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Angiotensin II in COVID-19, Correlation with Morbidity and Mortality

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Abstract

In cases of viral pneumonia, serum angiotensin II levels were believed to be linked to lung damage. According to some research, lung damage and the COVID viral load are positively correlated with the serum level of angiotensin II. Evaluation of the serum angiotensin II levels in critically ill patients with COVID-19 infection during the course of the disease and its correlation with morbidity and mortality. In this prospective observational study, 108 critically ill patients who had been admitted to Cairo University's critical care unit due to a COVID-19 infection were included. On admission, on days 7 and 14, three serum angiotensin II samples were taken for each patient. From the time of admission until their discharge or death, patients were clinically and laboratory monitored, and their care was conducted in accordance with the Egyptian Ministry of Health Protocol. Between survivors and non-survivors, comparisons were made regarding demographic information, comorbidities, clinical features, serum Angiotensin II level, inflammatory markers, treatment received, complications, need for mechanical ventilation, and mortality. A total of 108 patients were included in the study: 60 male patients (55.6%) and 48 female patients (44.4%), aged 65.17±11.41 years. On admission to ICU, the average duration of symptoms was (5.00± 0.86) days. In all three samples, serum angiotensin II levels in COVID-19 critically ill patients rose above the normal range. At day 7 post- admission, the serum angiotensin II level was significantly lower in non-survivors compared to survivors. The best cutoff point (≤508.5 pg/ml) with sensitivity 59.7%, specificity 73.9%, area under the curve (0.672), and a P value of 0.002 was found to have statistically significant predictive value in terms of mortality related to COVID-19. With a P value of 0.002, there was a statistically significant relationship between angiotensin II levels on day 7 and the use of invasive mechanical ventilation. There was a negative correlation between angiotensin II level and SOFA score at day 7 in non-survivors, while there were insignificant correlations between the three angiotensin II levels and length of stay. The level of serum angiotensin II exhibited a noteworthy predictive value for COVID-19-related severity and death, suggesting its potential utility in assessing the disease's severity.

Keywords: Covid 19; Angiotensin II; Mortality; Invasive Mechanical Ventilation

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1. Introduction

The recent coronavirus disease pandemic is caused by SARS-CoV-2, an encapsulated, nonsegmented single-stranded RNA virus (COVID-19) [1]. The seventh coronavirus, known as SARS-CoV-2, can cause symptoms that range from a moderate cold to severe respiratory illnesses like Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which have death rates of 37% and 10%, respectively [2]. Early on in the symptomatic phase, COVID-19 characteristics such as acute respiratory distress syndrome (ARDS), sepsis, and an elevated inflammatory response can have catastrophic repercussions [3]. COVID-19 has also addressed thrombotic events and coagulation diseases. Patients with COVID-19 are more likely to develop severe symptoms if they are older, male, obese, and have comorbidities. Symptoms can swiftly increase from mild to severe without notice [4]. COVID-19 is a novel viral respiratory infection that damages the lungs and causes severe pneumonia and ARDS. According to recent studies, the SARS-CoV-2, like the SARS-CoV (severe acute respiratory syndrome coronavirus), uses the angiotensin-converting enzyme 2 (ACE2) as a functional receptor to infect the host cell [5]. After binding to the ACE2 receptor through the S-protein, the virus transfers its RNA to human cells, where it is translated into new viral particles. It is believed that the viral S-protein binds to the ACE2 receptor on the cell, resulting in a decrease in ACE2 activity and an imbalance in the renin-angiotensin-aldosterone pathway [6]. Under normal conditions, the ACE2 enzyme converts angiotensin I (1-10) to angiotensin (1–9) and angiotensin II (1-8) to angiotensin (1–7) [7]. Angiotensins (1–9) and (1–7) decrease in a manner akin to this when ACE2 levels decline due to viral inhibition. In contrast, a rise in Angiotensin II (1–8) is

