THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021), No 2, p.86-91

CLINICAL FEATURES OF DEATH PATIENTS WITH COVID-19

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Received 15.11.2020; accepted for printing 15.12.2020

Abstract

Pantiwilasa dr. Cipto Hospital, Semarang, Indonesia, was a private tertiary hospital appointed by the Public Health Office Semarang City to provide health services for suspected and confirmed COVID-19 patients. It is challenging due to the variety of clinical manifestations that occurred and the lack of existing research on this disease. The aim of this study is to examine the clinical characteristics of COVID-19 patients who have died.

This was a cross sectional study. The study was conducted from May to July 2020. Obtained data included anamneses, physical examination, and adjunct examination.

Altogether 113 patients were observed at the initial examination. Mean age was 53 years (standard deviation: 14.04 years), mean onset was 5.93 days (SD: 4.27 days). A total of 41 patients non-survived (36.28%) with mean age 58.73 years (SD: 11.87 years). Mean respiratory rate and SpO_2 were 28.38 x/minute (SD: 1.71 x/minute) and 90.95% (SD: 8.84%). We found some variables that related to death were age older than 58 years old (p=0.009), had ≥2 comorbidities (p=0.000), fever t>38°C (p=0.001), respiration rate >28x/minute (p=0.010), SpO_2 <90% (p=0.000), blood lymphocyte count <1.2x10^3/µL (p=0.014), neutrophil-to-lymphocyte ratio >7.4 (p=0.004), bronchopneumonia with other complications (p=0.011).

Factors related to the death of COVID-19 patients were age older than 58 years old, had ≥2 comorbidities, body temperature above 38°C, respiratory rate >28 x/minutes, oxygen saturation below 90%, neutrophil-to-lymphocyte ratio >7.4, lymphocyte count <1.2 x 103/µl, and x-ray result showing bronchopneumonia with other complications.

Keywords: *. characteristics, clinical features, COVID-19, death, mortality, survived.*

Introduction

Coronavirus disease 2019 (COVID-19) has been a lingering worldwide public health emergency. It is a viral respiratory illness caused by a novel coronavirus that was first identified in Wuhan, Hubei province, China in 2019 and has since spread throughout the world. COVID-19 is spread through droplets in the air, intimate contact, and infection results in pneumonia [*Zhu N et al., 2020*]. COVID-19 is highly contagious, with more than 48.5 million cases and nearly 1,231,027 deaths worldwide, according to WHO on November 6, 2020 [*WHO, 2020*]. Indonesia had reported 429,574 cases, the highest in Southeast Asia, ahead of the Philippines. Central Java province was ranked as the fourth-highest case in Indonesia according to data from the Indonesian Ministry of Health by November 1, 2020. Semarang, the capital city of Central Java Province, was ranked as the second city in Indonesia with the highest mortality rate (40.13 per 100,000 population).

COVID-19 is caused by SARS-CoV-2, a coronavirus that has never been identified in humans before. COVID-19 transmission is known as interhuman transmission. The rapid increase in the number of COVID-19 cases and interhuman transmission has made COVID-19 is more accessible to transmit than SARS and MERS [*Nastiti R et al., 2020*]. The SARSCoV-2 genome is a 30,000-nu-

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cleotide single-stranded positive-sense RNA. Additionally, the contact between the host and the virus that causes infection necessitates a sophisticated immune response [*Nidom R et al., 2020*]. The incubation time for SARS-CoV-2 is five to six days and two weeks after virus exposure. Current evidence suggests that the main transmissions are via droplet, contact, and aerosol transfer [*Adriana D, Miftahussurur M, 2020*].

Fever and a dry cough are frequent symptoms of SARS-CoV2 infection.

Certain patients report sore throats, runny noses, anosmia (loss of smell), and diarrhea [*Maranatha D et al., 2021*]. Ageusia (loss of taste sensation) was recently identified as a symptom in confirmed cases [*Soedarsono S, 2020*]. According to data from hospitalized patients, the majority of COVID-19 cases (approximately 80%) is presented without symptoms (asymptomatic) or with moderate symptoms, while the remainder is presented with serious symptoms or is in critical condition. Patients with serious cases complain of shortness of breath and/or hypoxia one week after onset of the disease, which rapidly progresses to acute respiratory distress syndrome, septic shock, and death [*Maranatha D et al., 2021*]. The infection response that develops into acute respiratory distress syndrome was caused by an increase in the release of pro-inflammatory cytokines known as the cytokine storm phenomenon or cytokine release syndrome [*Mahmudah I et al., 2020*].

