Impact of Statin or Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker on the In-Hospital Mortality of COVID-19 Patients

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Abstract

Background: It is important to determine the risk factors that contribute to the mortality of a disease and take measures to prevent or alleviate it. In the case of COVID-19, old age, male gender, and comorbidities such as diabetes (DM) and hypertension (HTN) have been identified as potential risk factors. However, there is conflicting information on the effects of statins and ACEI/ARB in COVID-19 patients admitted to the ICU, particularly those with diabetes or hypertension. This study aims to investigate the effects of these drugs on the in-hospital prognosis of ICU COVID-19 patients, with a focus on patients with DM or HTN.

Methods: During 18 months, we conducted a descriptive-analytical observational analysis on 391 patients who were admitted to the ICU. The study focused on COVID-19 patients and aimed to identify mortality risk factors by assessing their demographic, clinical, pharmaceutical, laboratory, and imaging data. We statistically analyzed the data to achieve this goal.

Results: Out of 391 patients, 83 received statins and 89 received ACEI/ARBs. The research has revealed that the use of ACEI/ARBs in COVID-19 patients admitted to the ICU may increase the risk of endotracheal intubation (P<0.0001) and mortality (P<0.0001). Additionally, patients treated with these drugs are more likely to experience secondary bacterial infections (P=0.007) and venous thromboembolism events (P=0.015). The results of a recent study analyzing diabetic and hypertensive patients hospitalized in ICU showed that there is no significant difference in clinical outcomes between COVID-19 patients who used ACEI/ARB and those who did not. Our study has found that the use of statins in diabetic patients is linked to a reduction in mortality rate (0.008) and secondary bacterial infections (P=0.035) of COVID-19 patients admitted to the ICU. In multivariate logistic regression, the use of statin or ACE/ARB was not identified as the mortality prediction factor.

Conclusion: Statins can help reduce mortality rates among COVID-19 patients, especially in diabetic patients, hospitalized in the ICU. So, they should be used to manage cardiovascular risk factors and lower the mortality risk. Statins and ACEI/ARB drugs were not predictors of mortality and did not decrease survival rates during ICU hospitalization.

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Keywords: Statin; COVID-19; Mortality; Intensive Care Unit

Introduction

MThe novel coronavirus disease, named COVID-19, was initially detected in Wuhan, China in December 2019 and has since become a global pandemic. COVID-19 can present itself as asymptomatic cases with mild clinical symptoms or as severe conditions(1). that require intensive care unit (ICU) admission with multiorgan failure, acute respiratory distress syndrome (ARDS), and ultimately, death. Approximately 5% of COVID-19 patients develop a severe respiratory condition that requires ICU hospitalization(2). "Cytokine storm" refers to the overproduction and release of inflammatory cytokines, often leading to ARDS, and is the leading cause of death in COVID-19 patients. Statins have been found to have pleiotropic properties, which means they have multiple beneficial effects including anti-inflammatory, immunomodulatory, and antioxidant properties. They could potentially be effective in reducing the cytokine storm in COVID-19 patients(3-6). Previous studies have shown that statins can improve clinical

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outcomes in patients with influenza infection(7). Using statins can inhibit the replication of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) and reduce the release of inflammatory factors, decreasing the intensity of cytokine storms. Additionally, some studies suggest that statins can improve the lipid profile of COVID-19 patients, reducing the risk of cardiovascular complications(8).

The virus uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter the cell. ACE-2 is highly expressed in the lung, particularly in endothelial and alveolar type 2 cells(9, 10). It appears that COVID-19 severity is influenced by a lack of ACE2 and an imbalance in the Renin-Angiotensin-Aldosterone System (RAAS) system(11).

The RAAS is responsible for regulating blood pressure in our body. The kidneys secrete renin that converts angiotensinogen to angiotensin (Ang) I. Ang I is then converted to Ang II by ACE. Ang II binds with angiotensin-2 receptor-1 (AT1R) and causes vasoconstriction, increased thrombosis, inflammation, and fibrosis(12, 13). ACE2 is responsible for converting Ang II into Ang (I -7) and Ang1 into Ang (I -9). Ang (I -7) has opposite effects to Ang II, causing vasodilation, anti-inflammatory and antithrombotic effects. ACE2 negatively regulates the RAAS(14). The interaction between the virus and ACE2 has led to the development of therapeutic strategies based on RAAS for the treatment of COVID-19(15). A proposed hypothesis suggests that this infection downregulates the ACE2 protein(16, 17). Ang II level in COVID-19 patients is inversely related to viral load(16). ACE inhibitors (ACEI) prevent the conversion of angiotensin I to angiotensin II, while angiotensin receptor blockers (ARB) block the Ang II receptor to inhibit its effects. The clinical impact of these drugs on COVID-19 outcomes is not well-established(18).

It is important to identify the risk factors that contribute to the mortality of a disease and implement measures to prevent or alleviate it. In the case of COVID-19, old age, male genders, and comorbidities such as diabetes (DM) and hypertension (HTN) have been identified as potential risk factors. However, there is conflicting information on the effects of statins and ACEI/ARB in COVID-19 patients admitted to the ICU, especially those with diabetes or hypertension. This study aims to investigate the effects of these drugs on the in-hospital prognosis of ICU COVID-19 patients, with a focus on patients with DM or HTN.