expected. Angiotensin II (1–8) has more pro-inflammatory effects than angiotensin I (1–9) and angiotensin (1–7) combined. Furthermore, since the virus most likely does not inhibit ACE1, it is expected that the conversion of angiotensin I to angiotensin II continues [6]. Angiotensin II causes vasoconstriction, cell proliferation, inflammatory responses, blood coagulation, and extracellular matrix remodelling as a result of its interaction with the angiotensin type 1 receptor (AT1R). Additionally, angiotensin II binds to the angiotensin type 2 receptor, blocking the effects of the AT1R [8]. In viral pneumonias, serum angiotensin II concentrations were thought to be associated with lung injury. Higher mortality rates following influenza A (H7N9) pneumonia were associated with blood levels of angiotensin II (1–8) [9]. Angiotensin II serum levels were found to be positively correlated with lung damage and the SARS-CoV-2 viral load in a study carried out during the COVID-19 pandemic [10]. There is no discernible sign of serum angiotensin II levels in COVID-19. A few studies have looked at the Angiotensin II level in COVID-19 patients since the pandemic began in an effort to learn more about the aetiology, severity, and prognosis of the illness. The purpose of this prospective observational study was to measure the blood angiotensin II level in critically ill COVID-19 patients admitted to the intensive care unit (ICU). To the best of our knowledge, there aren't enough studies on this topic in Arab underdeveloped nations like Egypt. But these investigations were carried out in wealthy nations.

2. Patients and methods

A prospective observational study is what this one is. Between June 2021 and February 2022, it was completed. Prior to participating in the trial, the involved patients or next of kin gave informed consent after being educated about the study's protocol and goal. The study was approved by Cairo University's medical faculty's medical research and ethical committee (MD-116-2021). 108 adult patients who were hospitalised to the intensive care unit at Cairo University Hospitals' faculty of medicine were included in the study. From the time of admission until their discharge or death, the patients were clinically and laboratoryly monitored, and their care was managed in accordance with Egyptian Ministry of Health protocol.

2.1 Inclusion criteria

Covid-19 infection in critically ill adult patients admitted to the ICU was identified by a positive PCR test and CT chest findings. Individuals with critical illness suffered acute respiratory failure, septic shock, and/or multiple organ dysfunctions.

2.2 Exclusion criteria

Patients under the age of 18, patients with possible high RAAS activity, such as those with heart failure, renal failure or known renal artery stenosis, liver cirrhosis, pregnancy, and hyperthyroidism, as well as those taking RAAS inhibitors such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), all were excluded from our study.

2.3 Study procedure

All participants included in the study were subjected to the following**:**

2.3.1 History taking

Including age, sex, admission complaint, onset of symptoms on admission, present and past histories of ischemic heart disease, diabetes mellitus, hypertension and chronic chest problems.

2.3.2 Clinical examination

Including vital signs, general and local examinations.

2.3.3 ECG

2.3.4 Daily chest x-ray

2.3.5 Laboratory investigations included:

1. PCR for Covid-19 for diagnosis.
2. Other labs (Complete Blood count, Arterial Blood Gases, Coagulation Profile, Kidney function tests and Liver functions test) for assessment of complications like Acute Kidney Injury (AKI) and Multiorgan Failure (MOF).
3. Cultures for patients with suspected secondary bacterial infections.

2.3.6 Inflammatory markers

Including serum Angiotensin II, Interleukin-6, CRP, D Dimer and Ferritin.

Evaluation of Prognostic scoring systems

Including

APACHE II: The Score was calculated on admission to ICU

SOFA score: The Score was calculated 3 times with each angiotensin II sample

2.3.7 Evaluation of Oxygen requirements

Including oxygen therapy via (simple nasal prong, simple face mask and non-rebreathing mask), noninvasive ventilation and invasive mechanical ventilation.

2.3.8 Evaluation of Outcome

Length of ICU stays and in hospital mortality.

