Severity of anxiety disorder and other factors associated with disease severity among COVID-19 patients in a hospital, Bali, Indonesia

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ABSTRACT

Introduction: COVID-19 pandemic has a substantial impact on human life including the tourism sector (TS). Bali as a tourism destinations and the TS as major incomes of its population is greatly impacted, causing many to be jobless among those involved in TS. This situation may give psychological impact causing anxiety disorder (AD).

Objective: To investigate the association between severe anxiety disorder and other factors with COVID-19 disease severity.

Methods: This was cross-sectional study during March - November 2020. The diagnosis of SARS-CoV-2 was done by using RT-PCR from throat swabs, based on WHO's interim guidelines. AD was measured using self-reporting Generalized Anxiety Disorder-7 (GAD-7). All participants underwent, history taking, physical examinations, blood routine examination and chest radiography. Association between severe AD and other factors with COVID-19 disease severity were analyzed. Chi-square test (bivariate) and Logistic regression (multivariate) with the precision value of 95% was done and p-value less than 5% was considered significant.

Results: Positive rate of Covid-19 patients was 43% (292 / 678). Among those 292 with Covid-19, 74 (25.3%) participants had severe disease. Multivariate analysis showed severe anxiety (OR 696.11; 95%CI: 78.54 to 6169.98; p<0.001), hypertension (OR 37.02; 95%CI: 4.49 to 305.39; p=0.001) and neutrophyl lymphocyte ratio (NLR) less than 2.89 (OR 0.15; 95%CI: 0.04 to 0.62; p=0.009).

Conclusion: Severe anxiety, hypertension and NLR less than 2.89 are potential independent risk factors for severe infection of SARS-CoV-2 (COVID-19).

KEYWORDS:
Covid-19, Disease severity, Severe anxiety, Positivity rate, Associated factors

INTRODUCTION

Coronavirus disease 2019 (COVID-19), of a RNA virus family infects the vertebrates. The '2019 novel coronavirus (2019 – n Cov)' that is now known as the COVID-19, occured in Wuhan, China and it was previously known as Novel Coronavirus Pneumonia (NCP).[1,2] According to the WHO that it spread rapidly to 25 other countries. The COVID-19 incubation period is about 2 to 14 days and based on a study in Wuhan, mostly 3-7 days. The main routes of transmission were considered via respiratory droplets and close individual to individual contact (within 6 feet). Any contacts of individuals on surface or an object that has the virus on it and then touches their own eyes, noses or mouths can mean a transmission can occur.[3-5]

Nowadays COVID-19 is considered as resulting in complex challenges for physic-psychosocial health problems due to some of drastic public health measures. COVID-19 has various clinical manifestations from mild to severe. The severe disease can be rapidly changing to fatal condition such as acute respiratory distress (ARDS), multiple organ damage and even death.[6-8] In Bali; 12,583 individuals were confirmed to have Coronavirus disease 2019 (COVID-19); 11,555 had recovered and 404 were dead. In Indonesia a total of 457,735 individuals were confirmed to have Coronavirus disease 2019 (COVID-19); 385,094 had recovered and 15,037 were dead.[9] The severe impact on tourism sectors and the economy of Bali that contribute to the psychological aspect as most people confirmed with COVID-19 show psychological disorders with the various levels of Generalized Anxiety Disorder (GAD).[10-12] Other frequent symptoms include fever, cough, shortness of breath, pneumonia, and severe respiratory syndrome.[2] In some comorbidities such as diabetes, hypertension, hypertensive heart disease (HHD), coronary heart disease (CHD), pulmonary tuberculosis (PTB), chronic kidney disease (CKD), dengue hemorrhagic fever (DHF) are also seen. We suggest that investigating the risk factors for the severity of COVID-19 is crucial to improve the outcome of the disease. COVID-19 patients with generalized anxiety disorder (AD) (moderate severe anxiety), older adults and comorbidities are more likely to be aggravated.[13-15]

This study was conducted to investigate the association between severe AD and other factors with disease severity of hospitalized COVID-19 patients at Wangaya Hospital (WH) in Denpasar, Bali, Indonesia.

