Characteristics of COVID-19 patients with malignancies comorbidity in Sanglah General Hospital, Bali, Indonesia

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ABSTRACT

Background: Cancer patients are at risk of exposing COVID-19 because of their weakened immune system, caused by tumor growth and anti-cancer therapy. Cancer patients can also increase the risk of severe infection. This study aims to determine the characteristic of COVID-19 patients with malignancies in our institution.

Methods: We analyze the data of 68 COVID-19 patients with malignancies as comorbidities who were hospitalized or treated in our institution using cohort retrospective design. Variables assessed in this study include gender, age, type of malignancy, organ involved, cancer treatment, the severity of COVID-19, and outcome. Data were analyzed using SPSS version 25 for Windows and interpreted as number and percentage.

Results: Solid malignancy was the most common type (82,4%). The lung and thorax were the most common organ involved, followed by the cervix, abdomen, breast, and nasopharynx. Most patients (66.2%) with malignancy suffered from COVID-19 with mild-moderate (non-severe) symptoms and 33,8% severe symptoms. Sixteen (23.5%) patients have died. Laboratory findings showed elevated NLR and D-dimer in both severe and non-severe cases. The median NLR of all cases was 5.97. The median D-dimer was 1.61 ìg/ml. Patients with solid malignancy (35.7%) are more exposed to severe COVID-19 than the hematological type (p=0.477). Patients with malignancy who had received therapy for their cancer had more severe symptoms than those who had not received cancer therapy (41.7% vs. 25%) (p=0.147), although not statistically significant.

Conclusion: Solid malignancy was the most common type diagnosed with COVID-19. More malignancy patients experienced mild to moderate COVID-19 symptoms, and one-third of them experienced severe symptoms.

Keywords: Characteristics, COVID-19, Malignancies.
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INTRODUCTION

Coronavirus Disease-2019 (COVID-19) is caused by a novel coronavirus that also results in a pandemic. The symptoms of COVID-19 vary and are influenced by comorbidities.[1,2] Chronic underlying diseases, such as cancers, are one of the most vulnerable. Cancer patients are included in a vulnerable group who are at risk of exposing COVID-19 because of their weakened immune system caused by tumor growth and anti-cancer therapy. Cancer patients are not only at risk of exposure to COVID-19 but can also increase the risk of severe infection.[2,3]

Although data collected are heterogeneous, 1%–8% of patients hospitalized with COVID-19 had a history of hematological malignancies or solid malignancies. Several studies reported that patients with cancer are possibly more likely to be infected by SARS-CoV-2 and tend to develop severe complications defined here as admission in intensive care, the need for ventilation devices or death as a result of COVID-19.[4-6] The mortality rate in patients with cancer has been reported to be 25%–30%.[7]

Our institution is a COVID-19 referral hospital and a cancer referral in the Bali area, so research on COVID-19 patients with malignancy is important. Based on those mentioned above, this study aims to evaluate the characteristics of COVID-19 patients with malignancies comorbidity in Sanglah General Hospital, Bali, Indonesia.

METHODS

This study was a descriptive-analytic study with a cohort retrospective design on 68 patients with confirmed cases of COVID-19 with malignancies as comorbidity. We retrospectively analyze the data of COVID-19 patients with malignancies as comorbidities who were hospitalized or treated in our institution, Sanglah General Hospital, a tertiary hospital in Bali and referral center of COVID-19 cases. Consecutive sampling was done retrospectively by collecting the data from May 2020 to August 2021 by managing the medical record; 68 patients with COVID-19 and malignancies could be identified. Data collected were socio-demographics, type of malignancies,

including solid malignancy, disease status at detection of SARS-COV-2 (on therapy or without therapy). Solid malignancy is defined as a malignancy that involves solid organs (e.g., lung, head and neck, abdominal, gynecology, prostate, mammae, and musculoskeletal).[8] Hematological malignancy is defined as a malignancy that involves blood and blood-forming tissues such as lymphoid and bone marrow (e.g., lymphoma, leukemia, and myeloma).[9]

As evidenced by imaging studies, patients with malignancies were described as patients already diagnosed by cytologic/histopathologic assessment or patients with suspected malignancy. The NLR ratio is the absolute number of neutrophils compared to the absolute number of lymphocytes obtained from the patient's complete blood count, and its value was grouped into normal ($\leq 3{,}3$) and high ($> 3{,}3$). The D-dimer level also divides into normal (<0,5 ìg) dan high. Clinical manifestation of COVID-19 was described as non-severe and severe symptoms. Symptoms of severe COVID-19 are described by clinical signs of pneumonia accompanied by signs of respiratory distress (respiratory rate > 30 breaths/minute, oxygen saturation < 93% room air). The statistical analysis of this study was performed using the IBM SPSS version 25 for Windows.