2.3.9 Measurement of Serum Angiotensin II

Three samples were obtained using ELISA from commercial kits from the Elabscience Company (Catalogue No: E-EL-H0326): the first sample was obtained at the time of ICU admission, the second sample was obtained seven days after admission or when there was a clinical deterioration, and the third sample was obtained fourteen days after admission. The level of angiotensin II was reported in pg/mL, with a detection range of 31.25 to 2000 pg/m and a sensitivity of 18.75 pg/mL. Angiotensin II reference values were typically between 25 and 60 pg/mL. All tests were performed by the two blindfolded individuals in accordance with the manufacturer's instructions. The results of these samples were examined and contrasted with the data acquired regarding the patients.

2.4 Statistical analysis

The statistical data was coded and entered using IBM Corp.'s (Armonk, NY, USA) statistical software for the social sciences (SPSS) version 26. The following metrics

were employed to analyse quantitative data: mean, standard deviation, median, minimum, and maximum; frequency (count) and relative frequency (%) were used to analyse categorical data. In order to determine the ideal cutoff value of angiotensin for the detection of mortality, a ROC curve was developed using area under the curve analysis. The threshold of 0.05 for a P-value was deemed statistically significant. [11,12]

3. Results and discussion

Our study was conducted on 108 patients included 60 male patients (55.6%) and 48 female patients (44.4%) with mean age 65.17±11.41 years. Of 108 patients; 62 patients (57.4%) died during ICU stay and 46 patients (42.6%) were discharged from ICU. There was statistically significant difference between survivors and non survivors regarding mean age which was higher in non survivors with predominance of male gender (P value = 0.030). Mean age was (68.29 ± 9.09) in non survivors versus (60.96 ± 12.88) in survivors with P value < 0.001. The mean APACHE II Score was (9.57 ± 2.51 SD) in survivors while it was (12.84 ± 3.42 SD) in non-survivors with statistically significant difference with P value <0.001. SOFA score was statistically significant higher in non-survivors than survivors on admission, at day 7 and at day 14 with P value <0.001 **(Table 1)**. The average age of the participants in our study was 65.17±11.41 years. 60 male patients (55.6%) and 48 female patients (44.4%) participated in our study. There was a gender difference in COVID- 19 studies, with a male majority. Men made up 60% of COVID-19 patients, according to early estimates, and they also died at a higher rate than women, most likely as a result of men's higher rates of smoking and cardiovascular disease [13]. Our study found that 64 patients (59.3%) had hypertension, 62 patients (57.4%) had diabetes, and 16 patients (14.8%) had a history of ischemic heart disease (IHD). Fifty percent of the 103 COVID-19 patients included in the Kutz et al. study had obesity, diabetes mellitus, and hypertension. The study compared the RAAS values of patients with and without COVID-19 [14]. All three of the samples had angiotensin II levels that were higher than the 25–60 pg/ml normal range, according to our investigation. Consistent with the research conducted by Wu et al 2020, which investigated the plasma levels of renin and angiotensin II in 82 COVID-19 non-hypertensive individuals (42 mild cases, 25 severe cases, and 15 severely ill), and 12 critically ill patients not infected by SARS-CoV-2 serving as a control) and found that the plasma levels of angiotensin II were higher than the normal range in more than 90% of cases and in all critically ill Covid-19 [15,16]. We discovered that, at 7 days, the non-survivors' serum Angiotensin II level (792.53 ± 640.25 pg/ml) was statistically significantly lower than that of the survivors (1073.02 ± 653.90 pg/ml), with a P value of 0.002. The first study to look at the Ag II levels in COVID-19 patients was Liu et al. Twelve COVID-19 patients and eight healthy people had their levels of Ag II evaluated. They found that the blood levels of Ag II were much greater in COVID-19 patients than in healthy people, and that they were linearly correlated with lung injury and viral load. All members of the infected group had AngII levels up to 500 pg/ml, whereas no one in the healthy control group had levels higher than 200 pg/ml [10]**.** Henry et al. discovered, with a P value of 0.990, that there was no statistically significant difference in the median levels of plasma Ang II between the COVID-19 patient group and the healthy control group using a larger sample of 30 patients and 14 healthy controls. When evaluating these findings, there are a few important disclaimers to take into account. First, it's possible that the pulmonary environment is not always represented by circulating Ang II. Second, because proteins degrade quickly and Ang II has a short half-life, measurement is difficult. Third, circulating Ang II may represent many changes in human physiology and the RAAS. Thus, in order to completely explain this, measures of additional RAAS components, such as ACE and ACE2, are necessary [17]**.**

