RESEARCH ARTICLE

Clinical findings and electrocardiography predicted mortality among COVID-19 patients with pre-existing hypertension: A cross-sectional study of East Java Province, Indonesia

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Abstract

Objective: To evaluate the factors associated with mortality among coronavirus disease-2019 patients with pre-existing hypertension.

Method: The retrospective, cross-sectional study was conducted from June 15 to July 7, 2021, after approval from Dr Soetomo General Province Hospital, Indonesia, and comprised data from the coronavirus disease-2019 registry in the East Java province of Indonesia from March 2020 to June 2021. Data was collected for adult patients infected by coronavirus disease-2019 with pre-existing hypertension Data was analysed using SPSS 23.

Results: Of the 2,732 patients in the registry, 425(15.6%) with median age 56.5 years (interquartile range: 50-64 years) had pre-existing hypertension. Of them, 251(59.06%) were males, and 110(25.9%) had died while in hospital. Mortality was associated with older age; higher white blood cell counts at admission and lower platelet count ($p<0.05$). In addition, electrocardiogram parameters associated with mortality were faster heart rate and ST abnormality ($p<0.05$).

Conclusion: Older age, high white blood cell level, lower platelet count, faster heart rate, and ST abnormality at admission were found to be the predictors of mortality among hospitalised coronavirus disease-2019 patients with pre-existing hypertension.

Key Words: COVID-19, Hypertension, Electrocardiography, Leukocytes.

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Introduction

The coronavirus disease-2019 (COVID-19) practically spread across nations and territories[1,2]. Due to high transmission and complication rates, particularly in patients with pre-existing cardiovascular comorbidities, like hypertension (HTN), the burden of the disease was relatively high[3,4].

HTN is one of the most prevalent cardiovascular comorbidities[5,6], and COVID-19 patients with pre-existing hypertension were at a significant risk of mortality[7-10]. Patients with pre-existing HTN were found to have angiotensin-converting enzyme 2(ACE2) overexpression[11], possibly facilitating higher viral entry as ACE2 was the receptor required for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry. Another possible mechanism was possibly mediated by dysregulation of the immune and autonomic nervous systems[11]. A cytokine storm is brought on by the unchecked release of pro-inflammatory cytokines and an imbalanced immunological response in hypertensive individuals[12]. Sympathetic overactivation was also found in hypertensive patients. It could trigger myocardial injury through catecholamine-induced vasospasm and direct catecholamine effect on myocytes, acute kidney injury, liver injury, pro-inflammatory effect, pulmonary HTN, pulmonary capillary leakage that favours acute respiratory distress syndrome (ARDS) progression, and restricted lung function[13].

Identifying factors associated with mortality in COVID-19 patients with pre-existing HTN is essential to precisely allocate health resources and choose the appropriate treatment, especially in settings with limited resources. Complete blood count (CBC) and electrocardiography (ECG) are simple, affordable and common modalities found in most hospitals[14]. the current study was planned to identify the predictors of mortality among hospitalised COVID-19 with pre-existing HTN.

Materials and Methods

The retrospective, cross-sectional study was conducted from June 15 to July 7, 2021, after approval from Dr Soetomo General Province Hospital, Indonesia, and

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comprised data from the COVID-19 registry (10.6084/m9.figshare.25531462) in the East Java province of Indonesia from March 2020 to June 2021. As per the World Health Organisation (WHO) guidelines, patients were characterised as confirmed COVID-19 cases on the basis of positive reverse transcription polymerase chain reaction (RT-PCR) status[15].

Data collected was related to all adult COVID-19 patients with pre-existing HTN. Patients aged <18 years and those with missing data were excluded. Demographic data as well as CBC, ECG and comorbidity data was noted. ECG abnormalities were determined in line relevant recommendations[16-19].

Each COVID-19 referral hospital ECG machine examined 12-lead standard ECGs upon admission. The ECG recordings were captured on camera and uploaded to the registry. The recordings were evenly distributed among 5 cardiology fellows for analysis under the supervision of senior electrocardiography specialists.