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MATERIALS AND METHODS

Study Design and Populations

A cross-sectional study single-center was conducted at Wangaya Hospital in Denpasar Bali Indonesia from March 2020 to November 2020. The diagnosis of SARS-CoV-2 using RT-PCR on samples from throat swabs, based on WHO's interim guidelines.[16] AD was measured using GAD-7. This questioner was used by self-reporting by participants to measure the severity of AD. It was reported that the sensitivity and specificity of this tool using optimal cut-off point were 89% and 82%, respectively.[11]

We collected throat swabs from 678 suspected of SARS-CoV-2 infection. Among those, 292 patients were reported as positive COVID-19, and hospitalized at WH were consecutively included. All of the participants underwent, history taking, physical examinations, blood routine examination and chest radiography. A written consent form was provided to the participants wherein the procedure of the study was explained.

Data collection

Data of GAD-7 and other factors such as demography, clinical manifestations, laboratory results, chest radiographic and comorbidities were collected. Severity of AD was classified into 2 groups: none, mild to moderate anxiety (score 9 or less) and severe anxiety (10 or more) disorder.[11] The clinical symptoms and signs, laboratory results and chest X-rays were extracted from WH medical records. The neutrophil-lymphocyte ratio (NLR) is an inflammatory marker that can be used as an indicator of systemic inflammation; the NLR is defined by the absolute number of blood neutrophils divided by the absolute number of lymphocytes. Hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure 90 mmHg.[17] Coronary arterial disease is defined as the inability of atherosclerosis coronary arteries to perfuse the heart due to partial or total occlusion of the coronary arteries. Typical angina (chest pain); substernal chest discomfort of specific quality and duration among the patients who are identified the atherosclerotic risk factors. This was also support by electrocardiogram and cardiac marker.[18,19] Renal insufficiency is defined as creatinine serum concentrations ≥ 1.2 mg/dL, irrespective of cause.[20] Diabetes mellitus is defined fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test or A1C ≥ 6.5% (48 mmol/mol) or in a patient with classic symptoms of hyperglycemia or hyperglycemia crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).[21] Abnormal chest X ray is defined according to radiologist expert that include previous conditions such as lung tuberculosis, chronic obstructive lung disease or associated with COVID-19 infection such as pneumonia.[22] Severity of COVID-19 was classified into: severe cases which should meet at least one of the conditions: shortness of breath with respiratory rate ≥ 30 (breath/min) or oxygen saturation (SpO2) ≤ 93 % in resting state. It included critical cases that should meet one of the following manifestations: respiratory failure and required mechanical ventilation or shock occurred, or combined with other organs damage and nursed in intensive care unit. All the data such as demography, history of travelling to region with COVID-19, history of contact, clinical manifestation, vital signs, laboratory, and underlying comorbidities such as hypertension and diabetes mellitus were obtained.

Statistical analysis

To describe the participant characteristics descriptive statistical tests were performed. The data distribution was tested by Kolmogorov-Smirnov test for normality. Mean and standard deviation were displayed for variables with numerical or continuous scales and normally distributed. If the data is not normally distributed, it was displayed in median and range values. The variables with categorical scale were displayed in frequencies (numbers and percents). The clinical and laboratory data were compared between the mild-moderate and severe groups. Simple logistic regression and multiple logistic regression were applied for bivariate and multivariate analysis. Statistically, significant level was set on p-value equal 5%, and data precision was expressed as 95% confidence interval.

RESULTS

Characteristics of Patients

Among the 678 patients who admitted to WH were diagnosed as suspect SARS-CoV-2 infection and collected throat swabs. In all 292 patients were reported as COVID-19 (43% positive rate). All those COVID-19 patients were enrolled in this study. Table I shows the clinical characteristics (demography, signs and symptoms, and laboratory findings) of the patients who participated.

Among 292 COVID-19 patients, 74 (28.1%) with severe disease. We found there were high prevalence (> 25%) of those with at least one co-morbid, abnormal chest X-ray, NLR < 2.89 and age ≥ 50 years. However, the prevalence of creatinine serum ≥1.2 mg/dL, hypertension, diabetes mellitus and coronary arterial disease were less than 25%. Severe AD and other factors (at least one comorbid, abnormal chest X-ray, NLR < 2.89, creatinine serum ≥1.2 mg/dL, age ≥ 50 years, hypertension, diabetes mellitus and coronary arterial disease) were selected as potential risk factors. It was shown that all those factors were significantly associated with disease severity. Among those, all positive strongly (potentially associated with increase risk) correlated with disease severity, except NLR ratio < 2.89 (shown negatively correlation) with potentially protective against severe COVID-19 disease (Table II).