Reddy et al. studied 39 ARDS patients who were enrolled within 24 hours of diagnosis before to the COVID-19 pandemic. They discovered that, although there was no statistically significant difference, survivors' plasma AgII levels were 0.76 ng/ml (0.07-2.22 ng/mL) and non-survivors' levels were 0.38 ng/ml (0.12-0.63 ng/mL), with a P value of 0.298. Additionally, no evidence of a significant difference in angiotensin II (1-8) levels was detected at any point during the three samplings that were conducted at the 24th, 48th, and 72nd hours between survivors and non-survivors [18]**.** Kutz et al. evaluated the association between equilibrium serum levels of RAAS peptides and an underlying SARS-CoV-2 infection in 103 patients in a 2021 study. The patients had COVID-19, were hospitalised, and were1:1 propensity-score matched with patients who had SARS-CoV-2- negative respiratory infections. They discovered that COVID-19 patients had about 50% lower equilibrium serum RAAS peptide levels than matched controls. Angiotensin II levels in COVID 19 patients were 37.7 vs. 92.5 pmol/L, −59.2% (95% CI: 72.1% to 46.3%) lower than in the control group [14]**.** Rieder et al. conducted a study wherein the serum levels of ACE-2, angiotensin II, and aldosterone were evaluated between 24 patients with COVID-19 and 61 control patients who reported with similar symptoms to the emergency room. Researchers discovered that mean blood concentrations of ACE2, aldosterone, and angiotensin II (4763 pg/ml vs. 4369 pg/ml) did not differ between the SARS-CoV-2 positive and control groups [19]**.** Angiotensin II levels were assessed in a study by Ozkan et al., 2021 in 112 Covid-19 patients, where three samples were taken for each patient, compared to 27 control patients, where one sample was taken. The results showed that the patients with Covid-19 had significantly lower serum angiotensin II levels than the healthy control group, where the median of the serum angiotensin II levels was 433.61 pg/mL versus 774.75 pg/mL in control group (P < 0.001). The serum angiotensin II levels assessed at the three different periods did not differ statistically (p > 0.05), despite the fact that the second sample was lower than the first and third samples. The blood angiotensin II levels of the patients who died were lower than those of the patients who lived, especially the second level, although there was no statistically significant difference in mortality at any of the three time periods (P > 0.05) [20]**.** According to our analysis, 61.1% of COVID-19 patients had severe ARDS, 57.4% required invasive mechanical ventilation, 57.4% required vasopressors when they went into shock, 57.4% had MOF, and 57.4% passed away.

Table 1: Comparison between survivors and non-survivors regarding Prognostic scoring systems

	Total (n =108)	Clinical Outcome		P
		Survivors (n =46)	Non-survivors (n =62)	
APACHE II Score				<0.001*
Mean ± SD.	11.44 ± 3.46	9.57 ± 2.51	12.84 ± 3.42	
SOFA Score				
Baseline	**(n =108)**	**(n =46)**	**(n =62)**	<0.001*
Mean ± SD.	3.44 ± 1.53	2.61 ± 1.11	4.06 ± 1.51	
After 7 days	**(n =108)**	**(n =46)**	**(n =62)**	<0.001*
Mean ± SD.	4.41 ± 2.46	2.74 ± 0.85	5.65 ± 2.53	
After 14 days	**(n =94)**	**(n =44)**	**(n =50)**	<0.001*
Mean ± SD.	6.30 ± 4.34	2.18 ± 0.58	9.92 ± 2.63	

