This article can be cited as: Gholinataj Jelodar M, Mirzaei S, Hajimaghsoudi M. Impact of preexisting hypertension and antihypertensive medication on prognosis of COVID-19 patients. Cardiovasc Biomed J. 2024; 4(1): 45-53.

Original Article

Impact of preexisting hypertension and antihypertensive medication on prognosis of COVID-19 patients

Mohsen Gholinataj Jelodar [1, 2], ***Samaneh Mirzaei*** [3,*], ***Majid Hajimaghsoudi*** [1]

[1] Clinical Research Development Center, Shahid Rahnemoon Hospital, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Department of Internal Medicine, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Department of Health in Emergencies and Disasters, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

*** Corresponding Author:**
Address: School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. **Postal code:** 8913814396; **Tel:** +98 9132577522; **Email:** s.mirzaei2113@gmail.com

Article Information:
Received: 27 Jun 2024; Revised: 06 Aug 2024; Accepted: 07 Aug 2024 DOI: 10.18502/cbj.v4i1.16227

Abstract

Objectives: Coronavirus disease-2019(COVID-19) patients with comorbidities experience severe disease. Hypertension (HTN) is one of the most common comorbidities seen in these patients. The published reports are conflicting regarding the role of HTN and antihypertensive medication on the in-hospital prognosis of COVID-19 patients. This study investigated the effect of HTN on the prognosis of hospitalized COVID-19 individuals and sought to identify the risk factors for worse clinical outcomes in this population.

Methods: This descriptive-analytical observational study was conducted on COVID-19 patients hospitalized in two teaching hospitals (Shahid Rahnemoon and Shahid Sadoughi) in Yazd, Iran from February 20, 2022, to April 20, 2022. All hospitalized patients with positive polymerase chain reaction (PCR) tests for COVID-19 were included in the study. The demographic, laboratory, imaging, pharmaceutical and clinical data were extracted and analyzed by SPSS v-26.

Results: Out of 615 participants, 243 had HTN. Hypertensive patients had significantly more need for Intensive Care Unit (ICU) admission (P=0.001) and endotracheal intubation (P<0.001) and experienced higher mortality (P<0.001). The length of hospital and ICU stay and duration of endotracheal intubation were not significantly different. No antihypertensive medication was found to impact the patient's prognosis significantly. In hypertensive individuals, the multivariate regression analysis revealed the vaccination status (OR=0.27; CI 95%: 0.10-0.69), a score of Computed tomography (CT) scan involvement (OR=7.49; CI 95%: 3.50-16.01), and neutrophil-to-lymphocyte ratio (NLR) (OR=1.05; CI 95%: 1.00-1.11) as the predictors of need to ICU admission.

Conclusions: Hypertensive COVID-19 patients experience higher mortality and require more ICU admission and endotracheal intubation. None of the antihypertensive drugs had a significant effect on prognosis. The vaccination status, NLR, and the degree of lung involvement in chest imaging predicted the need for ICU admission in this subgroup of patients.

Keywords: SARS-CoV-2, Coronavirus, Hypertension, Antihypertensive Agents, Prognosis

Introduction

After the initial reports of the novel pneumonia in December 2019 and its rapid spread worldwide, the World Health Organization (WHO) declared coronavirus disease-2019(COVID-19) a pandemic in March 2020(1). It was reported that the risk of severe disease is higher in patients who are male, elderly, or have chronic comorbidities (2). Hypertension (HTN) is one of the most common cardiovascular comorbidities associated with COVID-19(3). Many studies revealed that the prevalence of HTN in COVID-19 patients has varied, with reported rates ranging from 15% to nearly 50% (4). Several factors may contribute to the increased severity of COVID-19 in patients with HTN, including long-standing hypertension leading to heart problems, higher occurrence of hypertension in older age groups, and the potential interaction between the virus and antihypertensive medications (5). Research suggests that HTN causes fibrotic changes in cardiac muscles, possibly leading to vulnerability in the face of COVID-19(6). Having identified angiotensin-converting enzyme (ACE)-2 as the virus entry receptor, researchers raised their concerns about the potential for ACE inhibitors (ACEI)/ Angiotensin receptor blockers (ARB) to worsen the clinical condition of COVID-19 patients(7). Research suggests that certain drugs might increase the expression of ACE2 in patients, potentially worsening the severity of COVID-19. The impact of antihypertensive drugs, especially ACEI/ARBs, on the prognosis of COVID-19 patients has shown inconsistent results based on available evidence (8). It remains unclear why infection with this virus in isolated populations with known and identical risk factors leads to varying degrees of disease severity(9). In recent years, conflicting reports have been published regarding the impact of HTN on the prognosis of hospitalized COVID-19 patients. This study aimed to explore the effect of HTN on the clinical outcomes and the need for ICU hospitalization in hypertensive individuals. Identifying the risk factors in this group is crucial for planning effective management and treatment strategies for these patients.