If all of significant associated factors are put into regression model (using backward LR multiple regression analysis), it was shown that when beginning (first step on the analysis) with those eight factors, finally (fifth step on the analysis) only three factors significantly (p-value less than 0.05) associated with disease severity as an independent factor, consisted of severe anxiety disorder, hypertension and NLR < 2.89 (Table III).

DISCUSSION

This study found that in multivariate analysis (logistic regression), statistically there are the significant association between the independent factors such as severe anxiety

Table I: Clinical characteristics of COVID-19 patients (n=292)

Characteristics	n (%)	Minimum-Maximum	Mean (SD)
Demography			
Age(years)		14-90	48 (14)
Gender			
Males	154 (52.7)		
Females	138 (47.3)		
Travelling history	22(7.5)		
Contact history	258(88.4)		
Signs and symtoms			
Fever	242(82.9)		
Cough	232(79.5)		
Shortness of breath	136(46.6)		
Anosmia	56(19.2)		
Blood pressure (BP)			
SBP (mm Hg)		100-170	120 (14)
DBP (mm Hg)		60-100	75(8)
Heart rate (beats/mnt)			92(6)
Respiration rate/mnt		18-38	25(4)
Body temperature (oC)		36-38	37(0.6)
Laboratory			
White blood cells (K/mm3)		1.4-21.4	9.1(3.3)
Neutrophils (K/mm3)		1.6-17.5	5.2(2.5)
Lymphocytes (K/mm3)		0.4-4.4	1.6(0.9)
NLR		0.54 - 26.30	4.48(3.72)
Hemoglobin (g/dL)		6.7-17.7	12.9(1.5)
Platelets (K/mm3)		108-615	241(95)
BUN (mg/dL)		10-171	32(20)
Creatinine Serum (mg/dL)		0.1-7.5	1.0(0.77)
Blood sugar (mg/dL)		76-582	169(78)
AST (u/L)		7-140	44(23)
ALT (u/L)		14-253	48(33)
Oxygen saturation (%)		89-98	94(2)

NLR = neutrophil-lymphocyte ratio; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = Alanine Aminotransferase

Table II: Association some associated factors and severity of COVID-19 patients.

Associated factors	Prev. (%)	Category	Severe		PR	CI 95%(PR)		P-value
			Yes	No		Lower limit	Upper limit	
Severe anxiety	28.1	severe	70	12	44.8	16.9	118.8	<0.001
		non-severe	4	206				
Comorbidities (≥1)	35.6	≥1	64	40	11.6	6.2	21.5	<0.001
		none	10	178				
Abnormal chest X-ray	49.3	yes	68	76	1.8	1.5	2.1	<0.001
		no	6	142				
NLR<median (2.89)	50.0	yes	6	140	0.08	0.04	0.2	<0.001
		no	68	78				
Renal insufficiency SC ≥1.2 mg/dL	19.2	yes	26	30	2.3	1.6	3.3	<0.001
		no	48	188				
Age (≥ 50 years)	52.7	≥ 50	60	94	1.5	1.3	1.7	<0.001
	<50	14	124					
Hypertension	18.5	yes	32	22	3.4	2.36	4.7	<0.001
		no	42	196				
Diabetes								
Mellitus	20.9	yes	47	14	6.6	4.5	9.6	<0.001
		no	27	204				
Coronary Arterial								
Disease	6.2	yes	12	6	2.9	1.99	4.37	<0.001
		no	62	212				

PR, prevalence ratio; NLR, neuhtophyl lymphocyte ratio; SC, serum creatinine. Significant p < 0.05

Table III: Multivariate analysis of association between comorbidities and the severity of COVID-19 patients

Factors*	B	P-value	Odds ratio	95% CI(odds ratio)	
				Lower	Upper
Severe Anxiety Disorder	6.55	<0.001	696.11	78.54	6169.98
Hypertension	3.61	0.001	37.02	4.49	305.39
NLR (< 2.89)	-1.871	0.009	0.15	0.04	0.62

*Only significant (P-value<00.5) variable were included in final step of multiple logistic regression
NLR, Neutrophil-lymphocyte ratio

disorder, hypertension and NLR with disease severity among COVID-19 patients at WH. But others factors such as age (≥ 50 years old) statistically is not associated with disease severity.

