not significantly impact mortality outcomes, which might suggest that the therapeutic benefit of antivirals does not markedly differ between cancer and non-cancer patients or that the progression of COVID-19 in cancer patients may be less influenced by viral replication and more by the host response [39].

Other laboratory findings such as alterations in levels of hemoglobin, leukocyte count, and albumin levels also provide valuable insights into the patient's state and risk of mortality [16]. Our study indicates an upsurge in death rate with low hemoglobin levels (<12 mg/dL) and leukocytosis (>10000 ug/dL), although there was no statistically significant association with mortality in this study. This observation is consistent with several studies that showed a marked association between increased mortality rate with abnormalities of complete blood count test in cancer patients with COVID-19 [11,12,20]. In their study, Da Silva et al. [20] found that low hemoglobin levels and lymphocytopenia are associated with higher mortality rates in cancer patients with COVID-19. Similarly, Yang et al. [11] noted leukocytosis is significantly associated with the mortality rate in cancer patients with COVID-19. Another study by Viana-Llamas et al. [40] indicated that measuring serum albumin upon admission could aid in identifying SARS-CoV-2 patients at high risk of developing severe complications and poor prognosis, as hypoalbuminemia was found to be one of the early predictors of in-hospital mortality in COVID-19 patients. Hence, these markers are generally considered crucial markers of systemic inflammation and patient prognosis in the context of COVID-19 and cancer.

Within the COVID-19 cohort of cancer patients in our study, there were notable irregularities in blood counts, as well as higher CRP and D-dimer levels**.** The research, undertaken at a national cancer referral hospital, indicated that the mortality rate was 36.7%, with all participants of the cohort being diagnosed with cancer. A significant challenge during the first two months of the study period was the absence of a dedicated intensive care unit for COVID-19 patients at the hospital, which therefore inevitably impacted the quality of care provided to the patients. This study has several limitations; the sample size this study is relatively small, with incomplete data on certain blood test results as dependent variables due to the varied management approaches across patients, thus the results may not represent the entirety of patients affected by COVID-19 in the broader population of cancer patients. It is also important to note that early in the pandemic, many patients received treatment solely in the emergency department and could not be hospitalized due to the limited capacity of isolation units. Additionally, factors such as the cancer stage and the therapy that the patient was undergoing at the time (such as surgery, chemotherapy, radiotherapy) were also not factored in the study analysis.

P-ISSN: 1978-3744 E-ISSN: 2355-6811

CONCLUSIONS

Cancer patients are at a heightened risk of severe complications and poorer disease progression, where COVID-19 infects their condition and delays definitive therapy. Our study analyzed the risk factors contributing to the mortality of hospitalized cancer patients with COVID-19 at the Dharmais National Cancer Center, Jakarta, Indonesia. Our findings robustly demonstrate that high D-dimer levels and diabetes mellitus are risk factors that significantly increase mortality risks in this vulnerable population. Notably, patients with elevated D-dimer levels were twice as likely to succumb to the disease, a critical insight that emphasizes the profound impact of coagulopathy in the progression of COVID-19 among cancer patients. The high incidence of coagulation disorders in this population necessitates stringent monitoring and management of coagulation parameters as part of their comprehensive care. Given the substantial clinical implications, proactive anticoagulant therapy should be considered to mitigate the heightened risk of thrombotic complications in this cohort. This study contributes to the broader understanding of COVID-19's impacts on oncological outcomes, reinforcing the need for better therapeutic strategies to improve survival rates among patients during the pandemic.

DECLARATIONS

Competing Interest

The authors declare that they have no competing interests.

Ethics Approval

The study was conducted after obtaining an ethical review certificate (082/KEPK/IX/2021) from the ethics committee of the Dharmais National Cancer Center.

Funding

This study was supported by a grant from Dharmais National Cancer Center (Jakarta)

Acknowledgments

The authors are thankful to Isthi Dyah Pangesti and Giovanni Anggasta Onggo for writing the project proposal.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497–506.
2. Yabroff KR, Wu XC, Negoita S, et al. Association of the COVID-19 Pandemic With Patterns of Statewide Cancer Services. J Natl Cancer Inst. 2022 Jun 13;114(6):907–909.
3. Jiang C, Yabroff KR, Deng L, et al. Prevalence of underlying medical conditions associated with severe COVID-19 illness in adult cancer survivors in the United States. J Natl Cancer Inst. 2022;114(1):156–159.
4. Grivas P, Khaki AR, Wise-Draper TM, et al. Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium. Ann Oncol. 2021 Jun;32(6):787–800.
5. Shi W, Lv J, Lin L. Coagulopathy in COVID-19: Focus on vascular thrombotic events. J Mol Cell Cardiol. 2020 Sep;146:32.
6. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020 Mar;21(3):335–337
7. Savvari P. Cancer-associated thromboembolism: could direct-acting oral anticoagulants be a promising therapeutic option? Literature review. Forum of Clinical Oncology. 2020;11:22–8.
8. Pan S, Jiang J, Chen Z, Yang L. Management and thinking on the treatment of cancer patients during the COVID-19. Front Mol Biosci. 2020;8.
9. Guidelines Review Committee. Therapeutics and COVID-19: living guideline [Internet]. World Health Organization; 2022 [cited 2022 May 3]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.
10. Mucha SR, Dugar S, McCrae K, et al. Update to coagulopathy in COVID-19: Manifestations and management. Cleve Clin J Med. 2021 Jun 2.
11. Yang K, Sheng Y, Huang C, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020 Jul;21(7):904–913.
12. Sorouri M, Kasaeian A, Mojtabavi H, et al. Clinical characteristics, outcomes, and risk factors for mortality in hospitalized patients with COVID-19 and cancer history: a propensity score-matched study. Infect Agent Cancer. 2020 Dec 17;15(1):74.
13. Guidelines Review Committee. Therapeutics and COVID-19: living guideline [Internet]. World Health Organization; 2022 [cited 2022 May 3]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.3
14. Abuhelwa Z, Alsughayer A, Abuhelwa AY, et al. In-hospital mortality and morbidity in cancer patients with COVID-19: a nationwide analysis from the United States. Cancers. 2022 Dec 30;15(1):222.
15. Kim SS, Kim HS. The impact of the association between cancer and diabetes mellitus on mortality. J Pers Med. 2022; 12(7):1099.
16. Ranc K, Jørgensen ME, Friis S. Mortality after cancer among patients with diabetes mellitus: effect of diabetes duration and treatment. Diabetologia. 2014; 57:927–934.

17. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight. 2019 Oct 17;4(20):e131774.
18. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020 Jun 6;395(10239):1763–1770.
19. Mangalmurti N, Hunter CA. Cytokine Storms: Understanding COVID-19. Immunity. 2020 Jul 14;53(1):19–25.
20. da Silva JL, de Souza BSW, de Albuquerque LZ, et al. Factors influencing COVID-19 mortality among cancer patients: A Brazilian multi-institutional study. PLoS One. 2023 Dec 21;18(12):e0295597.
21. Mehta V, Goel S, Kabarriti R, et al. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. Cancer Discov. 2020 Jul; 10(7):935–41.
22. Dai M, Liu D, Liu M, et al. Patients with Cancer Appear More Vulnerable to SARS- CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov. 2020 Jun; 10(6):783–91.
23. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. Lancet Oncol. 2020 Oct;21(10):1309–16.
24. Iba T, Levy JH, Connors JM, et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020 Jun 18;24(1):360.
25. Xiong B, Liu T, Luo P, et al. Prominent Hypercoagulability Associated With Inflammatory State Among Cancer Patients With SARS-CoV-2 Infection. Front Oncol. 2020 Jul 16;10:1345.
26. Elgohary G. COVID-19 infection in cancer patients: a systematic review and meta-analysis with emphasizing the risk and prognosis stratification. Hematol Transfus Cell Ther. 2020 Oct;42:24–5.
27. Sukrisman L, Sinto R. Coagulation profile and correlation between D-dimer, inflammatory markers, and COVID-19 severity in an Indonesian national referral hospital. J Int Med Res. 2021 Nov;49(11):3000605211059939.
28. Zhan H, Chen H, Liu C, et al. Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. Clin Appl Thromb Hemost. 2021 Jan;27:10760296211010976.
29. Li Y, Deng Y, Ye L, et al. Clinical Significance of Plasma D-Dimer in COVID-19 Mortality. Front Med. 2021 May 25;8:638097.
30. Patell R, Bogue T, Bindal P, et al. Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19. J Thromb Haemost. 2020 Sep;18(9):2349–57.
31. Li A, Kuderer NM, Warner JL, et al. Incidence of and Risk Factors for Venous Thromboembolism Among Hospitalized Patients with Cancer and COVID-19: Report from the COVID-19 and Cancer Consortium (CCC19) Registry. Blood. 2020;136(Supplement 1):56–58.
32. Salunke AA, Nandy K, Pathak SK, et al. Impact of COVID-19 in cancer patients on severity of disease and fatal outcomes: A systematic review and meta-analysis. Diabetes Metab Syndr. 2020 Sep;14(5):1431–7.
33. Wool GD, Miller JL. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. 2021;88(1):15–27.
34. Zhou X, Cheng Z, Luo L, et al. Incidence and impact of disseminated intravascular coagulation in COVID-19 a systematic review and meta-analysis. Thromb Res. 2021 May;201:23–9.
35. Horowitz NA, Brenner B. Thrombosis and Hemostasis Issues in Cancer Patients with COVID-19. Semin Thromb Hemost. 2020 Oct;46(7):785–8.
36. Han MA, Hwang EC, Jung JH. Prognostic factors of mortality in patients with cancer infected with COVID-19: a systematic review protocolBMJ Open 2023;13:e071810.
37. Kollias A, Kyriakoulis KG, Dimakakos E, et al. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol. 2020 Jun;189(5):846–7.
38. Zavras PD, Mehta V, Goel S, Pradhan K, Billett HH. Increased Incidence of Thrombosis in a Cohort of Cancer Patients with COVID-19. Acta Haematol. 2022;145(2):152–159.
39. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708–1720.
40. Viana-Llamas MC, Arroyo-Espliguero R, Silva-Obregón JA, et al. Hypoalbuminemia on admission in COVID-19 infection: An early predictor of mortality and adverse events. A retrospective observational study. Med Clin (Barc). 2021;156(9):428–436.