Materials and Methods

The study is a descriptive-analytical observational study on COVID-19 patients hospitalized in two teaching hospitals in Yazd, Iran. The participants were all hospitalized patients, aged at least 18 years old, who tested positive for coronavirus using PCR and were hospitalized between February 20 and April 20, 2022. The data was obtained from the medical records of hospitalized patients and included demographic information such as age, gender, underlying diseases, and body mass index (BMI). In addition, the patients underwent clinical evaluation, encompassing factors such as the need for ICU hospitalization, length of hospital and ICU stay, need for endotracheal intubation and its duration, and mortality. Laboratory data, including inflammatory parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR), were analyzed. Imaging findings were also examined. In the imaging tests, a single radiologist evaluated the extent of lung involvement in patients using computed tomography (CT) scans based on the criteria outlined by the Fleischner Society Glossary (10). Fleischner Society Glossary assigns a score of 0 to 5 to each lung lobe based on the degree of parenchymal involvement. The overall score is obtained from the sum of the scores of the five lung lobes. We classified scores from 0 to 8 as mild, 9 to 16 as moderate, and above 16 as severe involvement. A history of using hypertensive medication was obtained from the patients. The medications were categorized into ACEI/ARBs, beta-blockers, calcium channel blockers, and diuretics. We considered medication use in the two weeks leading up to admission. We collected data on the COVID-19 vaccination status of the patients. Based on this information, we categorized the patients into two groups: those with incomplete vaccination (including patients with no history of vaccine administration, those who received one or two doses of the vaccine and at least six months have passed since the second dose) and those with complete vaccination (including patients who have received three doses of the vaccine or those who have received two doses and less than six months have passed since the second dose). To achieve the study objectives, we initially compared the two groups: one group with no history of hypertension and the other with hypertensive patients. We used statistical analysis to determine the effects of primary variables on the prognosis of hypertensive individuals. The statistical analysis was conducted using SPSS version 26. We presented continuous variables as mean and standard deviation and categorical variables were reported as numbers (percentages). The groups were compared using an independent t-test for continuous variables and a chi-

square test for categorical variables. Only variables with a P-value≤ 0.05 were considered significant. Additionally, we used multivariate regression analysis to identify predictors of worse outcomes. This study was conducted with the permission of the ethics committee in the research of Shahid Sadoughi University of Medical Sciences with the ethics ID: IR.SSU.SRH.REC.1402.021.

Results

Out of the 615 participants, 39.5% had preexisting hypertension (HTN). The average age of hypertensive participants was higher than that of patients without a history of hypertension, although there was no significant difference between genders. Table 1 shows the other demographic characteristics of the patients.