Table 2: Comparison between survivors and non-survivors regarding Clinical characteristics

	Total (n =108)	Clinical Outcome		P
		Survivors (n =46)	Non-survivors (n =62)	
Duration of Symptom on admission (in days)				
Mean ± SD.	5.00 ± 0.86	4.8 9± 0.60	5.08 ± 1.01	0.206
Oxygen Saturation on room air on admission (%)				
Mean ± SD.	74.52 ± 10.87	76.91 ± 10.10	72.74 ± 11.15	0.025*
Oxygen dependency days				
Mean ± SD.	13.94 ± 9.78	16.04 ± 12.16	12.39 ± 7.27	0.002*
Length of stay (LOS)				
Mean ± SD.	13.28 ± 10.03	14.65 ± 12.82	12.26 ± 7.28	0.306

Table 3: Comparison between survivors and non-survivors regarding serum inflammatory markers

	Total (n =108)	Clinical Outcome		P
		Survivors (n =46)	Non-survivors (n =62)	
Interleukin-6 (pg/ml)				
Baseline				0.203
Mean ± SD.	79.87 ± 89.36	56.63 ± 51.29	97.11 ± 106.56	
After 14 days				<0.001*
Mean ± SD.	244.68 ± 190.77	168.58 ± 162.0	301.14 ± 192.01	
Ferritin (ng/ml)				
Baseline	(n =108)	(n =46)	(n =62)	0.176
Mean ± SD.	601.65 ± 329.86	556.23 ± 333.48	635.35 ± 325.74	
After 7 days	(n =108)	(n =46)	(n =62)	0.076
Mean ± SD.	799.33 ± 379.52	743.87 ± 428.17	840.48 ± 336.70	
After 14 days	(n =94)	(n =44)	(n =50)	<0.001*
Mean ± SD.	959.77 ± 394.56	741.86 ± 319.87	1151.52 ± 354.29	

CRP (mg/L)				
Baseline	(n =108)	(n =46)	(n =62)	0.466
Mean ± SD.	60.89 ± 43.77	58.41 ± 42.06	62.73 ± 45.26	
After 7 days	(n =108)	(n =46)	(n =62)	0.691
Mean ± SD.	42.77 ± 34.01	40.88 ± 33.03	44.18 ± 34.92	
After 14 days	(n =94)	(n =44)	(n =50)	0.010*
Mean ± SD.	19.42 ± 23.16	11.50 ± 14.46	26.38 ± 26.99	
D-diamer (mg/L)				
Baseline	(n =108)	(n =46)	(n =62)	0.006*
Mean ± SD.	1.39± 1.72	0.84± 0.63	1.80 ± 2.12	
After 7 days	(n =108)	(n =46)	(n =62)	<0.001*
Mean ± SD.	2.07± 1.92	1.16± 0.85	2.74 ± 2.21	
After 14 days	(n =94)	(n =44)	(n =50)	<0.001*
Mean ± SD.	2.41 ± 2.18	1.18 ± 1.10	3.49 ± 2.33	

Table 4: Comparison between survivors and non-survivors regarding complication

Complication & Disease Progression	**Total (n =108)**		**Clinical Outcome**				
			Survivors (n =46)		**Non-survivors (n =62)**		**P**
	No.	**%**	**No.**	**%**	**No.**	**%**	
ARDS	66	61.1	4	8.7	62	100.0	<0.001*
Shock state	62	57.4	0	0.0	62	100.0	<0.001*
Acute kidney Injury	38	35.2	0	0.0	38	61.3	<0.001*
Acute Coronary Syndrome (ACS)	10	9.3	0	0.0	10	16.1	0.005*
Arrhythmias	6	5.6	0	0.0	6	9.7	0.037*
Delirium	6	5.6	0	0.0	6	9.7	0.037*
Stroke	2	1.9	0	0.0	2	3.2	0.506
MOF	62	57.4	0	0.0	62	100.0	<0.001*
Secondary bacterial infection	18	16.7	8	17.4	10	16.1	0.862
Thrombocytopenia	18	16.7	4	8.7	14	22.6	0.056
Critical illness myopathy	4	3.7	0	0.0	4	6.5	0.135