Methods

This is a retrospective descriptive-analytical observational study conducted on COVID-19 ICU patients over 18 months. The study included all patients who had tested positive for coronavirus through a polymerase chain reaction (PCR) test and were admitted to the COVID ICU between March 20, 2020, and September 1, 2021. The Ethics Committee of Shahid Rahnamon Hospital in Yazd assigned the study to the Code of Ethics IR.SSU.SRH.REC.1402.022

Patient data was collected from their files to gather necessary information. The required information includes demographic findings such as age, gender, and comorbidity. Clinical findings such as arterial oxygenation levels during hospitalization and discharge from ICU, duration of hospitalization and ICU, endotracheal intubation, and complications caused during hospitalization including secondary bacterial infection, venous thromboembolic events, gastrointestinal bleeding, and mortality were also gathered. Laboratory and imaging information including the extent of chest high-resolution computed tomography (HRCT) scan involvement on admission to the ICU was collected, along with medication information such as the previous history of taking statins or ACEI/ARBs, and drugs used to treat DM and COVID-19. The Fleischner Society uses a scoring system to determine lung involvement in CT scans. This method evaluates each lung lobe separately and assigns a score of 0 to 5 based on the level of lobar involvement of the lung tissue. The final score is calculated by adding up the involvement scores of all five lobes, which range from 0 to 25(19).

This study compared patients who were taking statins and ACE/ARBs with those who were not, based on various demographic, clinical, and paraclinical criteria. The investigation also examined diabetic and hypertensive patients who were using these medications and those who were not.

Data analysis was performed using the statistical software SPSS version 26.0. The quantitative data were expressed as mean ± standard deviation. The two groups were compared using an independent t-test for continuous variables. Numerical data was represented using percentages, and group differences were compared using the chi-square test or exact probability method. The researchers investigated the factors that increase mortality risk in ICU patients with COVID-19. The investigation involved the use of bivariate analysis and multivariate regression. Only factors with a P-value of 0.05 or less in the bivariate analysis were considered by the researchers for the multivariate analysis. Furthermore, a separate examination of the survival rate without and with statin and ACEI/ARBs use was conducted using the Kaplan-Meier test.

Results

In the study, a total of 391 patients who tested positive were included. Out of them, 83 patients received statins while 89 patients received ACEI/ARBs. Table 1 shows a comparison of demographic information, basic characteristics, and clinical results of patients in groups with and without statin use, and with and without ACEI/ARB use.

Table 1. Baseline characteristics and outcome of patients based on the use of statin and ACEIs/ARBs.

		Statin			ACEIs/ARBs		
	General Data	*Yes (n=83)*	*NO (N=308)*	*P-value*	*Yes (89)*	*NO (N=302)*	*P-value*
		n (%)	*n (%)*		*n (%)*	*n (%)*	
Age	**<=60 y**	23(27.7)	133(43.2)	0.011	24(27)	132(43.7)	0.005
	>60 y	60(72.3)	175(56.8)		65(73)	170(56.3)	
	Mean±SD	67.05±16.63	62.66±17.97	0.046	67.58±15.14	62.42±18.32	0.016
Sex	**Male**	42(50.6)	182(59.1)	0.165	41(46.1)	183(60.6)	0.015
	Female	41(49.4)	126(40.9)		48(53.9)	119(39.4)	
O2Sat, Baseline	**O2 < 88%**	72(86.8)	244(79.2)	0.197	75(84.3)	241(79.8)	0.515
	92% > o2 >=88%	10(12.0)	49(15.9)		12(13.5)	47(15.6)	
	O2 >= 92%	1(1.2)	15(4.9)		2(2.2)	14(4.6)	
	Mean±SD	78.30±9.44	77.69±12.06	0.672	76.51±12.23	78.21±11.33	0.221
Comorbidities	**HTN**	58(69.9)	104(33.8)	<0.0001	71(79.8)	91(30.1)	<0.0001
	AF	9(10.8)	14(4.5)	0. 03	7(7.9)	16(5.3)	0.366
	IHD	31(37.3)	51(16.6)	<0.0001	28(31.5)	54(17.9)	0.006
	CHF	15(18.1)	17(5.5)	<0.0001	10(11.2)	22(7.3)	0.232
	DM	61(73.5)	95(30.8)	<0.0001	63(70.8)	93(30.8)	<0.0001
	CKD	21(25.3)	60(19.5)	0.246	21(23.6)	60(19.9)	0.446
	COPD	14(16.9)	40(13)	0.363	14(15.7)	40(13.2)	0.550
	CVA	16(19.3)	24(7.8)	0.002	17(19.1)	23(7.6)	0.002
	DLP	11(13.3)	27(8.8)	0.221	18(20.2)	20(6.6)	<0.0001
	ESRD	3(3.6)	21(6.8)	0.210	5(5.6)	19(6.3)	0.816
	Cancer	2(2.4)	10(3.2)	0.514	4(4.5)	8(2.6)	0.281
	Hypothyroidism	1(1.2)	8(2.6)	0.397	2(2.2)	7(2.3)	0.664
	Seizure	1(1.2)	8(2.6)	0.397	2(2.2)	7(2.3)	0.664
	IPF	0(0)	7(2.3)	0.185	2(2.2)	5(1.7)	0.499
	Cirrhosis	2(2.4)	3(1)	0.288	1(1.1)	4(1.3)	0.680
	Parkinson	2(3.6)	0(0)	0.009	1(1.1)	2(0.7)	0.540
	Rheumatoid arteritis	0(0)	2(0.6)	0.622	1(1.1)	1(0.3)	0.406
Diabetes Drugs	**EMPA**	17(20.5)	39(12.7)	0.071	22(24.7)	34(11.3)	0.001
	DPPI	29(34.9)	29(9.4)	<0.0001	29(32.6)	29(9.6)	<0.0001
	Sulfonylurea	24(28.9)	35(11.4)	<0.0001	18(20.2)	41(13.6)	0.124
	Biguanides	51(61.4)	69(22.4)	<0.0001	49(55.1)	71(23.5)	<0.0001
	Insulin	30(36.1)	44(14.3)	<0.0001	37(41.6)	37(12.3)	<0.0001
	Anti-coagulant	9(10.8)	19(6.2)	0.143	10(11.2)	18(6)	0.09
	statin	-	-	-	44(49.4)	39(12.9)	<0.0001
	ACEIs/ARBs	44(53)	45(14.6)	<0.0001	-	-	-
COVID19 Drugs	**Tocilizumab**	12(14.5)	65(21.1)	0.177	15(16.9)	62(20.5)	0.443
	Favipiravir	8(9.6)	25(8.1)	0.658	14(15.7)	19(6.3)	0.005
	Hydroxychloroquine	9(10.8)	22(7.1)	0.268	12(13.5)	19(6.3)	0.027
	Remdesivir	41(49.4)	162(52.6)	0.605	39(43.8)	164(54.3)	0.082
	Lopinavir/Ritonavir	25(30.1)	75(24.4)	0.285	26(29.2)	74(24.5)	0.371
	Interferon beta-1a	23(27.7)	71(23.1)	0.378	29(32.6)	65(21.5)	0.032

