COVID-19 PATIENT SURVIVALITY FACTORS AT RSUP DR. KARIADI SEMARANG

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ABSTRACT

Introduction: The clinical manifestations of Covid-19 patients are various, related to several factors including: age, gender, previous comorbid diseases, the first time they visited a health facility, the length of treatment, and the presence of abnormal laboratory values. Several cases of patients with severe symptoms had a history of previous disease, chronic obstructive pulmonary disease (4.8%), coronary heart disease (10.4%), hypertension (38.7%), diabetes (19.3%), asthma (4.8%), with patients aged over 65 years (56.9%) and having a history of smoking (19.2%).
Aim: Analyzing the survival factors of PDP Covid-19 patients at RSUP Dr. Kariadi
Methods: A retrospective cohort study conducted at Dr. Kariadi Semarang. The independent variables of the study were the characteristics of the research subjects based on the patient's medical record data. The dependent variable of the study was the degree of patient survival. This study used 291 confirmed COVID-19 patients at dr. Kariadi who met the inclusion criteria and did not have the exclusion criteria.
Results: Based on 291 research subjects, research subjects were dominated by men (55%), with an age range of 51-60 years (34.4%). The highest degree of COVID-19 was suffered by moderate degrees (62.2%). Most of the study subjects were alive at the end of the study (92.1%). The most frequently complained symptoms of COVID-19 were dry cough (58.8%), shortness of breath (56%), and fever (50.9%). The most frequently reported comorbid disease was diabetes mellitus (27.1%). There was a significant difference in hemoglobin levels (P=0.039) and CRP levels (P=0.015) between the living and dead groups. In the dead group, the hemoglobin level was lower, while the CRP level was higher. Factors that affect the survival of COVID-19 patients include the degree of COVID-19 (P=0.010; OR=3.00) and CKD conditions (P=0.007; OR=0.21). Factors that influence the degree of COVID-19 include gender (P=0.045), dry cough symptoms (P=0.034) and shortness of breath (P=0.049). Female gender, not having a dry cough, and not experiencing shortness of breath are protective factors for the incidence of severe COVID-19.
Conclusion: Female gender is a protective factor against severe cases of COVID-19. There is a relationship between the degree of COVID-19 and the survival of the research subjects. So, it can be concluded that indirectly, gender is a survival factor for COVID-19 patients. There is no relationship between age and survival of COVID-19 patients. CKD comorbidity is associated with the survival of the study subjects.

1. INTRODUCTION

On December 31, 2019, the WHO China Country Office reported a case of pneumonia of unknown etiology in Wuhan City, Hubei Province, China. Pneumonia whose spread was so massive that appeared in wuhan, Hubei Province, China, until the end of March 100 countries around the world were infected.[1] On January 7, 2020, China identified pneumonia of unknown etiology as a new type of coronavirus (novel). coronavirus). In early 2020 NCP began to become a global pandemic and became a health problem in several countries outside the PRC.

Indonesia, one of the countries with a large population density in the world is also a distribution area for the SARS COV-2 / Covid 19 virus. Since it was first announced in Indonesia in early February 2020 until the end of April 2020, there have been recorded cases of Covid 19 positive patients in Indonesia. Indonesia has over 9000 cases with more than 700 deaths caused by Covid-19.

The increase in patient cases and cases that caused the death of Covid-19 patients in Indonesia, led the government to declare a National Emergency on February 28, 2020.[2] The Government of the Republic of Indonesia through BNPB and the Ministry of Health made several policy policies in accordance with WHO guidelines to deal with the Covid-19 outbreak.

This study was conducted to analyze the survival factors of Covid-19 patients at Dr. Kariadi.

2. METHODS

A retrospective cohort study conducted at Dr. Kariadi Semarang. The independent variables of the study were the characteristics of the research subjects based on the patient's medical record data. The dependent variable of the study was the degree of patient survival. This study used 291 confirmed COVID-19 patients at dr. Kariadi who met the inclusion criteria and did not have the exclusion criteria.

Inclusion criteria included complete medical records, diagnosed as COVID 19 based on PCR swab results and EWS covid-19, discharge from the hospital for medical indications in a state of death during treatment by meeting the clinical criteria for COVID-19 as the main and immediate cause, patient age $\geq$ 18 years Exclusion criteria included incomplete medical records.