Generally, laboratory results indicated that white blood cell count was within the normal range, lymphocyte count was decreased, and C-reactive protein level was elevated [*Soedarsono S, 2020*]. A recent study in 191 patients showed that increased IL-6 was found significantly higher in patients who did not survive than survived patients. Large of cytokine IL-6 released in SARS-CoV-2 infection is activated by the innate immune system, which causes increased vascular permeability resulting in the process of alteration of fluids and blood cells to the alveoli, resulting in the clinical appearance of dyspnea and respiratory failure [*Mahmudah I et al., 2020*]. COVID-19 manifests radiographically as patchy ground glass opacity with or without consolidation involving multiple lobes, mostly in the peripheral region, and accompanied by halo or air bronchogram sign. However, some new COVID-19 clinical symptoms have been identified recently. This made it impossible to diagnose COVID-19 solely on the basis of clinical symptoms [*Soedarsono S, 2020*].

The impact of COVID-19 was also felt by Indonesia as a country with relatively high disparities in the availability of health facilities and infrastructure, causing health facilities, both at the primary level, such as clinics and primary health care (Puskesmas), as well as the referral level, namely hospitals, facing new challenges as health service providers. Hospitals, in this case, take the portion as a place to care for patients with moderate to severe symptoms, face challenges in the form of minimal and still developing science and research on this disease, the availability of both reliable self-protection, diagnostic and therapeutic facilities to diagnose and treat patients with COVID-19, as well as the variety of clinical manifestations that have been reported in patients with COVID-19. Therefore, it is necessary to analyze the characteristics of COVID-19 patients to provide better care. This research is expected to help physicians identify patients with poor prognoses early and guide researchers in developing future management.

Material and methods

Study Designs and Participants: This retrospective study was conducted in Pantiwilasa dr. Cipto Hospital, Semarang, Indonesia. Inclusion criterion was hospitalized patients with PCR-Confirmed SARS-CoV-2 with an admission period from May to July 2020 and completed treatment at the hospital. Patients who underwent self-isolation at home were excluded from this study. Patients referred to other hospitals or insisted on going home before completing treatment at our hospital were discontinued from this study.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Data Collection: All included patients' medical records were checked, and clinical and laboratory data were obtained. A standard form was used to record data, including anamneses, physical examination, and adjunct examination on admission time. Anamneses consisted of age, sex, number of comorbidities, symptoms. Physical examination included blood pressure, heart rate, temperature, respiratory rate, oxygen saturation. We also collected laboratory and chest x-ray results. All data were verified by four researchers.

Definitions: All the anamneses, physical examination, laboratory, and x-ray results in this research were taken on the admission day. In our terms, intensive care unit (ICU) was a surveillance room with a ventilator. Inclusion criteria for ICU were patients with moderate to severe acute respiratory distress syndrome, received ≥2 therapies requiring a syringe pump, received hydrocortisone injection, intubated, requires multidiscipline care from internist and intensivist. The x-ray results were classified into "normal or bronchopneumonia without complication" and "bronchopneumonia with complication". The complication was associated with other abnormalities in the heart (e.g., cardiomegaly, aortic calcification) or lung (e.g., pleural effusion, mass, pneumothorax).

Statistical Analysis: Statistical tests were performed using SPSS23.0 (www.spss.com). Continuous variables were compared by using the Student's *t-tests* or the Mann-Whitney *U*-test, as appropriate. Categorical variables were assessed using the γ^2 test or the Fisher exact test if the cell counts were small. The significance was recognized at a $p<0.05$.

Results

Altogether 113 patients with confirmed COVID-19 were included in this study (Table 1). The mean age was 53 years (standard deviation (SD): 14.04 years), the mean onset was 5.93 days (SD: 4.27 days), and more than half of the patients were recovered.

Table 2 shows the distribution of non-ICU and ICU Patients. Of all the patients, 18 (15.93%) were admitted to the ICU, most of them were men (77.78%). There was no difference in age between non-ICU and ICU Patients.