Table 1. Continued

			Statin			ACEIs/ARBs		
	General Data		*Yes (n=83)*	*NO (N=308)*	*P-value*	*Yes (89)*	*NO (N=302)*	*P-value*
			n (%)	*n (%)*		*n (%)*	*n (%)*	
Imaging Result (Score of lung involvement) at baseline	**Mild (0-8)**		16(19.3)	65(21.1)	0.551	16(18)	65(21.5)	0.702
	Moderate (9-16)		40(48.2)	128(41.6)		38(42.7)	130(43)	
	Severe (17-25)		27(32.5)	115(37.3)		35(39.3)	107(35.4)	
	Mean±SD		13.64±6.05	14.13±6.04	0.511	14.80±6.12	13.80±6.00	0.170
Laboratory Findings	**CRP**	**Negative**	13(15.7)	65(21.1)	0.177	18(20.2)	60(19.9)	0.754
		+	22(26.5)	55(17.9)		19(21.3)	58(19.2)	
		++	(7.2723(	108(35.1)		32(36)	99(32.8)	
		+++	1((30.25	80(26)		20(22.5)	85(28.1)	
				Mean± SD		**Mean± SD**		
	WBC		9.51±6.82	9.20±5.20	0.659	10.14±5.77	9.01±5.50	0.091
	ESR		46.08±28.79	46.04±28.78	0.991	44.85±29.45	46.40±28.66	0.656
	BS		160.09±51.23	148.35±52.35	0.069	158.92±55.79	148.46±51.04	0.097
	NLR		9.08±7.37	10.74±8.96	0.121	11.01±8.77	10.20±8.63	0.443
	PLT		198.20±84.41	204.85±93.79	0.559	211.94±83.24	200.93±94.17	0.321
	BUN		62.16±46.35	60.66±53.35	0.816	63.38±46.88	60.28±53.33	0.621
	Cr		1.62±0.87	1.80±2.08	0.450	1.76±1.22	1.76±2.04	0.975
	AST		55.48±55.16	75.96±150.42	0.227	63.88±63.46	73.90±151.88	0.542
	ALT		44.59±46.77	69.18±142.13	0.121	52.74±55.60	67.27±142.76	0.349
	ALP		210.71±126.27	216.25±120.98	0.714	229.79±112.61	210.74±124.45	0.196
	LDH		679.12±374.73	787.65±567.89	0.10	819.51±568.47	748.44±523.55	0.271
Outcomes & Complications	**Intubation**		40(48.2)	112(36.4)	0.05	53(59.6)	99(32.8)	<0.0001
	Death		39(47.0)	110(35.7)	0.061	54(60.7)	95(31.5)	<0.0001
	Infection		13(15.7)	41(13.3)	0.582	20(22.5)	34(11.3)	0.007
	GI. Bleeding		7(8.4)	20(6.5)	0.536	9(10.1)	18(6)	0.175
	Thrombosis		3(3.6)	14(4.5)	1.000	8(9)	9(3)	0.015
O2Sat, discharge with supplementary o2	**O2 < 88%**		4(9.3)	7(3.5)	0.172	2(5.4)	9(4.4)	0.942
	92% > o2 >=88%		17(39.5)	99(49.7)		17(45.9)	99(48.3)	
	O2 >= 92%		22(51.2)	93(46.7)		18(48.6)	97(47.3)	
	Mean±SD		92.42±2.83	92.67±3.13	0.631	92.51±2.91	92.64±3.11	0.813
Hospital length of stay	**Mean±SD**		11.24±7.26	13.31±9.82	0.073	11.90±7.07	13.16±9.93	0.264
ICU length of stay	**Mean±SD**		9.17±7.41	11.41±9.87	0.055	9.94±7.08	11.22±10.02	0.262

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; ESRD: End Stage Renal Disease; IPF: Idiopathic Pulmonary Fibrosis;; AF: Atrial fibrillation; ACEIs: Angiotensin-converting enzyme Inhibitors ; ARBs: angiotensin receptor blockers ; EMPA: Empagliflozin; DDPI: Dipeptidyl peptidase-4 inhibitor; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; CPK: Creatine Phosphokinase ; LDH: Lactate Dehydrogenase; WBC: White Blood Cells; NLR: Neutrophil-Lymphocyte Ratio; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; BS: Blood Sugar; O2Sat: Oxygen Saturation.; Cons: Considerations; GGO: Ground-glass opacification; PE: pleural effusion; y:year; N: Number; NIV: Non-Invasive Ventilation

Table 2 presents the basic information and clinical outcomes of patients with diabetes and hypertension who received or did not receive ACEI/ARBs.

Table2. Baseline characteristics and outcome of COVID-19 patients with DM or HTN based on the use of ACEI/ARBs.