RESULTS

A total of 68 COVID-19 patients with malignancies treated in our institution were included in our study. Among them, 57.4% were male and 42.6% were female patients. Most of the patients (69.1%) were 18-65 years old. Solid malignancy was the most common type among them (82.4%). A total of 14 (20.6%) patients with head and neck malignancy diagnosed with COVID-19, 11 (16.2%) patients with lung malignancy, 7 (10.3%) patients with mammary malignancy, 12 (17.6%) patients with hematological malignancy, 9 (13.2%) patients with abdominal organ malignancy, 10 (14.3%) patients with gynecological malignancy, 5 (7.4%) patients with urological and musculoskeletal malignancy. Cancer therapy has been administered to 47.1% of patients diagnosed with COVID-19. Most patients (66.2%) with malignancy suffered

from COVID-19 with mild-moderate (non-severe) symptoms and 33.8% severe symptoms. Sixteen (23.5%) patients have died. All data can be seen in Table 1.

Laboratory findings showed elevated NLR and D-dimer in both severe and non-severe cases. The median NLR of all cases was 5.97, the median of the non-severe and severe group was 5.38 and 11.21, respectively. At the same time, the median D-dimer of all patients, non-severe and severe cases, was 1.61 ìg/ml, 1.57 ìg/ml, and 2.99 ìg/ml respectively.

We tried to analyze with the Chi-Square test, as seen in Table 2, whether some variables such as type of cancer and cancer therapy were correlated with COVID-19 severity. There were more COVID-19 patients in this study with non-severe symptoms in solid and hematological types. The patients with solid malignancy (35,7%) are more exposed to severe

COVID-19 than the hematological type (p=0.477) (Table 2). Patients with malignancy who had received therapy for their cancer had more severe symptoms than those who had not received cancer therapy (41.7% vs. 25%) (p=0.147) (Table 2).

DISCUSSION

Cancer patients are included in a vulnerable group who are at risk of exposing COVID-19 because of their weakened immune system caused by tumor growth and anti-cancer therapy. Cancer is a disease characterized by the uncontrolled growth of abnormal cells and can invade and spread to other organs.[5]

In our study, solid malignancy was the most common type diagnosed with COVID-19. The lung and thorax are the most common organ involved, followed by the cervix, abdomen, breast, and

Table 1. **Characteristic of Malignancy Patients with COVID-19.**

Variable	Total (N=68)
Sex, n (%)	
Male	39 (57,4)
Female	29 (42,6)
Age (Years), n (%)	
<18	6 (8,8)
18-49	26 (38,2)
50-65	21 (30,9)
>65	15 (22,1)
Type of Malignancy, n (%)	
Solid	56 (82,4)
Hematology	12 (17,6)
Organ Involved, n (%)	
Lung and Thorax	11 (16,2)
Head and Neck	14 (20,6)
Thyroid	3 (4,5)
Brain	3 (4,5)
Nasopharynx	7 (10,3)
Mammae	7 (10,3)
Hematology	12 (17,6)
Abdomen	9 (13,2)
Gynecology	10 (14,7)
Cervix	9 (13,2)
Ovarium	1 (1,5)
Urology	2 (2,9)
Musculoskeletal	3 (4,5)
Cancer Treatment, n (%)	
Yes	32 (47,1)
No	36 (52,9)
COVID-19 severity, n (%)	
Non-Severe	45 (66,2)
Severe	23 (33,8)
Outcome, n (%)	
Died	16 (23,5)
Alive	52 (76,5)

Table 2. The relationship of COVID-19 severity and type of malignancy.

Variable	Non-Severe (N=45)	Severe (N=23)	p
Type of malignancy, n (%)			
Hematology	9 (75.0)	3 (25.0)	0.477
Solid	36 (64.3)	20 (35.7)	
Malignancy therapy, n (%)			
Yes	21 (58.3)	15 (41.7)	0.147
No	24 (75.0)	8 (25.0)	

*Chi-Square: statistically significant if p-value less than 0.05

nasopharynx. A total of 17,6 % of patients had hematology malignancy. Dai M et al., conducted a cohort study of 105 cancer patients and reported that lung cancer was the most frequently exposed cancer (20.95%), followed by gastrointestinal cancer (12.38%) and breast cancer (10.48%).[10] Patients with thoracic malignancy, age >65 years, smoking habits, history of chemotherapy, and the presence of comorbidities are associated with an increased risk of mortality due to COVID-19.[5] Lung cancer patients share fragility related to defective pulmonary and alveolar architecture caused by previous surgery, radiation, or airway obstruction that may induce severe infection.[11] As studied in various literature, 83% of cells expressing Angiotensin-Converting Enzyme 2 (ACE2) are type II alveolar epithelial cells, making these cells seem viral reservoirs. Angiotensin-Converting Enzyme 2 gene expression in the lungs also correlates with smoking, frequent in patients with lung cancer.[12]