Table 5: Correlation of Angiotensin II Levels with SOFA Score

	Survivors (n =46)		**Non-survivors (n =62)**		**Total (n =108)**	
	rS	**P**	**rS**	**P**	**rS**	**P**
	Angiotensin II Level at admission					
SOFA Score on admission	0.098	0.517	-0.172	0.181	-0.077	0.426
	Angiotensin II Level (at 7 days)					
SOFA Score on day 7	-0.008	0.957	-0.457*	<0.001*	-0.404*	<0.001*
	Angiotensin II Level (at 14 days)					
SOFA Score on day 14	-0.291	0.055	-0.119	0.410	0.033	0.749

*rs: Spearman coefficient *: Statistically significant at p ≤ 0.05*

Table No 6: Correlation of Angiotensin II Levels with Length of stay

		Angiotensin II Level on admission	Angiotensin IILevel on day 7	Angiotensin II Level on day 14
Length of stay (LOS)	**Correlation Coefficient**	0.063	0.041	-0.143-
	P value	0.516	0.671	0.169

Table 7: Correlation of Angiotensin II levels and invasive mechanical ventilation

Invasive Mechanical ventilation			**P value**
	Angiotensin II Level 1 (on admission)		
	Mean	± SD	
Yes	582.52	± 365.34	0.580
No	662.39	± 444.88	
	Angiotensin II Level 2 (on day 7)		
	Mean	± SD	
Yes	792.53	± 640.25	0.002
No	1073.02	± 653.90	
	Angiotensin II Level 3 (on day 14)		
	Mean	± SD	
Yes	732.54	± 553.17	0.196
No	503.93	± 308.31	

Table 8: Comparison between survivors and non-survivors regarding Angiotensin II Level

Angiotensin II Level (pg/ml)	**Total**	**Clinical Outcome**		**P**
		Survivors	**Non-survivors**	
Baseline	(n =108)	(n =46)	(n =62)	0.580
Mean ± SD.	616.54 ± 401.13	662.39 ± 444.88	582.52 ± 365.34	
After 7 days	(n =108)	(n =46)	(n =62)	0.002*
Mean ± SD.	912.0 ± 657.98	1073.02 ± 653.90	792.53 ± 640.25	
After 14 days	(n =94)	(n =44)	(n =50)	0.196
Mean ± SD.	625.53 ± 467.25	503.93 ± 308.31	732.54 ± 553.17	

Table 9: Receiver-operating characteristic (ROC) curve analysis for the prognostic value of Angiotensin II levels in the prediction of mortality

	AUC	P value	95% Confidence Interval				
			Lower Bound	Upper Bound	Cut off	Sensitivity %	Specificity %
Angiotensin II Level (on day 7)	0.672	0.002*	0.569	0.775	≤ 508.50	59.7	73.9

Angiotensin II levels were lower in non-survivors, which may be explained by the fact that patients with severe ARDS have more endothelial and epithelial damage in their lungs, which decreases the levels of ACE1 and ACE2. When ACE2 and ACE1 decline, so will the levels of angiotensin II. The discrepancies between the findings of the aforementioned studies and our own could have been caused by variations in study methodology, patient sample sizes, patient profile heterogeneity, and the measurement difficulties associated with angiotensin II due to its short half-life and rapid protein degradation. The sensitivity was 59.7%, specificity was 73.9%, area under the curve was 0.672, P value was 0.002, and the cut-off point for Angiotensin II levels on day 7 to predict mortality was (≤ 508.5 pg/ml). Ozkan et al. conducted a receiver operating