		HTN(N=162)			DM(N=156)		
		ACEI/ARBs			ACEI/ARBs		
		Yes	No	Pvalue	yes	No	Pvalue
Age	<=60 y	19(26.8)	18(19.8)	0.005	13(20.6)	24(25.8)	0.456
	>60 y	52(73.2)	73(80.2)		50(79.4)	69(74.2)	
	Mean±SD	67.11±14.03	70.51±14.47	0.136	67.81±15.39	69.45±16.02	0.524
Sex	Male	31(43.7)	46(50.5)	0.384	31(49.2)	55(59.1)	0.221
	Female	40(56.3)	45(49.5)		32(50.8)	38(40.9)	
O2Sat, Baseline	O2 < 88%	58(81.7)	80(87.9)	0.419	53(84.1)	85(91.4)	0.366
	92% > o2 >=88%	11(15.5)	8(8.8)		8(12.7)	6(6.5)	
	O2 >= 92%	2(2.8)	3(3.3)		2(3.2)	2(2.2)	
	Mean±SD	76.55±12.63	76.46±10.92	0.962	78.14±10.32	75.54±11.13	0.142
Comorbidities	HTN				50(79.4)	47(50.5)	<0.0001
	AF	6(8.5)	7(7.7)	0.860	4(6.3)	4(4.3)	0.414
	IHD	25(35.2)	36(39.6)	0.571	14(22.2)	22(23.7)	0.835
	CHF	9(12.7)	14(15.4)	0.624	4(6.3)	6(6.5)	0.627
	DM	50(70.4)	47(51.6)	0.016	-	-	-
	CKD	13(18.3)	21(23.1)	0.460	17(27.0)	25(26.9)	0.989
	COPD	12(16.9)	17(18.7)	0.769	10(15.9)	12(12.9)	0.601
	CVA	12(16.9)	10(11.0)	0.276	11(17.5)	8(8.7)	0.097
	DLP	17(23.9)	15(16.5)	0.237	16(25.4)	12(12.9)	0.046
	ESRD	4(5.6)	4(4.4)	0.496	3(4.8)	5(5.4)	0.586
	Cancer	4(5.6)	4(4.4)	0.496	2(3.2)	7(7.5)	0.217
	Hypothyroidism	1(1.4)	6(6.6)	0.109	1(1.6)	2(2.2)	0.643
COVID19 Drugs	Tocilizumab	13(18.3)	17(18.7)	0.952	7(11.1)	15(16.1)	0.377
	Favipiravir	12(16.9)	5(5.5)	0.019	8(12.7)	7(7.5)	0.282
	Hydroxychloroquine	9(12.70	4(4.4)	0.051	9(14.3)	8(8.6)	0.264
	Remdesivir				25(39.7)	53(57.0)	0.034
	Lopinavir/Ritonavir	22(31.0)	17(18.7)	0.069	21(33.3)	27(29.0)	0.568
	Interferon beta-1a	25(35.2)	16(17.6)	0.01	21(33.3)	24(25.8)	0.309

Table 2. Continued

			HTN(N=162)			DM(N=156)		
			ACEI/ARBs			ACEI/ARBs		
			Yes	**No**	**Pvalue**	**yes**	**No**	**Pvalue**
Imaging Result (Score of lung involvement) at baseline	**Mild (0-8)**		10(14.1)	21(23.1)	0.339	10(15.9)	16(17.2)	0.830
	Moderate (9-16)		32(45.1)	35(38.5)		29(46.0)	46(49.5)	
	Severe (17-25)		29(40.8)	35(38.5)		24(38.1)	31(33.3)	
	Mean±SD		15.17±6.02	14.05±6.41	0.262	14.49±5.79	13.99±5.72	0.593
Laboratory Findings	**CRP**	**Negative**	15(21.1)	15(16.5)	0.181	12(19.0)	13(14.0)	0.094
		+	12(16.9)	18(19.8)		14(22.2)	22(23.7)	
		++	28(39.4)	25(27.5)		24(38.1)	23(24.7)	
		+++	16(22.5)	33(36.3)		13(20.6)	35(37.6)	
			Mean±SD					
	WBC		9.79±4.79	8.63±5.35	0.155	10.22±6.27	8.04±4.53	0.013
	ESR		43.58±26.90	48.31±29.33	0.293	42.30±27.80	50.10±28.71	0.094
	BS		157.26±57.36	154.36±56.26	0.747	169.04±59.30	176.40±67.63	0.458
	NLR		10.98±9.28	10.09±7.95	0.510	10.08±6.77	9.97±7.78	0.923
	PLT		212.72±81.28	171.33±71.02	0.001	210.84±84.27	186.33±77.02	0.062
	BUN		62.23±48.29	61.14±45.26	0.882	63.96±40.10	64.29±44.85	0.963
	Cr		1.72±1.25	1.60±1.09	0.523	1.87±1.28	1.77±1.60	0.694
	AST		64.39±66.09	76.44±165.12	0.563	69.98±72.81	48.53±36.96	0.017
	ALT		79.92±49.18	63.18±136.88	0.438	57.51±61.75	45.84±56.73	0.226
	ALP		221.37±108.61	222.14±147.83	0.970	236.65±119.69	200.24±103.15	0.044
	LDH		838.23±579.61	703.41±762.55	0.102	782.55±588.10	666.64±328.65	0.118
Outcomes & Complications	**Intubation**		40(56.3)	44(48.4)	0.313	39(61.9)	51(54.8)	0.381
	Death		42(59.2)	46(50.50	0.275	39(61.9)	53(57.0)	0.540
	Infection		19(26.8)	15(16.5)	0.111	12(19.0)	19(20.4)	0.832
	GI. Bleeding		6(8.5)	797.7)	0.86	7(11.1)	10(10.8)	0.944
	Thrombosis		6(8.5)	4(4.4)	0.230	7(11.1)	5(5.4)	0.187
O2Sat, discharge with supplementary o2	**O2 < 88%**		2(6.7)	1(2.3)	0.652	1(3.8)	4(10.0)	0.633
	92% > o2 >=88%		15(50.0)	22(51.2)		14(53.8)	19(47.5)	
	O2 >= 92%		13(43.3)	20(46.5)		11(42.3)	17(42.5)	
	Mean±SD		92.23±3.09	92.65±2.80	0.550	92.50±2.73	92.13±3.24	0.628
Hospital length of stay	**Mean±SD**		12.82±7.51	12.13±7.18	0.556	12.24±7.66	13.26±9.46	0.478
ICU length of stay	**Mean±SD**		10.77±7.50	10.19±7.36	0.619	10.22±7.60	11.19±9.50	0.499