Table1. Demographics and baseline characteristics of participants

variables	General Data	HTN(N=243) N (%)	Non-HTN(N=372) N (%)	P-value
Age	Mean± SD	64.55±14.39	53.81±18.88	<0.001**
Sex	Male	100(41.2)	180(48.4)	0.078*
	Female	143(58.8)	192(51.6)	
BMI	<30	148(60.9)	277(74.5)	*<0.001
	>30	95(39.1)	95(25.5)	
Comorbidities	DM	129(53.1)	59(15.9)	<0.001*
	IHD	61(25.1)	36(9.7)	<0.001*
	CKD	45(18.5)	32(8.6)	<0.001*
	COPD	8(3.3)	18(4.8)	0.351*
	CVA	4(1.6)	7(1.9)	0.546*
	DLP	87(35.8)	56(15.1)	<0.001*
	Hypothyroidism	13(5.3)	27(7.3)	0.348*
	Asthma	5(2.1)	9(2.4)	0.769*
COVID-19 Vaccination status	complete	120(49.4)	210(56.5)	0.086
	incomplete	123(50.6)	162(43.5)	
Laboratory Findings	CRP Negative	60(24.7)	73(19.6)	0.408
	CRP +	44(18.1)	82(22.0)	
	CRP ++	76(31.3)	118(31.7)	
	CRP +++	63(25.9)	99(26.6)	
	ESR	47.70±32.26	44.84±28.21	**0.247
	NLR	8.22±7.42	6.50±5.50	**0.001
Imaging Result (Score of lung involvement) at baseline	Mild (0-8)	158(65.0)	281(75.5)	0.015*
	Moderate (9-16)	68(28.0)	76(20.4)	
	Severe (17-25)	17(7.0)	15(4.0)	

N: Number; SD: Standard Deviation; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; DLP: Dyslipidemia; COPD: Chronic Obstructive Pulmonary Disease; CVA: cerebral vascular accident; BMI: Body Max Index; CKD: Chronic kidney disease *: Chi-squared test, **: Independent t-Test

Figure 1 shows the in-hospital outcomes of patients. As illustrated, hypertensive patients had a significant need for ICU admission and endotracheal intubation and experienced higher mortality. The length of hospital and ICU stay and duration of endotracheal intubation have shown.

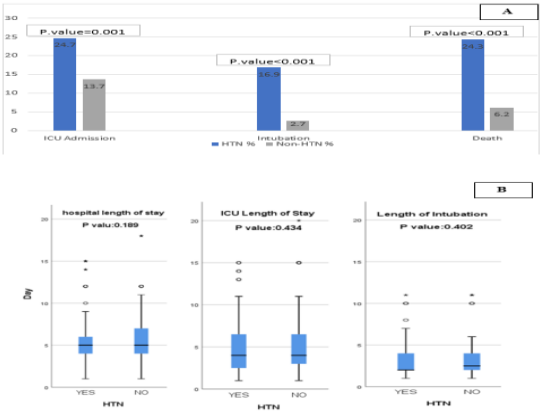

Figure1: comparison of clinical outcomes between two groups of patients with and without HTN; A: categorical outcomes, B: numerical outcomes

Two groups of hypertensive patients, one needed ICU hospitalization, and the other without the need for ICU hospitalization were compared. According to Table 2, hypertensive patients with the need for ICU admission had significant differences in some primary variables: vaccination status, the existence of diabetes mellitus (DM), NLR level, and the severity of lung involvement on CT scans.

Table2. Association between Demographic and Primary with ICU admission in hypertension Patient

Variable			ICU admission			P-value
			Yes	No	Total	
Sex, N (%)		Male	24(40)	76(41.5)	100(41.2)	0.834
		Female	36(60)	107(58.5)	143(58.8)	
Age		Mean ± SD	62.02±20.13	65.38±11.89	243	0.116
BMI		<30	35(58.3)	113(61.7)	148(60.9)	0.638
		>30	25(41.7)	70(38.3)	95(39.1)	
COVID-19 Vaccination status		complete	9(15)	111(60.7)	120(49.4)	<0.001
		incomplete	51(85)	72(39.3)	123(50.6)	
Comorbidity, N (%)	DM	Yes	42(70)	87(47.5)	129(53.1)	0.002
	IHD		20(33.3)	41(22.4)	61(25.1)	0.090
	CKD		12(20)	33(18)	45(18.5)	0.734
	COPD		1(1.7)	7(3.8)	8(3.3)	0.416
	CVA		2(3.3)	2(1.1)	4(1.6)	0.237
	DLP		16(26.7)	71(38.8)	87(35.8)	0.089
	Hypothyroidism		3(5)	10(5.5)	13(5.3)	0.890
	Asthma		1(1.7)	4(2.2)	5(2.1)	0.806
Laboratory Findings	CRP	Negative	16(26.7)	44(24)	60(24.7)	0.063
		+	5(8.3)	39(21.3)	44(18.1)	
		++	25(41.7)	51(27.9)	76(31.3)	
		+++	14(23.3)	49(26.8)	63(25.9)	
		N (%)				
	ESR	Mean ± SD	48.46±31.84	47.45±32.47	243	0.834
	NLR	Mean ± SD	12.96±8.92	6.66±6.14	243	<0.001
Imaging Result (Score of lung involvement) at baseline	Mild (0-8)	Yes	12(20)	146(79.8)	158(65)	<0.001
	Moderate (9-16)		31(51.7)	37(20.2)	68(28)	
	Severe (17-25)		17(28.3)	0	17(7)	