Anxiety disorder and COVID-19

AD is an adaptive emotional and behavioral response to threaten stimuli and is essential for survive. Chronic and persistent worry are characterized for AD. The worry, may relate to health, finances (salary deduction due to job losses), family (separation from family members and colleagues), social isolation, school closure and the future, excessive and mostly difficult to control.[11,12,14] As well as particularly in Bali due to tourism lock down.

This study found that in multivariate analysis (logistic regression), statistically there are the significant association between severe anxiety AD and disease severity (p<0.001; CI: 95% (78.54-6169.98) (Table II). In India, AD was found in 39.5% of 152 participants. Other study was reported that the lower frequencies of AD 13.0% in Wuhan and 10.8% in Singapore.[15,23,24] The factors that explain the difference are particularly cultural patterns and psychosocial, environmental, and work influence.[15] Another study among Italian and Iranian populations found that fear of COVID-19 was significantly correlated with anxiety, as a measured by the hospital anxiety scale.[25,26] Moreover, 25.4% of the participants experienced that their mental health (anxiety) had deteriorated since the pandemic. This alarming situation suggests that the COVID-19 pandemic has substantially contributed the AD in Hong Kong.[11] Among the Pakistani Social Media Users during COVID-19 pandemic, found 31% (94 of 303 participants) were AD.[27] A significant higher percentage of individuals with anxiety vs without considerable anxiety among Bangladeshi during COVID-19 pandemic (96.1% vs 69.8%, p < 0.001).[14]

Hypertension and COVID-19

The cytokines imbalance is considered as an explanation for the association between hypertension and severe COVID-19, cytokine storms and deterioration of COVID-19 due to exaggerated of IL-6 and TNF-alfa.28

This study found that in multivariate analysis (logistic regression), statistically there is the significant association between hypertension and disease severity (p = 0.001; CI: 95%(4.49-305.39) (Table II).

Another recent study by Huang reported that COVID-19 patients with hypertension were more likely than patients without hypertension to have severe pneumonia, excessive inflammatory reactions, organ and tissue damage and deterioration of the disease.28 Pittito (2020), reported that the hypertension was moderately and respectively associated with severity and mortality for COVID-19 patients (OR 2.50; 95% CI: 1.74-3.59).[29]

Neutrophil Lymphocyte Ratio (NLR) and COVID-19

Neutrophils represent the nonspecific immune system that initiate the body responses to inflammation, whereas the lymphocytes represent the protective component against inflammation. The inflammatory condition will trigger hypersecretion of inflammatory cytokines; IL-6 and TNF-α, resulting in a permanently high neutrophil count, but on the other hand the increased proinflammatory mediators will bind to lymphocyte surface receptors and subsequently initiate apoptosis of the lymphocytes, thus causing lymphopenia.[30] Neutrophil Lymphocyte Ratio (NLR) shows the inflammatory status. It is used as a marker of prognosis of several conditions included the acute inflammatory disease.

In this study we found an association between severity anxiety and NLR < 2.89 (OR 0.15; 95%CI: 0.04 to 0.62; p=0.009), shown negatively correlation with potentially protective against severe COVID-19. Other studies revealed that NLR has been shown to be an independent risk factor for diseases severity of COVID-19.[31-34] Long L et al (2020) found that 75.8% of patients with disease progression had an NLR of 2.973 during hospitalization, which may imply the severity of COVID-19 infection.[34,35] High NLR was shown by binary logistic analysis; hazard risk (HR): 2.46, 95% confidence interval (CI): 1.98-4.57 as an independent factor for poor clinical outcome of COVID-19, confirmed by a meta-analysis that reported significant increases in NLR values in severe COVID-19 patients.[36,37]

LIMITATION OF THE STUDY

This study has several limitations, such as; the study population only recruited patients within at WH.

CONCLUSION

Our study found a statistically significant association between hypertension, NLR and the severity of COVID-19 patients. The assessment of severe AD, hypertension and NLR may help identify the severity of the disease.

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AUTHOR CONTRIBUTIONS

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors declared that there is no conflict of interest related to this study.

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ETHICAL APPROVAL

The study procedure was approved by Ethical Committee of WH in Denpasar, Bali, Indonesia with register number: 14/RSUDW/Litbang/2020. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants.

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