Table 3 shows the distribution of recovered and non-survived patients. A total of 41 patients did not survive (36.28%), with mean age of 58.73 years (*SD*: 11.87 years). The non-survivor group consisted of more men than women (60.97% vs 39.03%).

The most found symptoms at admission were cough (91.20%), followed by dyspnea (89.40%),

Table 1.

Baseline Characteristics

Characteristics	Numbers (n=113)
Sex	
Male	62 (54.87%)
Female	51 (45.13%)
Mean Age ± SD	53.00 ± 14.04 years
Mean Onset ± SD	5.93 ± 4.27 days
Number of patients in	
ICU	18
non ICU	94 (1 died at the ER)
Number of patients	
recovered	72 (63.71%)
non-survived	41 (36.28%)

SD = Standard Deviation

Table 2.

Distribution of Non-ICU and ICU Patients

	Non-ICU (n=95)	ICU (n=18)
Sex		
male	48 (50.53%)	14 (77.78%)
female	47 (49.47%)	4 (22.22%)
Mean Age ±SD (years)	53.43 ± 14.26	50.06 ± 12.85
Recovered	69 (72.63%)	3 (16.67%)
Non-survived	26 (27.37%)	15 (83.33%)

SD = Standard Deviation

Table 3.

Distribution of Recovered and Non-Survived Patients

	Recovered (n=72)	Non-Survived (n=41)
Sex		
male	37 (51.38%)	25 (60.97%)
female	35 (48.61%)	16(39.03%)
Mean Age ±SD (years)	49.74 ± 14.1	58.73 ± 11.87
ICU	3 (4.17%)	15 (36.59%)
non ICU	69 (95.83%)	26 (63.41%)

SD = Standard Deviation

fever (78.80%), fatigue (52.20%), nausea vomitus (50.40%), and diarrhea (13.30%). The prevalence of patients with more than two comorbidities was 50.44%. There were 50.44% of patients with chest x-ray showing bronchopneumonia with complications. Moreover, table 4 shows the mean of physical examination parameters at the initial assessment of patients. The mean respiratory rate at admission was 28.38 *x/minute* (SD*:* 1.71 *x/minute*), while mean oxygen saturation was 90.95% (SD*:* 8.84%).

The patients were divided into two groups based on the survival status (Table 5). The clinical characteristics of the two groups were compared. We found some variables that related to death were age older than 58 years old (p=0.009), had ≥2 comorbidities (p=0.000), fever t >38°C (p=0.001), respiration rate >28x/minute (p=0.010), SpO_2 <90% (p=0.000), blood lymphocyte $<1.2x10^3/\mu L$ (p=0.014), neutrophil-to-lymphocyte ratio (NLR) >7.4 (p=0.004), bronchopneumonia with other complications (p=0.011).

Discussion

The study found that more men were admitted to the ICU and died from COVID-19, compared to women. The mortality of patients over 58 years old was significantly higher than patients under this age. Men developed more severe cases than women, and deceased patients were slightly older than survivors, which is consistent with a previous report [*Jin J et al., 2020*]. The size of the upper airway decreases in both men and women as they were aging [*Perrotta F et al., 2020*]. However, men have a greater risk of upper airway collapsibility than women. This could be an important point explaining the difference in the prevalence of COVID-19 infection according to gender. Also,

Table 4.

Mean of Physical Examination Parameters at Initial Assessment

Physical Examination	**Mean ± SD**
Blood pressure (*mmHg*) Systole (*mmHg*) Diastole (*mmHg*)	 135.13 ± 24.17 83.56 ± 18.96 mmHg
Heart rate (*x/minute*)	102.17 ± 20.56
Respiratory rate (*x/minute*)	28.38 ± 1.71 x/minute
SpO_2 (%)	90.95 ± 8.84 %

SD = Standard Deviation

Table 5.