N: Number; SD: Standard Deviation; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; DLP: Dyslipidemia; COPD: Chronic Obstructive Pulmonary Disease; CVA: cerebral vascular accident; BMI: Body Max Index; CKD: Chronic kidney disease *: Chi-squared test, **: Independent T-Test

The data on the categories of antihypertensive drugs used by the patients and their relationship with the clinical outcomes are shown in Table 3.

Table 3. Relationship between the antihypertensive agent's classification and patients' clinical outcomes

		ICU admission			intubation			death		
		Yes	**No**	**p-value**	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
Ca-blocker	Yes N (%)	5(8.3)	24(13.1)	*0.321	5(12.2)	24(11.9)	*0.955	6(10.2)	23(12.5)	*0.631
Beta-blocker		5(8.3)	23(12.6)	*0.373	5(12.2)	23(11.4)	*0.882	10(16.9)	18(9.8)	*0.790
ACE/ARB		23(38.3)	69(37.7)	*0.931	17(41.5)	75(37.1)	*0.602	27(45.8)	65(35.3)	*0.150
Diuretic		18(30.0)	38(20.8)	*0.140	10(24.4)	46(22.8)	*0.823	15(25.4)	41(22.3)	*0.618
		Hospital length of stay			**ICU length of stay**			**Length of intubation**		
		Mean± SD		**p-value**	**Mean± SD**		**p-value**	**Mean± SD**		**p-value**
Ca blocker	Yes	4.97±1.37		**0.150	3.0±1.73		0.184	2.20±1.09		**<0.001
	No	5.92±3.50			5.33±3.81			2.20±2.66		
Beta-blocker	Yes	5.50±2.08		**0.611	4.20±2.28		0.564	3.80±2.04		**0.146
	No	5.84±3.46			5.22±3.84			2.05±2.57		
ACE/ARB	Yes	6.16±3.68		**0.189	5.30±3.36		0.742	2.30±2.43		**0.806
	No	5.58±3.09			5.03±3.98			2.14±2.66		
Diuretic	Yes	6.79±5.57		**0.012	5.61±4.28		0.521	2.22±3.19		**0.965
	No	5.51±2.21			4.93±3.50			2.19±2.28		

Performing a multivariate analysis to identify risk factors for critical consequences using a model consisting of primary variables with a P-value less than 0.2.The results of the final step are presented in Table 4.

Table 4. Relationship between Demographic and Primary variables with mortality based on multivariate logistic regression

Variable	**P-value**	**Odds ratio (OR)**	**95% C.I. for OR**	
			Lower	**Upper**
DM	.196	1.782	.743	4.274
IHD	.821	1.124	.408	3.091
DLP	.436	.698	.283	1.722
COVID-19 Vaccination status	.007	.272	.106	.695
NLR	.035	1.059	1.004	1.118
CT score2	.000	7.491	3.504	16.014
CRP3+	.744	1.062	.740	1.523
Age	.895	1.002	.973	1.031
ACE/ARB	.513	1.342	.556	3.239

The table shows all the variables: -2loglikelihood= 161.31; $\chi 2 = 110.317$, $p<0.0001$.Hosmer-Lemeshow statistics= 9.8 with df=8, p=0.279.