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; ESRD: End Stage Renal Disease; IPF: Idiopathic Pulmonary Fibrosis;; AF: Atrial fibrillation; ACEIs: Angiotensin-converting enzyme Inhibitors ; ARBs: angiotensin receptor blockers ; EMPA: Empagliflozin; DDPI: Dipeptidyl peptidase-4 inhibitor; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; CPK: Creatine Phosphokinase ; LDH: Lactate Dehydrogenase; WBC: White Blood Cells; NLR: Neutrophil-Lymphocyte Ratio; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; BS: Blood Sugar; O2Sat: Oxygen Saturation.; Cons: Considerations; GGO: Ground-glass opacification; PE: pleural effusion; y:year; N: Number; NIV: Non-Invasive Ventilation

The following information should be noted: 162 COVID-19 patients with diabetes and 156 COVID-19 patients with hypertension were hospitalized in ICU. The data of patients with and without statin usage were compared separately for the two conditions mentioned above. The comparison is presented in Table 3.

Table 3. Baseline characteristics and outcome of COVID-19 patients with DM and HTN based on the use of statin

		HTN(N=162)			DM(N=156)		
		Statin			**Statin**		
		Yes	**no**	**Pvalue**	**yes**	**No**	**pvalue**
Age	**<=60 y**	23(27.7)	133(43.2)	0.011	14(23.0)	23(24.2)	0.857
	>60 y	60(72.3)	175(56.8)		47(77.0)	72(75.8)	
	Mean±SD	69.48±14.03	68.76±14.56		68.16±16.65	69.19±15.20	0.693
Sex	**Male**	25(43.1)	52(50.0)	0.399	31(50.8)	55(57.9)	0.386
	Female	33(56.9)	52(50.0)		30(49.2)	40(42.1)	
O2Sat, Baseline	**O2 < 88%**	49(84.5)	89(85.6)	0.645	54(88.5)	84(88.4)	0.812
	92% > o2 >=88%	8(13.8)	11(10.6)		6(9.8)	8(8.4)	
	O2 >= 92%	1(1.7)	4(3.8)		1(1.6)	3(3.2)	
	Mean±SD	78.81±10.02	75.21±12.34		78.20±9.76	75.56±11.44	0.139
Comorbidities	**HTN**	-	-	-	43(70.5)	54(56.8)	0.086
	AF	6(10.3)	7(6.7)	0.417	3(4.9)	5(5.3)	0.924
	IHD	26(44.8)	35(33.7)	0.159	14(23)	22(23.2)	0.976
	CHF	12(20.7)	11(10.6)	0.077	5(8.2)	5(5.3)	0.465
	DM	43(74.1)	54(51.9)	0.006	-	-	-
	CKD	13(22.4)	21(20.2)	0.739	17(27.9)	25(26.3)	0.831
	COPD	11(19.0)	18(17.3)	0.792	10(16.4)	12(12.6)	0.510
	CVA	9(15.5)	13(12.5)	0.591	8(13.1)	11(11.6)	0.775
	DLP	10(17.2)	22(21.2)	0.549	9(14.8)	19(20.0)	0.405
	ESRD	3(5.2)	5(4.8)	0.555	2(3.3)	6(6.3)	0.329
	Cancer	1(1.7)	7(6.7)	0.151	1(1.6)	8(8.4)	0.072
	Hypothyroidism	1(1.7)	6(5.8)	0.214	0	3(3.2)	0.223
COVID19 Drugs	**Tocilizumab**	9(15.5)	21(20.2)	0.463	7(11.5)	15(15.8)	0.450
	Favipiravir	6(10.3)	11(10.6)	0.963	5(8.2)	10(10.5)	0.426
	Hydroxychloroquine	7(12.1)	6(5.8)	0.157	7(11.5)	10(10.5)	0.853
	Remdesivir				32(52.5)	46(48.4)	0.623
	Lopinavir/Ritonavir	17(29.3)	22(21.2)	0.244	21(34.4)	27(28.4)	0.428
	Interferon beta-1a	14(24.1)	27(26.0)	0.798	17(27.9)	28(29.5)	0.829
Imaging Result (Score of lung involvement) at baseline	**Mild (0-8)**	11(19)	20(19.2)	0.352	10(16.4)	16(16.8)	0.846
	Moderate (9-16)	28(48.3)	39(37.5)		31(50.8)	44(43.3)	
	Severe (17-25)	19(32.8)	45(43.3)		20(32.8)	35(36.8)	
	Mean±SD	13.76±6.27	14.98±6.23	0.234	13.57±5.82	14.59±5.68	0.282