characteristic analysis and discovered that blood angiotensin II levels had an 82% sensitivity, 48% specificity, and a cut-off value of < 513.59 pg/mL for ARDS onset detection [20]. The mean duration of symptoms on admission (in days) was (4.89± 0.60 SD) in survivors, while in non-survivors it was (5.08 ± 1.01 SD) with a statistically insignificant difference (P value = 0.206). The mean oxygen saturation on room air on admission was statistically significantly lower in non-survivors (72.74 % ± 11.15 % SD) compared to survivors (76.91% ± 10.10 % SD) with (P value = 0.025). The duration of oxygen dependency days was statistically significantly higher in survivors (16.04 ± 12.16) compared to non-survivors (12.39 ± 7.27) with (P value = 0.002). There was a statistically insignificant difference between survivors and non-survivors regarding the length of stay. The mean length of stay in survivors was (14.65 ± 12.82 SD) days, while in non- survivors it was (12.26 ± 7.28 SD) days (P value = 0.306). (Table 2). The study showed that inflammatory markers was higher in non-survivors than survivors especially on day 14. Interleukin-6 level at day 14 (P <0.001), ferritin level at day 14 (P <0.001), CRP level at day 14 (P = 0.010), D-diamer level on admission, on day 7 and on day 14 with (P=0.006), (P <0.001) and (P <0.001) respectively. (Table 3). The reported parameters of complications were higher in non survivors such as severe ARDS, Shock state required Vasopressors, MOF, acute kidney Injury, ACS, Arrhythmias (AF) and Delirium. Other complications like Stroke, Critical illness myopathy and neuropathy, Thrombocytopenia and Secondary bacterial infection showed no significant difference between both groups. (Table 4).

3.1 Correlation of Angiotensin II level to Morbidity

There was a negative correlation between angiotensin II Level and SOFA Score at day 7 in non-survivors and total study group (Table 5). There were insignificant correlations between angiotensin II Levels and length of stay (Table 6). Our study showed that there was a statistically significant difference between the survivor and non-survivors groups as regard the need for non-invasive and invasive mechanical ventilation, which was higher in non-survivors than survivors with a P value <0.001. In non-survivors, the average duration of invasive mechanical ventilation was 3.65 ± 2.10 days. There was statistically significant relation between level of Angiotensin II on day 7 and use of invasive mechanical ventilation with P value=0.002 being lower in ventilated patients, while there was no significant relation on admission and on day 14 with P value=0.580 & 0.196 respectively (Table 7).

3.2 Correlation of Angiotensin II level to Mortality

Our study showed that serum Angiotensin II level was higher than the normal reference range with the mean serum level on admission was (616.54 ± 401.13) pg/ml, after 7 days was (912.00±657.98) pg/ml and after 14 days was (625.53 ± 467.25) pg/ml. There was statistically significant relation between level of Angiotensin II after 7 days and outcome with P value = 0.002 being lower in non-survivors than survivors with mean level (792.53 ± 640.25 pg/ml) in non-survivors and (1073.02 ± 653.90 pg/ml) in survivors. There was statistically insignificant difference between Angiotensin II Level (baseline & after 14 days) and outcome with P value=0.580 & 0.196 respectively (Table 8). ROC curve show cut-off point for Angiotensin II on day 7 to predict mortality was (≤ 508.5 pg/ml) with sensitivity 59.7% and specificity 73.9%, with area under curve (0.672) and P value = 0.002 (Table 9).

4. Conclusion

In the current study, a lower oxygen saturation on room air at admission, a higher APACHE II score and SOFA score, elevated inflammatory markers, and the need for invasive ventilation were all significantly associated with mortality among COVID-19 critically ill patients. Serum angiotensin II levels increased above normal range in critically ill COVID-19 patients, but there was a statistically significant decrease in non-survivors compared to survivors on day 7 after admission.

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Ethical approval

The study was approved by the Institutional Ethics Committee.

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