Discussion

The present study revealed that COVID-19 patients with high blood pressure have a higher mortality rate compared to those without a history of hypertension. However, it is worth noting that a previous study of these patients found that HTN was not an independent risk factor of mortality according to multivariate regression analysis (11). There is insufficient evidence to associate HTN with the severity of COVID-19 and patient mortality. However, earlier studies have reported that the rate of

HTN is significantly higher among hospitalized patients who die (12). In a pooled analysis, Lippi et al. demonstrated that hypertension is associated with a 2.5 times higher risk of severe COVID-19 and patient mortality (13). However, another study in Italy has not identified HTN as a predictor for mortality in COVID-19 patients (2). Similar results were reported in other studies (14, 15). In a more recent study, D'Elia et al. concluded in a meta-analysis that HTN is not an independent risk factor for mortality in COVID-19 patients (16). Contrary to previous studies, a study on the Japanese population revealed that preexisting hypertension is a risk factor and a predictor for mortality (OR=1.35, 95% CI: 1.05-1.73) in COVID-19 patients (17). This current study determined that hypertensive patients need hospitalization in the ICU to a greater extent, and the need for endotracheal intubation and mechanical ventilation is more remarkable in them. However, there was no significant difference in the length of stay at the hospital and ICU, nor was there a difference in the duration of endotracheal intubation. In a retrospective and multicenter study, Xiong et al. concluded that the likelihood of ICU admission and mechanical ventilation is higher for hypertensive patients (18).Another study on the Italian population showed that HTN is one of the independent risk factors (OR=1.31, CI 95%: 1.03-1.66) for the need for ICU admission (19). According to the results of the meta-analysis of 18 studies, Qian et al. showed that the simultaneous presence of HTN in COVID-19 patients is related to an increased need for ICU hospitalization (RR=1.86, CI 95%: 1.13-3.07) and mechanical ventilation (RR=2.99, CI 95%: 1.73-5.17) (20). In the present study, hypertensive patients had more comorbidities, as well as higher age and BMI than the group without a history of hypertension. These factors may have contributed to the increased severity of the disease and worse clinical outcomes in this group. Many studies have revealed that the simultaneous presence of DM, chronic kidney disease, and congestive heart failure are associated with mortality and worse clinical consequences in COVID-19 patients (6, 21).A retrospective study in India has reported that old age, along with comorbidities are independent risk factors for mortality in COVID-19 patients. This study introduced DM (OR=2.39, CI 95%: 2.31-2.47) as the more dangerous risk factor, followed by cardiovascular diseases (22). Due to the chronic inflammatory condition, elderly patients have higher levels of pro-inflammatory cytokines, which provides the basis for the worsening of COVID-19 in this group of patients (23). As the age increases, Immunosenescence occurs, including a progressive decrease in the immune system function and a decrease in the response to foreign pathogens (24).

Another study revealed that obesity not only reduces respiratory reserve (25) but also causes an imbalance in the body's immune system and impairs immune response (26). A recent study spanning 142 countries found a connection between the mortality rate among COVID-19 patients and the prevalence of obesity. The study revealed that in developed countries, a one percentage point increase in the obese population is associated with a 1.5% rise in mortality (27). Another study indicated that medical conditions related to obesity may exacerbate the disease. According to the findings, patients with a BMI above 30 kg/m2 or below 18 kg/m2 are at a higher risk of experiencing severe clinical outcomes. The researchers concluded that although obesity is associated with worse clinical outcomes in COVID-19 patients, mortality in these patients is primarily caused by obesity-related health conditions such as diabetes and hypertension rather than obesity itself (28).