Bivariate analysis was conducted to find correlations between variables. Data normality test was conducted using Kolmogorov Smirnov because the number of research subjects was >50 samples. If the p value > 0.05 then the data is said to be normally distributed, but if the p value < 0.05 then the data is said to be not normally distributed. The difference test uses the Independent T-test if the two variables are normally distributed. The difference test uses Mann Whitney U if one or both of the variables are not normally distributed. The correlation test uses Chi-Square. The significance test was assessed at α= 0.05. If the p-value is less than 0.05, it indicates a significant correlation or difference. The data that has been collected will be processed and analyzed using the SPSS version 26 for Windows application.

3. RESULTS

Variable	n (%)
Gender	
• Male	160 (55)
• Female	131 (45)
Age	
• 17-30 years	20 (6.9)
• 31-40 years	42 (14.4)
• 41-50 years	57 (19.6)
• 51-60 years	100 (34.4)
• 61-70 years	49 (16.8)
• >70 years	23 (7.9)
COVID-19 Severity	
• Mild	0 (0)
• Moderate	181 (62.2)
• Secere	103 (35.4)
Survivalitas	
• Died	23 (7.9)
• Alive	268 (92.1)
Symptom COVID-19	
• Fever	148 (50.9)
• Dry Cough	171 (58.8)
• Cold	12 (4.1)
• Sore Throat	9 (3.1)
• Swallowing Pain	19 (6.5)
• Dyspnea	163 (56)
• Sputum Production	44 (15.1)
• Diarrhea	31 (10.7)
• Abdominal Pain	28 (9.6)
• Nauseous vomit	94 (32.3)
• Black Stool	9 (3.1)
• Constipation	5 (1.7)
Comorbid	
• Chronic Obstructive Pulmonary Disease (COPD)	5 (1.7)
• Stroke	5 (1.7)
• Deep Vein Thrombosis (DVT)	2 (0.7)
• Coronary Artery Disease (CAD)	4 (1.4)

Variable	n (%)
• Alcohol	2 (0.7)
• Smoking	4 (1.4)
• Hepatitis B	7 (2.4)
• Hepatitis C	0 (0)
• Cirrhosis	2 (0.7)
• Jaundice	3 (1)
• Ascites	1 (0.3)
• Malignancy	21 (7.2)
• Heart Failure	12 (4.1)
• Chronic Kidney Disease (CKD)	15 (5.2)
• Diabetes Mellitus (DM)	79 (27.1)

Table 1. Characteristics of research subjects

Gender, there were 160 (55%) male subjects and 131 (45%) female subjects. Age of research subjects, there were 20 (6.9%) subjects had an age range of 17-30 years, 42 (14.4%) subjects had an age range of 31-40 years, 57 (19.6%) subjects had an age range of 41-50 years, 100 (34.4) %) subjects had an age range of 51-60 years, 49 (16.8%) subjects had an age range of 61-70 years, and 23 (7.9%) subjects had an age >70 years. The degree of COVID-19, there were 181 (62.2%) subjects having moderate degrees and 103 (35.4%) subjects having severe degrees. Survival, 23 (7.9%) subjects died at the end of the study, 268 (92.1%) subjects remained alive at the end of the study.

Symptoms of COVID-19, 148 (50.9%) subjects complained of fever, 171 (58.8%) subjects complained of dry cough, 12 (4.1%) subjects complained of a runny nose, 9 (3.1%) subjects complained of sore throat, 19 (6.5%) subjects complained of painful swallowing, 163 (56%) subjects complained of shortness of breath, 44 (15.1%) subjects complained of sputum production, 31 (10.7%) subjects complained of diarrhea, 28 (9.6%) subjects complained of abdominal pain, 94 (32.3%) subjects complained of nausea/vomiting, 9 (3.1%) subjects complained of black bowel movements, and 5 (1.7%) subjects complained of constipation.