Table 3. Continued

			HTN(N=162)			DM(N=156)		
			Statin			**Statin**		
			Yes	**no**	**Pvalue**	**yes**	**No**	**pvalue**
Laboratory Findings	**CRP**	**Negative**	9(15.5)	21(20.2)	0.735	10(16.4)	15(15.8)	0.668
		+	13(22.4)	17(16.3)		17(27.9)	19(20.0)	
		++	18(31.0)	35(33.7)		16(26.2)	31(32.6)	
		+++	18(31.0)	31(29.8)		18(29.5)	30(31.6)	
			Mean±SD					
	WBC		8.48±4.53	9.51±5.42	0.225	9.0±6.28	8.87±4.77	0.876
	ESR		44.64±26.74	47.13±29.22	0.593	43.49±28.29	49.17±28.58	0.226
	BS		160.87±55.69	152.71±57.14	0.380	167.73±54.15	177.9±70.08	0.377
	NLR		8.71±7.23	11.47±9.08	0.049	8.77±6.95	10.81±7.55	0.092
	PLT		187.81±69.09	190.39±83.17	0.841	197.56±81.88	195.38±80.35	0.870
	BUN		63.67±49.87	60.48±44.66	0.676	60.44±38.04	66.54±45.72	0.387
	Cr		1.62±0.87	1.66±1.30	0.827	1.64±0.87	1.92±1.76	0.251
	AST		54.12±69.99	80.66±154.54	0.218	49.57±38.85	62.08±63.19	0.168
	ALT		39.24±31.67	67.47±131.30	0.110	44.57±48.35	54.39±64.72	0.311
	ALP		206.24±135.39	230.48±129.44	0.263	206.33±100.43	220.48±117.80	0.440
	LDH		657.82±377.35	820.88±577.83	0.055	654.80±375.02	751.11±496.71	0.197
Outcomes & Complications	**Intubation**		28(48.3)	56(53.8)	0.496	30(49.2)	60(63.2)	0.085
	Death		27(46.6)	61(58.7)	0.138	28(45.9)	64(67.4)	0.008
	Infection		10(17.2))	24(23.1)	0.382	7(11.5)	24(25.3)	0.035
	GI. Bleeding		5(8.6)	8(7.7)	0.835	7(11.5)	10(10.5)	0.853
	Thrombosis		1(1.7)	9(8.7)	0.072	2(3.3)	10(10.5)	0.085
O2Sat, discharge with supplementary o2	**O2 < 88%**		1(3.3)	2(4.7)	0.950	3(9.1)	2(6.1)	0.226
	92% > o2 >=88%		15(50.0)	22(51.2)		13(39.4)	20(60.6)	
	O2 >= 92%		14(46.7)	19(44.2)		17(51.5)	11(33.3)	
	Mean±SD		92.33±2.27	92.58±3.30	0.723	92.45±2.91	92.09±3.18	0.630
Hospital length of stay	**Mean±SD**		11.19±6.03	13.13±7.88	0.107	11.44±8.02	13.75±9.14	0.109
ICU length of stay	**Mean±SD**		9.19±6.15	11.14±7.98	0.108	9.43±8.07	11.68±9.12	0.117

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; ESRD: End Stage Renal Disease; IPF: Idiopathic Pulmonary Fibrosis;; AF: Atrial fibrillation; ACEIs: Angiotensin-converting enzyme Inhibitors ; ARBs: angiotensin receptor blockers ; EMPA: Empagliflozin; DDPI: Dipeptidyl peptidase-4 inhibitor; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; CPK: Creatine Phosphokinase ; LDH: Lactate Dehydrogenase; WBC: White Blood Cells; NLR: Neutrophil-Lymphocyte Ratio; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; BS: Blood Sugar; O2Sat: Oxygen Saturation.; Cons: Considerations; GGO: Ground-glass opacification; PE: pleural effusion; y:year; N: Number; NIV: Non-Invasive Ventilation

In our previous study(20), we utilized Multivariate logistic regression analysis to determine the factors that affect mortality rates in ICU patients. The study was based on primary factors, which include clinical, demographic, imaging, and laboratory data. The validity of the model was demonstrated by the Hosmer-Lemeshow test, with a p-value of 0.901. The following variables were found to be significant and were added to the baseline model: age, DM, HTN, HLP, CVA, CKD, brain hemorrhage, cancer, primary O2 saturation, duration of hospital and ICU stay, NLR, and score of lung involvement. We included the use of statin and ACE/ARBs in the model, and the analysis was performed. In

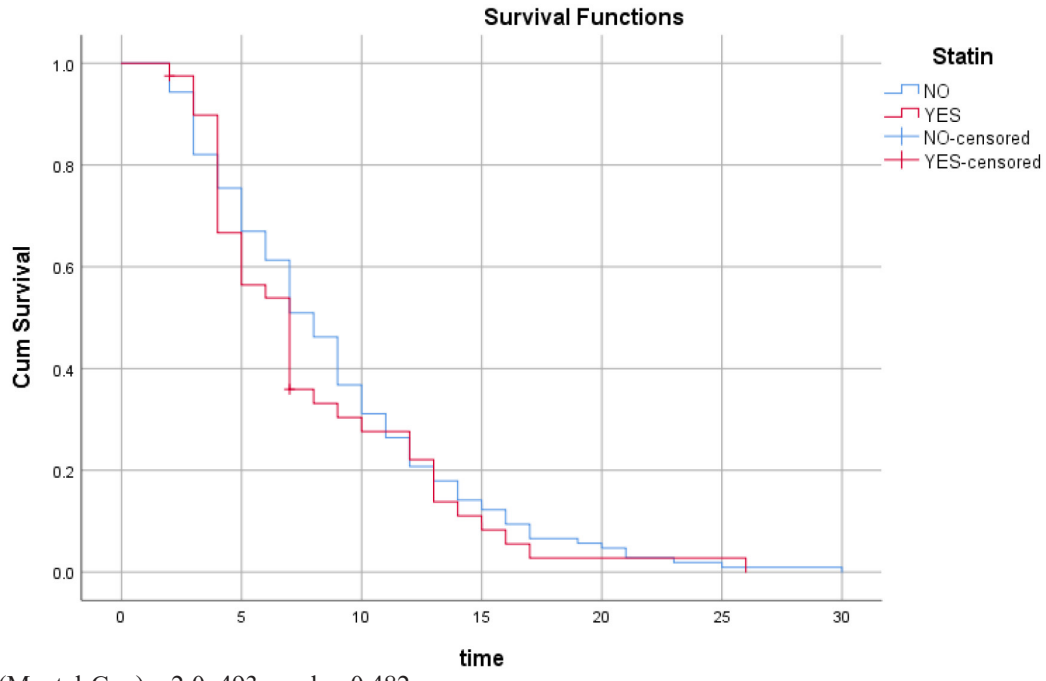
the final step of the model, it was revealed that the variables DM, HTN, CKD, CVA, brain hemorrhage, NLR index, initial O2 saturation, and CT scan score have an impact on the mortality rate of COVID-19 patients. (Table 4)

Table4. Relationship between variables and outcome with mortality based on multivariate logistic regression.