The current study's findings indicate that the specific antihypertensive drug used by patients with HTN did not significantly impact their clinical outcomes. These results align with Xiong et al.'s study, which involved 472 patients. They found no association between the type of hypertensive agents and patients' clinical results. The study's stepwise regression analysis demonstrated that none of the antihypertensive drugs predicted worse participant outcomes (29). Contrary to these findings, a recent meta-analysis indicated that continued use of hypertensive drugs was associated with a decrease in mortality in COVID-19 patients (30). It implies that ACEI/ARBs may worsen COVID-19 by increasing the expression of ACE2, which the new coronavirus uses to enter the cells. However, it should be noted that ACE2 can break down angiotensin II, a substance with inflammatory and vasoconstrictive effects (31).The present study demonstrated that using these drugs to control blood pressure in hypertensive patients did not result in an increased risk of mortality, ICU admission, or the need for mechanical ventilation. Multiple studies have investigated the impact of ACEI/ARB on the clinical outcomes of COVID-19 patients, but the findings have been inconsistent. A recent meta-analysis of COVID-19 patients showed that continued use of these drugs did not increase the need for hospitalization in the ICU and mechanical ventilation. The study concluded that in severe

COVID-19, the initiation of the new renin-angiotensin-aldosterone system (RAS) blockers was associated with an increased risk of death (32). The results of another study indicate that while these drugs reduced the length of hospitalization, they did not decrease in-hospital mortality (33). The study by Liu et al. showed that using these drugs has reduced the duration of ICU hospitalization, the need for mechanical ventilation, and the mortality of patients (34). Currently, the evidence is not in favor of discontinuing these drugs in hypertensive patients, and it may even lead to an increase in the risk of complications caused by concomitant diseases. Therefore, it is recommended that treatment with these drugs continue (35). Statistical analysis in hypertensive patients revealed that patients with a higher need for ICU admission in this subgroup tended to have incomplete vaccination status, DM, higher NLR, and more lung involvement in chest CT scans. In the multivariate regression analysis conducted in hypertensive patients, vaccination status, lung involvement in chest CT scans, and NLR were identified as predictors of the need for hospitalization in the ICU. It is essential to carefully assess these factors in hypertensive patients at the onset of COVID-19 hospitalization to identify those at high risk for ICU admission and severe outcomes. It will enable medical staff to provide these patients with attention and care. Attention should be paid to preventive measures, focusing on COVID-19 vaccination for patients with hypertension. Our study revealed that 85% of hypertensive patients who needed ICU hospitalization were not fully vaccinated. Similar findings have been reported in other studies. A study conducted in India demonstrated a 70% decrease in mortality among hospitalized patients who were fully vaccinated (36NLR has been used as a predictive mortality index in many diseases(37). In severe cases of COVID-19, the excessive inflammatory response causes changes in the count of peripheral blood cells, resulting in an increase in neutrophils and a decrease in lymphocytes (38). Various studies have investigated the role of the NLR on the prognosis of COVID-19 patients. The studies reported that a higher index at the time of admission is associated with higher mortality and worse clinical outcomes(39).The meta-analysis by Sarkar et al. revealed that patients with severe COVID-19 had significantly higher NLR levels than those with milder disease (40). There are some limitations to our study. Firstly, we only included patients with a positive PCR test, which may have ended in excluding some patients due to the false negative results of this diagnostic test. Secondly, our evaluation was limited to the patient's hospitalization period, so we had no information about them after discharge. Lastly, our study only involved patients from two inpatient centers, and it lasted two months to collect data. It is recommended to conduct more studies with a larger number of participants over a long period to achieve more generalizability.

Conclusion

Hypertensive COVID-19 patients have a higher mortality rate and are more likely to require ICU admission and endotracheal intubation. Factors such as vaccination status, NLR (neutrophil-to-lymphocyte ratio), and the severity of lung damage seen in chest imaging can help predict the need for ICU admission in these patients.

Ethical statements

This study was conducted with the permission of the ethics committee in the research of Shahid Sadoughi University of Medical Sciences with the ethics ID: IR.SSU.SRH.REC.1402.021.

Acknowledgments

The authors express their sincere gratitude to the authorities at Shahid Sadoughi University of Medical Sciences for their invaluable assistance throughout the study.