Although not significant, patients with solid malignancies (35,7%) in our study experienced more severe COVID-19 symptoms than hematological malignancies. Various studies stated hematological malignancies tend to experience more severe events than solid cancers. They showed a trend towards a longer duration of hospitalization and a longer time to improve. Higher levels of proinflammatory cytokines IL-6 in hematologic malignancies, indicating a more inflammatory response in these patients, results in sepsis with multi-organ failure and mortality. This study only involves one institution so that the possible number of visits and the variety of cases differ from other countries.[13,14]

Our study found that more malignancy patients experienced mild to moderate COVID-19 symptoms, and 33,8%

experienced severe symptoms. Cancer patients are not only at risk of exposure to COVID-19 but can also increase the risk of severe infection. The study of Liang W et al., showed 39% of cancer patients with COVID-19 experienced severe symptoms, compared with 8% of patients without cancer.[4] Another retrospective study showed that hematologic malignancies and solid metastatic tumors were at risk for severe symptoms. The COVID-19 and Cancer Consortium (CCC19) study reports that cancer patients are at risk for mortality and serious illness compared to the general population.[6] The retrospective study by Zhang L et al., showed that 53.6% of cancer patients had severe symptoms and the mortality rate was 28.6%.[15]

Patients with malignancy in our study who had received therapy for their cancer had more severe symptoms (41.7%) than those who had received cancer therapy, although it was not statistically significant. Cancer treatment uses agents that can kill or stop cell growth. However, these drugs have the side effect of suppressing the growth of other normal cells such as white blood cells, which can weaken the immune system. Patients with decreased immunity have a higher risk of being exposed to COVID-19. This group is also easily exposed to nosocomial viruses from the hospital because they visit the hospital regularly. Zhang L et al., showed that cancer therapy is given within 14 days, it will significantly increase the risk of severe COVID-19 symptoms.[15] Other studies also reported that cancer therapy, for example, surgery and chemotherapy within 4 weeks, had a significantly higher risk of experiencing severe events and death caused by COVID-19 infection.[4,5,10] Patients who received immunotherapy tended to have high death rates and develop severe symptoms. Patients who received radiotherapy did not show

significant differences in severe symptoms. Lung cancer patients with tyrosine kinase inhibitors had a decreased risk of having severe symptoms.[4,5,10]

Laboratory findings showed elevated NLR and D-dimer in both severe and non-severe cases. The median NLR of severe cases was 11.21, while the D-dimer level was 2.99 ìg/ml. One of the markers of inflammation is Neutrophils Lymphocytes Ratio (NLR), and associated with the poor prognosis of many diseases.[16,17] The NLR describes the ratio between innate immune response and adaptive related to the pro-inflammatory cytokines.[18] Several studies demonstrated that severe COVID-19 patients had elevated NLR levels than non-severe patients.[19,20] Yang AP et al., showed that elevated NLR was an independent marker of poor clinical outcomes for COVID-19 patients.[19] The study revealed that patients with NLR greater than 3.3 should be closely observed because 46.1 % would transform into severe cases. A previous study also revealed that the NLR level in severe COVID-19 was 11.4 and there was a significant difference between severe and non-severe COVID-19 patients (95% CI: 1.081 – 4.641; p=0.023).[20]

Coagulation disorders are often found in COVID-19 patients, especially those with severe symptoms. A multicenter study in China showed 46,4% of COVID-19 patients had elevated D-dimer ($\geq$0.5 mg/L).[21] The D-dimer elevation was more common in severe cases (59.6% vs. 43.2% for non-severe ones).[21] Plasma D-dimer is the lysis end-product of cross-linked fibrin protein degradation and is a critical forecast indicator of coagulation dysfunction. The increase of D-dimer levels is the result of fibrin formation and fibrinolysis. Some studies found that high D-dimer may be related to the poor prognosis in tumor patients. Tumor cells can also promote the coagulation system, increase platelet activity, and damage the vascular endothelial cells.[22] Another study revealed that activation of the blood coagulation system is related to invasive and migration of the tumors. This group's increase in D-dimer levels could be due to COVID-19, malignancy, or both factors.[23-25] Our study was limited to a single institution; therefore, it cannot be generalized.

CONCLUSION

Solid malignancy was the most common type diagnosed with COVID-19; in addition, the lung and thorax is the most common organ involved. More malignancy patients experienced mild to moderate COVID-19 symptoms, and one-third of them experienced severe symptoms. Elevated NLR and D-dimer were detected among all patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest or personal relationship that could have appeared to influence the work reported in this study.

ETHICS CONSIDERATION

This study had obtained ethical approval from the Ethics Committee of Medical Faculty of Universitas Udayana, Sanglah General Hospital, Bali, Indonesia, accompanied with informed consent before the study was started.

FUNDING

AUTHOR CONTRIBUTION

All authors contribute to the study from the conceptual framework, data acquisition, data analysis until reporting the study results through publication.

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