			95% C.I. for OR	
Variable	**p.value**	**Odds ratio (OR)**	**Lower**	**Upper**
DM	<0.0001	4.145	2.267	7.576
HTN	0.013	2.171	1.180	3.997
HLP	0.736	0.864	0.370	2.020
CVA	<0.0001	5.516	2.170	14.024
CKD	0.003	2.689	1.390	5.200
Brain hemorrhage	0.003	27.530	3.083	245.828
Hospital length of stay	0.877	1.018	0.814	1.273
ICU length of stay	0.983	0.998	0.799	1.246
NLR	0.011	1.042	1.009	1.075
CT score	<0.0001	1.096	1.042	1.153
Statin	0.190	0.629	0.314	1.259
ACE.ARBE	0.169	1.624	0.813	3.245
Age	0.311	1.346	0.758	2.389
O_2 saturation	<0.0001	0.941	0.918	.965
Constant	0.651	1.677		

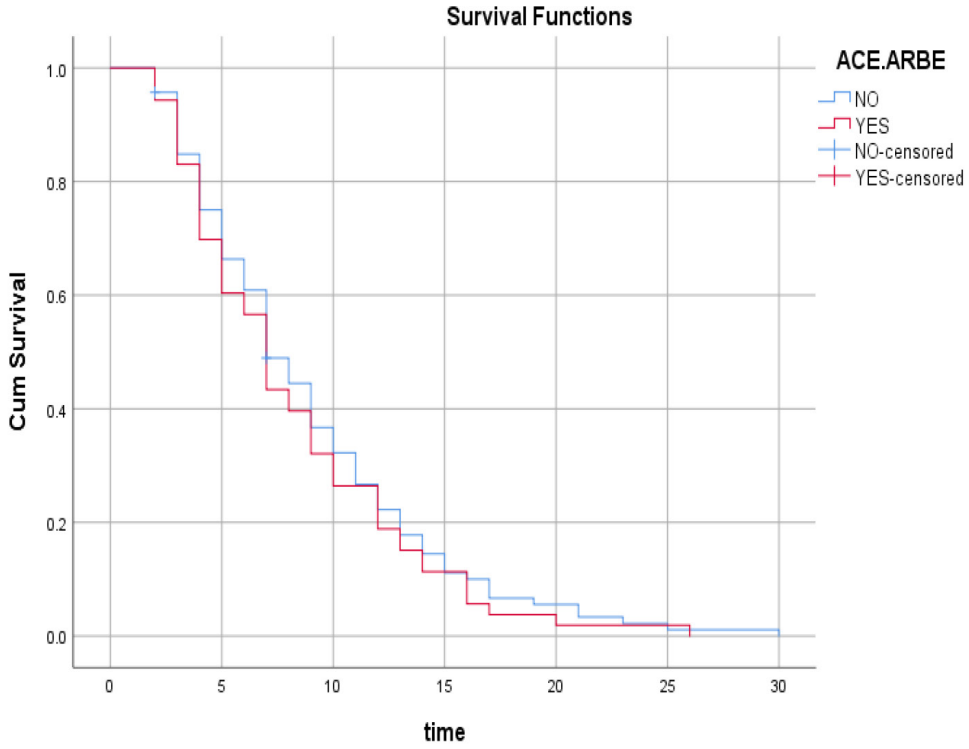
The table shows all the variables: -2loglikelihood= 346.59; $\chi 2 = 173.11$, p<0.0001. Hosmer-Lemeshow statistics= 3.48 with df=8, p=0.901.

The Kaplan-Meier graphs show the survival rate in ICU patients with and without statin use and ACEI/ARBs use. (figure1 ,figure2)



Log Rank (Mantel-Cox), x2:0 .493, pvalue:0.482

Figure 1. Kaplan-Meier diagram survival rate in patients with and without statin use



Log Rank (Mantel-Cox), x2:0 .519, pvalue:0.471

Figure 2. Kaplan-Meier diagram survival rate in patients with and without ACE use

Discussion

After identifying ACE2 as a receptor for the virus, there has been concern that using ACEI/ARB drugs may worsen the disease's clinical condition(21). This concern arises because these drugs can increase ACE2 expression, making it easier for the virus to enter host cells and exacerbate the disease(22). However, it should also be noted that during COVID-19, decreased ACE2 levels can lead to an increase in Ang II, which in turn raises the activity of nuclear factor kappa-chain-enhancer of activated B cell (NF-κB) and metalloproteinase 17 (ADAM17). Ultimately, this leads to increased tumor necrosis factor (TNF)-α production, further raising NF-κB activity and inflammation(23). Therefore, it seems that both the increase and decrease of ACE2 expression may be effective in the exacerbation of COVID-19. Our research has revealed that the use of ACEI/ARBs in COVID-19 patients admitted to the ICU may increase the risk of endotracheal intubation and mortality. Additionally, patients treated with these drugs are more likely to experience secondary complications such as bacterial infections and venous thromboembolism events. However, there was no significant difference in the length of hospital and ICU stays between the groups with and without ACEI/ARB use. It is important to note that patients treated with ACEI/ARB have shown a higher incidence of comorbidity. According to this study, there was a significant association between the use of these drugs and conditions such as diabetes mellitus, hypertension, dyslipidemia, and ischemic heart disease, compared to patients not taking these medications. Chronic inflammatory conditions that are linked to COVID-19, such as diabetes, hypertension, cardiovascular diseases, cancer, and obesity, can result in increased activity of the RAAS. When COVID-19 disease occurs in combination with these conditions and with ACE2 deficiency, it can exacerbate the disease and lead to a worsening of clinical conditions(24, 25).