Author’s contributions

Study concept and design: M.Gh and S.M
Acquisition of data: S.M
Interpretation of data:M.Gh and S.M
Drafting of the manuscript: M.Gh, S.M, and M.H
All authors agree to be fully accountable for ensuring the study’s accuracy and have read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no Conflicts of interest.

Funding

This study was approved by the Clinical Research Development Center at Shahid Rahnemoon Hospital, Yazd, Iran.

References

1.Krammer F. The role of vaccines in the COVID-19 pandemic: what have we learned? *Semin Immunopathol*. 2024; 45(4-6):451-468.

2.Iaccarino G, Grassi G, Borghi C, et al. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian Society of Hypertension. *Hypertension*. 2020;76(2):366-372.

3. Arutyunov GP, Tarlovskaya EI, Arutyunov AG, et al. International register "Dynamics analysis of comorbidities in SARS-CoV-2survivors" (AKTIV SARS-CoV-2): analysis of 1,000 patients. *Russ J Cardiol*. 2020; 25(11):4165.

4.Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. 2020323(18):1775-1776.

5.Al-Qudimat AR, Ameen A, Sabir DM, et al. The Association of Hypertension with Increased Mortality Rate During the COVID-19 Pandemic: An Update with Meta-analysis. *J Epidemiol Glob Health*.2023;13(3):495-503.

6.Tadic M, Cuspidi C, Grassi G, et al. COVID-19 and arterial hypertension: hypothesis or evidence? *J Clin Hypertens (Greenwich)*. 2020;22(7):1120-1126.

7.Henry BM, Vikse J, Benoit S, et al. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin Chim Acta*. 2020;507:167-173.

8.Gallo G, Calvez V, Savoia C. Hypertension and COVID-19: current evidence and perspectives. *High Blood Press Cardiovasc Prev*. 2022;29(2):115-123.

9.Vahedian-Azimi A, Mohammadi SM, Beni FH, et al. Improved COVID-19 ICU admission and mortality outcomes following treatment with statins: a systematic review and meta-analysis. *Arch Med Sci*.2021;17(3):579-595.

10.Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. *Radiology*. 2008;246(3):697-722.

11.Gholinataj Jelodar M, Mirzaei S, Saghafi F, et al. Impact of vaccination status on clinical outcomes of hospitalized COVID-19 patients. *BMC Infect Dis*.2024; 24(1):254.

12.Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;323(16):1574-1581.

13.Lippi G, Wong J, Henry BM. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. *Pol Arch Intern Med*. 2020;130(4):304-309.

14.McFarlane E, Linschoten M, Asselbergs FW, et al. The impact of pre-existing hypertension and its treatment on outcomes in patients admitted to hospital with COVID-19. *Hypertens Res*. 2022;45(5):834-845.

15.Matsumoto C, Shibata S, Kishi T, et al. Long COVID and hypertension-related disorders: a report from the Japanese Society of Hypertension Project Team on COVID-19.*Hypertens Res*. 2023;46(3):601-619.

16.D'Elia L, Giaquinto A, Zarrella AF, et al. Hypertension and mortality in SARS-COV-2 infection: A meta-analysis of observational studies after 2 years of pandemic. *Eur J Intern Med*. 2023;108:28-36.

17.Sakurai K, Chubachi S, Asakura T, et al. Prognostic significance of hypertension history and blood pressure on admission in Japanese patients with coronavirus disease 2019: integrative analysis from the Japan COVID-19 Task Force. *Hypertens Res*. 2024;47(3):639-648.

18.Xiong T-Y, Huang F-Y, Liu Q, et al. Hypertension is a risk factor for adverse outcomes in patients with coronavirus disease 2019: a cohort study. *Ann Med*. 2020;52(7):361-366.

19.Iaccarino G, Grassi G, Borghi C, et al. Gender differences in predictors of intensive care units admission among COVID-19 patients: The results of the SARS-RAS study of the Italian Society of Hypertension. *PLoS One*. 2020;15(10):e0237297.

20.Qian Z, Li Z, Peng J, et al. Association between hypertension and prognosis of patients with COVID-19: A systematic review and meta-analysis. *Clin Exp Hypertens*. 2022;44(5):451-458.