Comorbid, 5 (1.7%) subjects had COPD, 5 (1.7%) subjects had stroke, 2 (0.7%) subjects had DVT, 4 (1.4%) subjects had COPD, 2 (0.7%) subjects drank alcohol, 4 (1.4) %) subjects smoked, 7 (2.4%) subjects had hepatitis B, 2 (0.7%) subjects had cirrhosis, 3 (1%) subjects had jaundice, 1 (0.3%) subjects had ascites, 21 (7.2%) subjects had malignancy , 12 (4.1%) subjects had heart failure, 15 (5.2%) subjects had CKD and 79 (27.1%) subjects had DM

Variable	Alive (n=268)		Died (n=23)		*p*
	Mean ± SD	**Median (Min-Max)**	**Mean ± SD**	**Median (Min-Max)**	
Age	52.1 ± 13.4	53 (18-88)	53.1 ± 14.3	55 (20-78)	0.768[#]
SpO_2	92.4 ± 12	96.3 (25-100)	89.3 ± 13.6	93.1 (40-100)	0.067[¥]
Leukocytes	10.9 ± 7.8	8.9 (2-72)	11.6 ± 8.5	10.6 (1.3-44.5)	0.511[¥]
Haemoglobin	12.7 ± 2.8	13 (0.5-19.7)	11.1 ± 3.1	12.2 (3.7-14.8)	**0.039[¥]**
ALC	1410 ± 1487	1181 (160-14400)	1748 ± 2604	1060 (130-10680)	0.223[¥]
NLR	12.49 ± 54.45	5.92 (0.21-670)	9.43 ± 9.85	7 (0.29-46.50)	0.511[¥]
CRP	9.39 ± 9.73	6.29 (0.04-48.2)	13.91 ± 11.07	11.14 (0.21-47.38)	**0.015[¥]**
D-Dimer	5959 ± 45142	1280 (145-720000)	7283 ± 15496	2755 (440-73950)	0.063[¥]
Creatinine	773.06 ± 5785.95	1.03 (0.4-44075)	5.68 ± 18.46	1.4 (0.59-88)	0.648[¥]
Ureum	45.26 ± 45.22	31.5 (1-372)	51.22 ± 42.25	43 (8-188)	0.257[¥]

[#]Independent T-test; [¥]Mann Whitney U test

Table 2. Differences in the characteristics of research subjects based on survival

All 291 study subjects were divided into 2 groups, namely the group of patients who lived at the end of the study (268 subjects) and the group of patients who died at the end of the study (23 subjects).

Based on the unpaired difference test conducted between the living group and the dead group at the end of the study, there were significant differences in hemoglobin levels (p=0.039) and CRP levels (p=0.015) between the two study groups. There were no significant differences in other variables.

		Survival		*p*	OR (95%CI)
		Alive	Died		
COVID-19 Severity	Moderate	172	9	**0.010**	3.00 (1.25-7.21)
	Severe	89	14		

Table 3. The degree of COVID-19 with survival

Subjects with moderate COVID-19 degrees, there were 172 living subjects and 9 dead subjects. Subjects with severe COVID-19 degrees, there were 89 living subjects and 14 dead subjects.

There is a relationship between the degree of COVID-19 and the survival of the research subjects (p=0.010).

The degree of COVID-19 has an OR = 3.00 of the survival of the research subjects. This means that subjects with moderate levels of COVID-19 were 3 times more likely to be alive at the end of the study.

	Survival	*p*	

		Alive	Died		OR (95%CI)
CKD	Yes	11	4	**0.007**	0.21 (0.06-0.73)
	No	246	19		

Table 4. CKD with survival

Subjects with CKD, 11 subjects lived and 4 subjects died. Subjects without CKD, 246 subjects were alive and 19 subjects died.

There is a relationship between CKD and survival of research subjects (p = 0.007).

CKD has an OR = 0.21 to the survival of the research subjects. This means that subjects without CKD become a protective factor so that patients do not die at the end of the study.

		COVID-19 Severity		*p*	OR (95%CI)
		Moderate	Severe		
Gender	Male	92	65	**0.045**	0.60 (0.36-0.99)
	Female	89	38		

Table 5. Gender with the severity of COVID-19

Subjects were male, there were 92 subjects having moderate COVID-19 severity and 65 subjects having severe COVID-19 severity. Subjects are female, there are 89 subjects who have moderate COVID-19 severity, and 38 subjects have severe COVID-19 severity.

There is a relationship between gender and the severity of COVID-19 (p=0.045).

Gender has an OR=0.60 of the severity of COVID-19. This means that the female subject is a protective factor so that the patient does not have a severe degree of COVID-19.