Data was analysed using SPSS 23. Kolmogorov-Smirnov test was employed to assess data normality. For continuous variables, baseline patient characteristics were expressed as median with interquartile range (IQR), and for categorical variables, the values were expressed as frequencies and percentages. Within each set of demographic data, laboratory results and ECG results, the mortality outcome (alive vs. deceased) was compared to look for significant differences. Independent t-test was used to compare continuous data having normal distribution that was expressed was mean +/- standard deviation. Where the data exhibited an aberrant distribution, Mann-Whitney test was used. If the frequency within a group was lower than the predicted value, the frequency within that group was compared using chi-square or Fisher exact test for categorical data. In multivariate analysis, variables with p=0.25 in the bivariate analysis were considered for logistic regression. P<0.05 was considered statistically significant.

Results

Of the 2,732 patients in the registry, 425(15.6%) with median age 56.5 years (IQR: 50-64 years) had pre-existing HTN. Of them, 251(59.06%) were males, and 110(25.9%) had died while in hospital (Table 1).

Mortality was associated with older age, higher WBC count and lower platelet count (p<0.05). In addition, ECG parameters associated with mortality were faster heart rate, PR interval, QTc interval and ST abnormality (Table 2).

Table-1: Bivariate analysis.

Clinical Findings	Total	Deceased (n=110)	Discharged (n=315)	P-value
Age (year)	56.5 (50.0-64)	60 (54.0-66.0)	55.0 (48.0-62.0)	<0.001**
Male	251 (59.1)	67 (60.9)	184 (58.4)	0.730
History of Cardiac Disease				
Coronary Artery Disease	19 (4.5)	8 (7.3)	11 (3.5)	0.111
Atrial Fibrillation	1 (0.2)	1 (0.9)	0 (0.0)	0.259
Diabetes	151 (35.5)	48 (43.6)	103 (32.7)	0.051
Comorbidities				
Severe Renal Failure	8 (1.9)	3 (2.7)	5 (1.6)	0.432
Immune disorder	1 (0.2)	1 (0.9)	0 (0.0)	0.259
COPD	2 (0.5)	1 (0.9)	1 (0.3)	0.451
Asthma	4 (0.9)	1 (0.9)	3 (1.0)	1.000
Bronchitis	2 (0.5)	0 (0.0)	2 (0.6)	1.000
Obesity	6 (1.4)	3 (2.7)	3 (1.0)	0.182
Hb g/dL	13.5 (12.4-14.7)	13.8 (12.6-15.0)	13.5 (12.4-14.5)	0.076
WBC cells/µL	7.6 (5.9-9.9)	8.85 (6.45-11.9)	7.30 (5.70-9.40)	0.001
Platelet 103/µL	253 (193-331)	223 (165.5-292.25)	268.5 (209-337.5)	<0.001**
Electrocardiographic Findings				
Heart Rate (bpm)	88.76 (78.95-101.0)	97.5 (85.4-114.0)	86.2 (78.0-97.0)	0.001**
PR Interval (ms)	154.0 (140.0-172.0)	151.0 (135.5-170.0)	156.0 (142.0-173.5)	0.042*
PR Segment (ms)	60.0 (45.0-80.0)	60.0 (40.0-80.0)	60.0 (48.0-80.0)	0.115
QRS duration (ms)	86.0 (80.0-96.0)	86.0 (80.0-98.0)	86.0 (80.0-96.0)	0.883
ST segment (ms)	80.0 (80.0-120.0)	80.0 (80.0-120.0)	80.0 (80.0-120.0)	0.279
ST interval (ms)	274.0 (244.0-296.0)	253.0 (238.0-282.0)	280.0 (252.0-320.0)	<0.001**
QTc interval (ms)	361.0 (332.0-390.0)	346.5 (320.0-372.0)	366.0 (340.0-392.0)	<0.001**
TQ Interval (ms)	320.0 (260.0-400.0)	280.0 (215.0-345.0)	330.0 (280.0-400.0)	<0.001**
Atrial Fibrillation	6 (1.4)	2 (1.8)	4 (1.3)	0.651
Left Axis Deviation	26 (6.1)	8 (7.3)	18 (5.7)	0.722
Right Axis Deviation	10 (2.4)	3 (2.7)	7 (2.2)	0.723
Indeterminate Axis	6 (1.4)	2 (1.8)	4 (1.3)	0.651
LVH	32 (7.5)	10 (9.1)	22 (7.0)	0.529
RVH	5 (1.2)	3 (2.7)	2 (0.6)	0.112
PVC	7 (1.6)	5 (4.5)	2 (0.6)	0.014*
PAC	6 (1.4)	1 (0.9)	5 (1.6)	1.000
First-degree AV block	12 (2.8)	4 (3.6)	8 (2.5)	0.517
LBBB	8 (1.9)	3(2.7)	5 (1.6)	0.432
RBBB	15 (3.5)	2 (1.8)	13 (4.1)	0.373
Non-specific IV block	8 (1.9)	2 (1.8)	6 (1.9)	1.000
T inversion	38 (9.2)	18 (16.4)	21 (6.7)	0.004*
ST Abnormality	65 (15.3)	31 (28.2)	34 (10.8)	<0.001**