21.Lian J, Jin X, Hao S, et al. Analysis of epidemiological and clinical features in older patients with coronavirus disease 2019 (COVID-19) outside Wuhan. *Clin Infect Dis*. 2020;71(15):740-747.

22.Singh P, Bhaskar Y, Verma P, et al. Impact of comorbidity on patients with COVID-19 in India: A nationwide analysis. *Front Public Health*.2023;10:1027312.

23.Gao Yd, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: a review. *Allergy*. 2021;76(2):428-455.

24.Lee K-A, Flores RR, Jang IH, et al. Immune senescence, immunosenescence and aging. *Front Aging*. 2022;3:900028.

25.Venkata C, Sampathkumar P, Afessa B. Hospitalized patients with 2009 H1N1 influenza infection: the Mayo Clinic experience. *Mayo Clin Proc*. 2010;85(9):798-805.

26.Maurizi G, Della Guardia L, Maurizi A, et al. Adipocytes properties and crosstalk with immune system in obesity-related inflammation. *J Cell Physiol*.2018;233(1):88-97.

27.Arulanandam B, Beladi H, Chakrabarti A. Obesity and COVID-19 mortality are correlated. *Sci Rep*.2023;13(1):5895.

28.Tong L, Khani M, Lu Q, et al. Association between body-mass index, patient characteristics, and obesity-related comorbidities among COVID-19 patients: A prospective cohort study. *Obes Res Clin Pract*.2023;17(1):47-57.

29.Xiong TY, Huang FY, Liu Q, et al. Hypertension is a risk factor for adverse outcomes in patients with coronavirus disease 2019: a cohort study. *Ann Med*.

2020;52(7):361-366.
30.Liu J, Huang L, Wei W, et al. Effects of Antihypertensive Agents on the Clinical Outcome of Hospitalized COVID-19 Patients Concomitant with Hypertension: A Systematic Review and Meta-Analysis. *Heart Lung*. 2024;63:78-85.
31.Chouchana L, Beeker N, Garcelon N, et al. Association of Antihypertensive Agents with the Risk of In-Hospital Death in Patients with Covid-19. *Cardiovasc Drugs Ther*. 2022;36(3):483-488.
32.Lee MMY, Kondo T, Campbell RT, et al. Effects of renin-angiotensin system blockers on outcomes from COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother*. 2024;10(1):68-80.
33.Braude P, Carter B, Short R, et al. The influence of ACE inhibitors and ARBs on hospital length of stay and survival in people with COVID-19. *Int J Cardiol Heart Vasc*. 2020;31:100660.
34.Liu Q, Fu W, Zhu CJ, et al. Effect of continuing the use of renin-angiotensin system inhibitors on mortality in patients hospitalized for coronavirus disease 2019: a systematic review, meta-analysis, and meta-regression analysis. *BMC Infect Dis*. 2023;23(1):53.
35.Busse LW, Chow JH, McCurdy MT, et al. COVID-19 and the RAAS-a potential role for angiotensin II? *Crit Care*. 2020;24(1):136.
36.Muthukrishnan J, Vardhan V, Mangalesh S, et al. Vaccination status and COVID-19 related mortality: A hospital based cross sectional study. *Med J Armed Forces India*. 2021;77:S278-S282.
37.Buonacera A, Stancanelli B, Colaci M, et al. Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases.*Int J Mol Sci*. 2022;23(7):3636.
38.Henry BM, de Oliveira MHS, Benoit S, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020;58(7):1021-1028.
39.Asperges E, Albi G, Zuccaro V, et al. Dynamic NLR and PLR in Predicting COVID-19 Severity: A Retrospective Cohort Study. *Infect Dis Ther*.2023;12(6): 1625-1640.
40.Sarkar S, Khanna P, Singh AK. The Impact of Neutrophil-Lymphocyte Count Ratio in COVID-19: A Systematic Review and Meta-Analysis. *J Intensive Care Med*. 2022;37(7):857-69.