		COVID-19 Severity		*p*	OR (95%CI)
		Moderate	Severe		
Dry Cough	No	80	32	**0.034**	1.73 (1.04-2.88)
	Yes	101	70		

Table 6. Dry cough with the severity of COVID-19

Subjects without dry cough, 80 subjects had moderate COVID-19 degrees and 32 subjects had severe COVID-19 degrees. Subjects with dry cough, 101 subjects had moderate COVID-19 degrees and 70 subjects had severe COVID-19 degrees.

There is a relationship between dry cough symptoms and the degree of COVID-19 (p=0.034).

Dry cough has an OR=1.73 against the degree of COVID-19. This means that subjects with dry cough have a 1.73 times greater risk of experiencing severe COVID-19.

		COVID-19 Severity		*p*	OR (95%CI)
		Moderate	Severe		
Dyspneu	No	85	36	**0.049**	1.64 (1.00-2.71)
	Yes	96	67		

Table 7. Dyspneu with the severity of COVID-19

Subjects without shortness of breath, there were 85 subjects had moderate COVID-19 degrees and 36 subjects had severe COVID-19 degrees. Subjects with shortness of breath, there were 96 subjects having moderate COVID-19 degrees and 67 subjects having severe COVID-19 degrees.

There is a relationship between the symptoms of shortness of breath and the degree of COVID-19 (p=0.049).

Shortness of breath has an OR = 1.64 to the degree of COVID-19. This means that subjects with shortness of breath have a 1.64 times greater risk of experiencing severe COVID-19.

4. DISCUSSION

The research subjects were dominated by men (55%), with an age range of 51-60 years (34.4%). The highest degree of COVID-19 was suffered by moderate degrees (62.2%). Most of the study subjects were alive at the end of the study (92.1%). The most frequently complained symptoms of COVID-19 were dry cough (58.8%), shortness of breath (56%), and fever (50.9%). The most frequently reported comorbid disease was diabetes mellitus (27.1%).

Alshukry A, et al who examined the clinical characteristics of 417 COVID-19 patients in Kuwait found that most of the subjects were male (52.4%) who were in the age range of 51-60 years (19.9%). The most common symptoms complained of were fever (34.3%), dry cough (32.6%) and shortness of breath (18.2%). The most frequently reported comorbid types were hypertension (26.9%) and diabetes mellitus (20.3%).[3] Bruminhent J, et al in their study of the characteristics of

COVID-19 patients in Thailand obtained similar results, where the most frequently complained symptom was cough (73.6%), fever (58.5%), sore throat (39.6%), and muscle pain (37.4%).[4] Khan MS, et al. also found the same thing where from an assessment of 470 study subjects, 74% of patients were over 50 years old. Most of the comorbidities suffered by patients with old age. The most frequently reported comorbid types were hypertension (62.8%), diabetes mellitus (40.4%), and COPD (18.5%).[5]

In this study, COVID-19 patients were dominated by men, presumably due to men's higher outdoor activities than women, thus increasing the possibility of exposure to SARS-CoV-2 from the environment. Another possibility is that men are more likely to be infected with COVID-19, namely that there are differences in immune responses between the sexes. Men and women differ in their immunological responses to foreign and self-antigens and exhibit differences in innate and adaptive immune responses.[6]

Several studies have shown that the innate and adaptive immune responses are generally greater in women than in men.[7] The activity of innate immune cells, such as macrophages and dendritic cells (DC), as well as the overall inflammatory response is generally greater in women than in men, especially during reproductive age.[8] Cytokine production following ex vivo stimulation of monocytes with lipopolysaccharide (LPS) is greater in male cells than in female cells, with evidence that female use of hormone-based contraceptives further reduces production of cytokines, including IFNɣ and TNF-α.[9]

Women had higher CD3+ and CD4+ T cell counts and a higher CD4+/CD8+ ratio than men, while the frequency of CD8+ T cells and NK cells was greater in men.[10] CD4+ and CD8+ T cell activity after stimulation was frequent. greater in females than males.[11] In addition, antigen-presenting cells (APCs) in female mice were reported to be more efficient at presenting antigens compared to APCs from male mice. Adult women have higher B cell counts than men.[12] Regardless of age, women tend to produce greater antibody responses than men, higher basal immunoglobulin levels and higher B cell counts.[13] Global analysis B-cell gene expression showed that the majority of genes expressed between the sexes were significantly upregulated in female B cells compared to males.[14]

Cough is one of the most common symptoms of COVID-19, along with fever. Coughs may persist for weeks or months after SARS-CoV-2 infection, often accompanied by chronic fatigue, cognitive impairment, dyspnea, or pain. A dry cough is one of the most common early symptoms of COVID-19, reported in approximately 60–70% of symptomatic patients.[15] A COVID-19-associated cough may be due to invasion of the vagus sensory nerves by SARS-CoV-2 or a neuroinflammatory response, or both, which causes peripheral and central hypersensitivity.