* p value <0.05

** p value <0.001

COPD: Chronic obstructive pulmonary disease, Hb: Haemoglobin, WBC: White blood cell, LVH: Left ventricular hypertrophy, RVH: Right ventricular hypertrophy, PVC: Premature ventricular contraction, PAC: Premature atrial contraction, AV: Atrioventricular, LBBB: Left bundle branch block; RBBB: Right bundle branch block, IV: Intravenous.

Table-2: Multivariate analysis.

Variable	OR	95%CI	*P*-value
Age	1.06	1.04 – 1.09	<0.001***
Coronary artery disease	1.82	0.53-6.29	0.342
Diabetes	1.27	0.73-2.19	0.189
Obesity	5.17	1.35 – 33.9	0.093
Hb	1.11	0.96-1.28	0.178
WBC	1.11	1.02 – 1.19	<0.01**
Platelet	0.96	0.94-0.97	<0.01**
HR (bpm)	1.03	1.02 – 1.05	0.034*
PR interval	0.99	0.97-0.99	0.03*
PR segment	0.99	0.98-1.01	0.363
TQ interval	0.99	0.98-1.03	0.078
QTc interval	0.99	0.98-0.99	0.01
RVH	6.69	0.85-52.7	0.071
PVC	9.73	0.99-.65.1	0.051
T inversion	1.61	0.49-5.35	0.237
ST Abnormality	3.26	1.45 – 6.31	<0.001***

* p value < 0.05; ** p value < 0.01; *** p-value < 0.001
Hb: Haemoglobin, WBC: White blood cell. RVH: Right ventricular hypertrophy. PVC: Premature ventricular contraction, OR: Odds ratio, CI: Confidence interval.

Discussion

HTN is diagnosed in one of three adults worldwide[5]. Patients with underlying comorbidities have worse outcomes[20]. One of the most prevalent comorbidities, HTN has been proposed as a factor that raises the risk of COVID-19 death.

A meta-analysis of 12 studies found that COVID-19 mortality was higher in patients aged >60 years with HTN [21]. It was significantly higher in patients aged <70 years compared to those aged >70 years [3]. Age was found to be a significant risk factor for the severity and mortality of COVID-19 in another study[22]. The current study showed that more than half of the patients were men, which was consistent with earlier research[3,23]. Chronic illnesses that also cause immunological senescence and greater susceptibility to infection are more likely to affect older adults[24,25].