According to the study, patients who were treated with ACEI/ARB had a higher average age. It has been found that as a person gets older, the expression of ACE2 decreases, which can worsen the disease and lead to a poorer prognosis for older patients(26). It's worth noting that there were no significant differences in clinical, laboratory, and imaging indicators of COVID-19 severity between two groups - one group that received the aforementioned drugs and another that didn't. This means that there was no significant difference in indicators such as oxygenation levels at the time of admission to the ICU and at the time of discharge from the hospital, the level

of lung parenchymal involvement in imaging, the level of neutrophil-lymphocyte ratio (NLR), and the serum levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Based on our study, it appears that the presence of comorbidity and advanced age among patients who use ACE/ARBs may result in increased complications and mortality rates. Consequently, the use of these drugs did not lead to improved survival rates for COVID-19 patients hospitalized in the ICU. Furthermore, our multivariate regression analysis did not identify the use of ACE/ARBs as a predictor for patient mortality.

Several studies have investigated the impact of using ACEI/ARB on the clinical severity and mortality of COVID-19 patients, but there is no consensus on the results. For instance, studies conducted in Italy and Denmark have not found any association between the use of these drugs and the severity of COVID-19 (27, 28). In Braude et al.'s study, the use of these drugs resulted in a shorter hospital stay but did not affect patient mortality(29). In a study of 1686 COVID-19 patients in the hospital, researchers found that using ACEI/ARBs was associated with lower in-hospital mortality, mechanical ventilation, and hemodialysis(30). involving 2823 patients diagnosed with COVID-19, it has been concluded that the continued use of ACEI/ARB in patients who were already taking these drugs has been associated with a decrease in ICU admission, mortality, and the need for invasive mechanical ventilation in COVID-19 patients(31).

The results of a recent study analyzing diabetic and hypertensive patients hospitalized in ICU showed that there is no significant difference in clinical outcomes between COVID-19 patients who used ACEI/ARB and those who did not. However, a retrospective observational study by Acharya et al on 500 COVID-19 patients with hypertension indicated that the use of ARBs may reduce disease severity and mortality(32). A meta-analysis was conducted on COVID-19 patients with hypertension, which involved 10 studies and 9890 patients. The study found that the use of ACEI, ARB, or both drugs together, did not increase the risk of severe COVID-19 or mortality when compared to patients who did not receive these drugs(33).

Statins have immunomodulatory properties and stabilize myeloid differentiation primary response protein 88 (MyD88) by reducing NF-κB activity(34-37). Statins may protect the lungs against the coronavirus by increasing the expression of ACE2(38). In our study, COVID-19 patients treated with statins had an increased rate of endotracheal intubation and mortality. However, this increase was not statistically significant, as the P value was only slightly higher than the significance level. It has been revealed that the hospitalization and ICU length of stay were not significantly reduced in patients treated with the drugs. These drugs were used to treat patients who had comorbidities such as HTN, atrial fibrillation, ischemic heart disease (IHD), congestive heart failure (CHF), DM, cerebral vascular accident (CVA), and Parkinson's disease. Statin users had a higher average age as well. Although not significant, these factors may play an important role in increasing the mortality of patients treated with statins. Recent studies have shown that statins are not a predictor of mortality in COVID-19 patients hospitalized in the ICU, and the survival rate in the ICU is not significantly different between patients with and without treatment with statins. However, there have been contradictory results in previous observational studies and meta-analyses conducted in this field(38-44). A retrospective study of 583 patients found that atorvastatin can protect COVID-19 patients from ICU admission, endotracheal intubation, and death. The use of statins has been linked with increased survival of hospitalized patients(45). In another study, this beneficial effect was not seen, and the use of statins did not lead to a reduction in the mortality of hospitalized COVID-19 patients(46). In a study conducted in the United States, prior statin use has been associated with a 40% reduction in the mortality of COVID-19 patients(47). In a meta-analysis, it was found that statins do not lower in-hospital mortality or COVID-19 severity. However, these studies were all observational(48). Xavier et al concluded in a meta-analysis of 4 randomized clinical trial (RCT)s that treatment with these drugs does not change the clinical results of COVID-19 patients. In the statin group compared to the control group, there is a statistically significant difference in terms of mortality rate, admission to ICU, and need for Invasive mechanical ventilation was not reported(49). In a meta-analysis conducted by Ren et al. on 7 RCTs, ambiguous results were reported(50). Kollia et al., in another meta-analysis including retrospective observational studies, reported a 35% reduction in the mortality rate of hospitalized COVID-19 patients(51).

Our study has found that the use of statins in diabetic patients is linked to a reduction in mortality rate and secondary bacterial infections of COVID-19 patients admitted to the ICU. However, this association was not observed in hypertensive patients and there were no significant changes in clinical results for these patients. Previous studies on the impact of statins on the prognosis of diabetic patients with COVID-19 have yielded inconsistent results. According to a retrospective

cohort study, the use of statins among diabetic patients with COVID-19 is linked with a significant reduction in mortality rate by 60%, a 40% reduction in the requirement of ICU hospitalization, and a 55% reduction in the requirement of mechanical ventilation(52). In a study by Saeed et al it was demonstrated that taking statins can lead to a decrease in-hospital mortality among COVID-19 patients who have diabetes(53). Contrary to previous studies, Wargny et al., found that statin treatment increased mortality in diabetic COVID-19 patients(54).

Our knowledge about the impact of statins on patients with COVID-19 who are admitted to the ICU is limited. A study was conducted on approximately 400 patients who were hospitalized in the ICU for a relatively long time. However, the study has certain limitations. Firstly, it was retrospective and observational. Secondly, the information we had was limited to the duration of hospitalization and we did not have any data available on patients after they were discharged from the hospital.

The study results indicate that taking statins can help reduce mortality among COVID-19 patients who are hospitalized in the ICU. Therefore, it is recommended to continue using statins to lower the risk of mortality and also manage cardiovascular risk factors in such patients. The study found that both statins and ACEI/ARB drugs were not linked to a decrease in survival rate during ICU hospitalization and were not considered to be predictors of mortality in these patients. However, more definitive results can be obtained through prospective studies and clinical trials in the future. For now, the recommendation is to continue using these drugs for ICU patients with COVID-19.

Conflict of interest: No potential conflict of interest was reported by the authors.

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