Clinical Features Related to Death of COVID-19 Patients

Category	Non-Survived	Recovered	p-value
Anamneses			
Age			
<58 years old	19 (27.14%)	51 (72.85%)	**0.009**
>58 years old	22 (51.16%)	21 (48.83%)	
Comorbidities			
<2 comorbidities	8 (14.28%)	48 (85.71%)	**0.000**
≥2 comorbidities	33 (57.89%)	24 (42.10%)	
Physical Examination			
Fever Status			
No fever & subfebrile (t<38 C)	17 (24.28%)	53 (75.71%)	**0.001**
Fever t >38 C	24 (55.81%)	19 (44.18%)	
Respiratory Rate			
<28 *x/m*	15 (25.42%)	44 (74.57%)	**0.010**
>28 *x/m*	26 (48.15%)	28 (51.85%)	
SpO_2			
<90%	26 (57.78%)	19 (42.22%)	**0.000**
>90%	15 (22.06%)	53 (77.94%)	
Laboratory and Thorax Xray			
Lymphocyte Count			
$<1.2x10^3/\mu L$	26 (47.27%)	29 (52.72%)	**0.014**
$>1.2x10^3/\mu L$	14 (25.45%)	41 (74.54%)	
Neutrophil- Lymphocyte Ratio (NLR)			
<7.4	19 (26.76%)	52 (73.23%)	**0.004**
>7.4	22 (53.65%)	19 (46.34%)	
Thorax Xray			
Normal lung / bronchopneumonia without complications	14 (25.00%)	42 (75.00%)	**0.011**
Bronchopneumonia with complications	27 (47.36%)	30 (52.63%)	

men produce a less intense immune response than women. Therefore, they are more susceptible to infectious agents. Indeed, men undergo a greater decline in total number of T and B cells as they age than women do. Additionally, elderly men's proliferative and cytokine secretory potential of T cells is significantly lower than that of women of the same generation.

A previous study demonstrated a similar result with our research, patients with more comorbidities were more likely to develop severe disease or die [*Zhang B et al., 2020*]. Because comorbidities often increase with age, the elderly population tends to suffer from fatal COVID-19. As people age, impairment of adaptive and innate immunity has been noted. Additionally, older people exhibit continuous production of inflammatory mediators and cytokines. Moreover, anomalies and irregularities that occur in ciliary function could interfere the clearance of SARS-CoV-2 particles in the elderly [*Perrotta F et al., 2020*].

Respiratory rate and oxygen saturation could be the first physical examination that should be aware of by the clinicians at first contact with patients, since respiratory failure is the leading cause of mortality [*Zhang B et al., 2020*]. Our study suggests that patients with saturation of pulse oximetry below 90% should be monitored closely in the surveillance room. However, the cardiac, renal, hepatic, and hemorrhagic damage by the virus and cytokine release should be taken seriously in the same way. We also observed that most of our admitted patients with high NLR and current lymphopenia did not survive. This finding is supported by a recent study that lymphopenia were confirmed as a statistically significant predictor of death risk [*De Vito A et al., 2020*]. Another study with 82 cases of death from COVID-19 discovered that most of their patients had a high NLR of >5 [*Zhang B et al., 2020*]. On the radiological findings, several studies revealed that the most typical features are the peripheral ground-glass opacities, followed by consolidation in the thorax CT scan [*De Vito A et al., 2020*]. Due to some limitations, thorax CT scan and other advanced laboratories parameter were unable to be tested in our hospital.

During this study period, Pantiwilasa Dr. Cipto Hospital, Semarang, Indonesia, only had 2 ICU rooms that made it a challenge in prioritizing the ICU patients. Further well-designed studies with a larger sample size in higher-level healthcare facilities are needed to validate the findings of our current study to provide a better illustration of characteristics of the death COVID-19 patients in Indonesia.

Conclusion

We assume that this was the first published research of non-survived COVID-19 patients held in a tertiary level hospital in Indonesia. We could conclude that factors related to the death of COVID-19 patients were age older than 58 years old, had ≥ 2 comorbidities, body temperature above 38˚C, respiratory rate >28 *x/minutes*, oxygen saturation below 90%, NLR >7.4, lymphocyte count <1.2 x $10^3/\mu L$ and x-ray result showing bronchopneumonia with other complications.

Acknowledgment

The authors wish to express their gratitude to all health-care personnel who assisted in diagnosing and treating COVID-19 patients at Pantiwilasa dr. Cipto Hospital in Semarang, Indonesia. We thank all the medical records and laboratory staff for helping with the data collectio; the hospital director and ethics committee for the permission granted to run this research. We also thank dr. Thomas Handoyo, MD for his help in substantial editing.

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THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021). No 2

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