A severe infection may trigger a response of systemic inflammation. Pro-inflammatory cytokines, including interleukin-2 (IL-2), IL-6 and IL-7, were found to be elevated in previous research that linked severe COVID-19 infection to these cytokines.[11]. Additionally, these cytokines are linked to the development of HTN[16]. Thus, COVID-19 patients aged >19 years who already had HTN were more likely to experience a more severe systemic inflammatory response[3].

One of the important risk variables for mortality in the current study was an elevated WBC count. Patients with HTN had greater WBC counts than those without HTN in a study[26]. In severe COVID-19 cases, WBC counts >10 x 10^9/L were a strong predictor of death[27,28]. Controlling and eradicating COVID-19 infections depends on the immune system. However, mounting research indicates that individuals with severe COVID-19 may also have cytokine storm syndrome[11].

One of the predictive indicators in the current study was an elevated heart rate, which was in line with literature[29]. It was discovered that hypertensive COVID-19 patients who did not survive had heart rates of >90 beats per minute[3]. In HTN patients, a higher heart rate was linked to raised blood pressure (BP)[4]. An increase in sympathetic activity could be the factor causing the heart rate to go up[13,29]. Imbalance in the autonomic nervous system affects organ structure and function, raising the possibility of a bad prognosis in a number of illnesses, including cardiovascular issues. Sympathetic overdrive that results from haemodynamic instability may also cause high heart rate and low blood pressure that can be reflected by shock index[29].

The time during which the myocardium continues to push blood out of the ventricles is represented by the ST segment. Any variations in the voltage gradient during the action potential's plateau phase result in variation of the ST segment. ST segment alterations can result from a variety of disorders. In the acute scenario, ST elevation can signify a coronary artery blockage that could be brought on by COVID-19. Acute myocardial infarction-mimicking circumstances include early repolarisation, left ventricular hypertrophy (LVH), ventricular aneurysm, left bundle branch block (LBBB) and other conduction. On the other hand, factors, such as hypokalaemia and myocardial ischaemia, and medications, like digitalis, may be linked to ST depression, among others. In a prior investigation, ST-T alteration was the most typical ECG abnormality in the severe group of hospitalised COVID-19 patients. ST-T alterations were linked to HTN, severe clinical status, D-dimer elevation, and myocardial damage, which was a sign of a poor prognosis[19].

Uncertainty surrounds the precise mechanism causing ECG abnormalities in COVID-19 patients. A plausible mechanism, nevertheless, has been suggested as cardiac involvement. ACE2 is found in high concentrations in the heart and lungs, and has been implicated as a coronavirus receptor. Stress cardiomyopathy, myocarditis, microvascular dysfunction, or cytokine storm that may weaken coronary artery plaques are some potential pathways of cardiac involvement. On the other hand, SARS-CoV-2, which caused focal myocyte necrosis and interstitial oedema with a predominance of lymphocyte

infiltration, could mediate the direct mechanism of myocardial injury[26].

Meanwhile, COVID-19 patients with HTN have a higher risk of mortality. Ineffective viral clearance by the immune system and pathological overproduction of cytokines caused by dysregulated high BP are also linked to a weak immune system, a reduced lymphocyte count and cluster of differentiation (CD)8+ T cell malfunction, which culminate in a cytokine storm in COVID-19 infection[30]. Both of these methods will make COVID-19 patients' prognoses worse, which may help to explain why these patients have a high mortality risk due to HTN.

The current study has limitations. First, because of the cross-sectional design of the study, the cause of mortality could not be determined. The causality of morality predicting factors needs to be established by longitudinal cohort research. Second, as the data was only collected from COVID-19 patients who were hospitalised in Indonesia's East Java province, a multiregional investigation with larger samples is necessary.

Conclusion

Pre-existing HTN was one of the cardiovascular comorbidities in COVID-19 infection and was found to increase the mortality risk. Older age, high WBC count, lower platelet count, faster heart rate, and ST abnormality at admission were among the predictors of mortality.

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