Coughing is a reflex that requires minimal conscious control, occurring via activation of peripheral sensory nerves into the vagus nerve, which provides input to the brainstem in the nucleus solitarius and spinal trigeminal nucleus.[16] It is possible that SARS-CoV-2 infects the sensory nerves that mediate coughing, causing coughing. neuroinflammation and neuroimmune interactions as a mechanism of cough hypersensitivity.

There were significant differences in hemoglobin levels and CRP levels between the living and dead groups. In the dead group, the hemoglobin level was lower, while the CRP level was higher.

The decrease in hemoglobin levels in COVID-19 patients is thought to be caused through two potential pathophysiological mechanisms: 1) the interaction of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) with hemoglobin molecules, via CD147, CD26 and other receptors located on erythrocytes. and/or blood cell precursors or 2) the hepcidin-mimetic action of the viral spike protein, inducing ferroportin inhibition.[17]

CRP is a non-specific acute phase reactant induced by IL-6 in the liver. Elevated CRP levels are directly correlated with the degree of inflammation and disease severity. In infections due to viruses, including COVID-19, CRP levels will rapidly increase >10 mg/L. In patients with COVID-19, the CRP examination is an important indicator to predict the severity and mortality of patients with COVID-19 who are hospitalized. In addition, CRP is useful for monitoring disease progression. CRP concentrations appear to be correlated with disease severity. A rapid decrease in CRP concentration is thought to be associated with a favorable response to initial antimicrobial treatment, so CRP is a useful biomarker for

monitoring disease progression. Changes in CRP levels are also an indication of knowing the success of treatment. In patients with inflammatory disease, CRP levels return to normal when immunosuppressive treatment is successful, so this parameter can be used to monitor treatment success.[18]

Factors that affect the survival of COVID-19 patients include the degree of COVID-19 and the condition of CKD.

Khan MS, et al in a study on the characteristics and clinical outcomes of COVID-19 patients in Ohio stated that patients with CKD stage 2 or more had an OR value of 2.5 for the incidence of death in patients. This means that patients with CKD stage > 2 have a 2.5 greater risk of dying.[19] Assal HH, et al in their study of predictors of severity and mortality in COVID-19 patients found that from an assessment of 175 patients the mortality rate in the cohort conducted was 19.4%, which was significantly associated with old age and comorbid disease, especially kidney disease, $p = 0.002$, 0.02, and <0.001. Elevated levels of AST, ALT, urea, creatine, ferritin, d-dimer, and CRP, as well as lower levels of lymphocytes, platelets, and hemoglobin, were found to be significantly associated with mortality.[18]

Factors that affect the degree of COVID-19 include gender, symptoms of dry cough and symptoms of shortness of breath. Female gender, not having a dry cough, and not experiencing shortness of breath are protective factors for severe COVID-19 incidence

Shortness of breath, also known as dyspnea, is a common and distressing symptom. It has been defined as the subjective experience of breathing discomfort, consisting of qualitatively distinct sensations that vary in intensity. Many different conditions, such as lung disease, chronic heart failure, and neurodegenerative diseases, cause similar subjective sensations. It has therefore been hypothesized that there may be a common central nervous system pathway involved in the perception of dyspnea, regardless of the underlying cause.[20]

5. CONCLUSION

Female gender is a protective factor against severe cases of COVID-19. There is a relationship between the degree of COVID-19 and the survival of the research

subjects. So, it can be concluded that indirectly, gender is a survival factor for COVID-19 patients. There is no relationship between age and survival of COVID-19 patients. CKD comorbidity is associated with the survival of the study subjects.

Conflict of Interest

The authors declare that they have no competing interests. that may be perceived as inappropriately influencing the representation or interpretation of reported research results

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References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054–62.
2. Djalante R, Lassa J, Setiamarga D, Sudjatma A, Indrawan M. Review and analysis of current responses to COVID -19 in Indonesia: Period of January to March 2020. Elsevier. 2020;(January).
3. Alshukry A, Ali H, Ali Y, Al-Taweel T, Abu-Farha M, AbuBaker J, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) patients in Kuwait. PLOS ONE. 2020 Nov 20;15(11):e0242768
4. Bruminhent J, Ruangsubvilai N, Nabhindhakara J, Ingsathit A, Kiertiburanakul S. Clinical characteristics and risk factors for coronavirus disease 2019 (COVID-19) among patients under investigation in Thailand. PLOS ONE. 2020 Sep 15;15(9):e0239250
5. Khan MS, Dogra R, Miriyala LK v., Salman FNU, Ishtiaq R, Patti DK, et al. Clinical characteristics and outcomes of patients with Corona Virus Disease 2019 (COVID-19) at Mercy Health Hospitals, Toledo, Ohio. PLOS ONE. 2021 Apr 22;16(4):e0250400
6. Klein SL, Flanagan KL. Sex differences in immune responses. Nature Reviews Immunology. 2016 Oct 22;16(10):626–38.
7. Villacres MC, Longmate J, Auge C, Diamond DJ. Predominant type 1 CMV-Specific memory T-helper response in humans: evidence for gender differences in cytokine secretion. Human Immunology. 2004 May;65(5):476–85

8. Xia HJ, Zhang GH, Wang RR, Zheng YT. The Influence of Age and Sex on the Cell Counts of Peripheral Blood Leukocyte Subpopulations in Chinese Rhesus Macaques. Cellular & Molecular Immunology. 2009 Dec;6(6):433–40
9. ter Horst R, Jaeger M, Smeekens SP, Oosting M, Swertz MA, Li Y, et al. Host and Environmental Factors Influencing Individual Human Cytokine Responses. Cell. 2016 Nov;167(4):1111-1124.e13
10. Abdullah M, Chai PS, Chong MY, Tohit ERM, Ramasamy R, Pei CP, et al. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cellular Immunology. 2012 Jan;272(2):214–9
11. Sankaran-Walters S, Macal M, Grishina I, Nagy L, Goulart L, Coolidge K, et al. Sex differences matter in the gut: effect on mucosal immune activation and inflammation. Biology of Sex Differences. 2013;4(1):10
12. Teixeira D, Longo-Maugeri IM, Santos JLF, Duarte YAO, Lebrão ML, Bueno V. Evaluation of lymphocyte levels in a random sample of 218 elderly individuals from São Paulo city. Revista Brasileira de Hematologia e Hemoterapia. 2011;33(5):367–71
13. Furman D, Hejblum BP, Simon N, Jojic V, Dekker CL, Thiébaut R, et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proceedings of the National Academy of Sciences. 2014 Jan 14;111(2):869–74
14. Fan H, Dong G, Zhao G, Liu F, Yao G, Zhu Y, et al. Gender Differences of B Cell Signature in Healthy Subjects Underlie Disparities in Incidence and Course of SLE Related to Estrogen. Journal of Immunology Research. 2014;2014:1–17
15. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020 Feb;395(10223):497–506
16. Canning BJ, Chang AB, Bolser DC, Smith JA, Mazzone SB, McGarvey L, et al. Anatomy and Neurophysiology of Cough. Chest. 2014 Dec;146(6):1633–48
17. Cavezzi A, Troiani E, Corrao S. COVID-19: Hemoglobin, Iron, and Hypoxia beyond Inflammation. A Narrative Review. Clinics and Practice. 2020 May 28;10(2):1271
18. Assal HH, Abdel-hamid HM, Magdy S, Salah M, Ali A, Elkaffas RH, et al. Predictors of severity and mortality in COVID-19 patients. The Egyptian Journal of Bronchology. 2022 Dec 26;16(1):18
19. Khan MS, Dogra R, Miriyala LK v., Salman FNU, Ishtiaq R, Patti DK, et al. Clinical characteristics and outcomes of patients with Corona Virus Disease 2019 (COVID-19) at Mercy Health Hospitals, Toledo, Ohio. PLOS ONE. 2021 Apr 22;16(4):e0250400
20. Hentsch L, Cocetta S, Allali G, Santana I, Eason R, Adam E, et al. Breathlessness and COVID-19: A Call for Research. Respiration. 2021;100(10):1016–26