

Case Report

Plasma Renin Concentration in Critically Ill COVID-19 Patients

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Abstract: Investigations of plasma renin concentration as a marker of organ perfusion in several intensive care settings have shown a significant correlation between its increase and a lack of perfusion in critical tissues, especially in septic patients. Castillo et al. proposed that activation of the non-canonical pathway of the renin–angiotensin–aldosterone system could improve cardiovascular homeostasis under COVID-19. During the first wave of COVID-19, we preliminarily enrolled a small cohort of subjects admitted to the Intensive Care Unit with a diagnosis of COVID-19 and acute respiratory distress syndrome. Their plasma renin value was measured in the first 24 h (T0), in the following 72 h (T1), and after one week (T2). In eight patients, we observed a higher plasma renin concentration—patients with difficulty weaning and in non-survivors. This is a preliminary observation. The variation of plasma renin levels in a septic condition is known, but settings such as COVID-19 infection have recently been investigated, showing a correlation with angiotensin-converting enzyme 2 receptor expression and functionality; in the near future, it will be interesting to have more data about its variation and value in COVID-19 patients.

Keywords: plasma renin; COVID-19; ICU biomarker



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1. Introduction

Investigations of plasma renin concentration as a marker of organ perfusion in several intensive care settings have shown a significant correlation between its increase and a lack of perfusion in critical tissues, especially in septic patients [1]. Unfortunately, it is not often used as a marker of perfusion failure severity, even though its levels do not follow significant circadian variations and are not affected by drugs or renal replacement, and its increase is not related to worse prognosis (especially if it is >84 pg/mL) [2]. Furthermore, the involvement of the angiotensin-converting enzyme receptor and its system is well described in COVID-19. Castillo et al. proposed that activation of the non-canonical pathway of the renin–angiotensin–aldosterone system (RAAS) could improve cardiovascular homeostasis under COVID-19. In particular, treatments with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB) may reduce hyperinflammation and viral propagation [3].

2. Case Presentation

During the first wave of COVID-19, we preliminarily enrolled a small cohort of subjects admitted to the Intensive Care Unit (ICU) with a diagnosis of COVID-19 and ARDS, without a previous hospitalization, from 1 April 2020 to 30 May 2020. All clinical data were gathered, and the plasma renin value was measured in the first 24 h (T0), in the following 72 h (T1), and after one week (T2). The percentage of survivors at the 90th day from admission was considered. We applied the ICU protocol with chloroquine, heparin

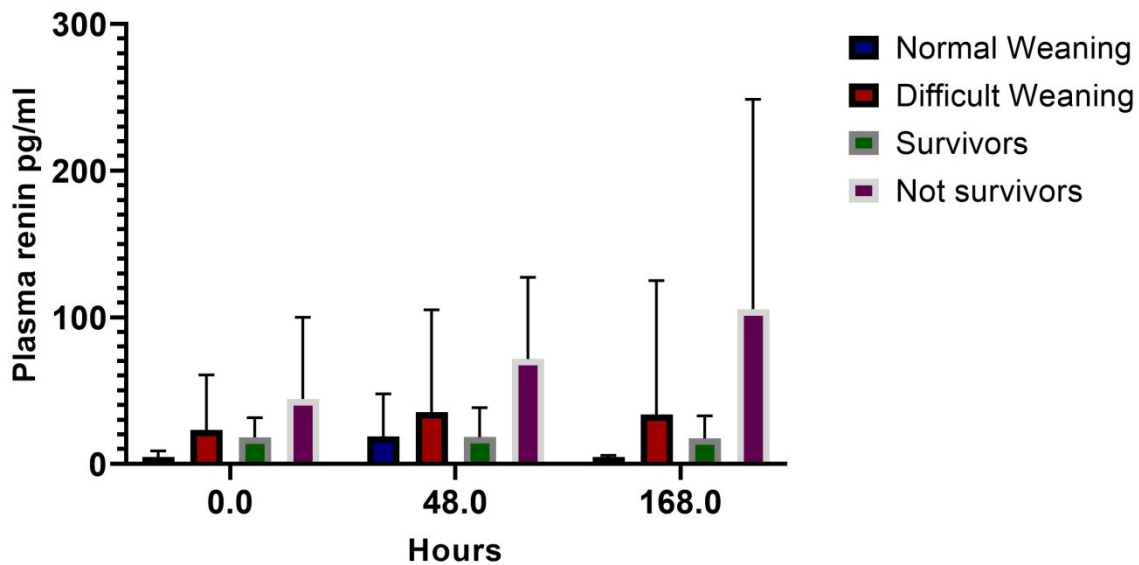
prophylaxis, and tocilizumab at admission (if administrable). Data analysis was conducted using GraphPad Prism 8[®] (GraphPad Software 2365 Northside Dr. Suite 560 San Diego, CA 92108, USA). The difference in plasma levels over time was measured via a multiple-way ANOVA test, survival was measured at 90 days, and difficult mechanical weaning was defined as invasive mechanical ventilation for more than 15 days and/or a tracheotomy performed for respiratory reasons.

We enrolled eight critical COVID-19 patients. There were no significant clinical differences at admission (T0) among the eight patients enrolled between survivors and non-survivors regarding their Sequential Sepsis-related Organ Failure Assessment (SOFA) score and their Simplified Acute Physiology Score (SAPS II). Two of them were in therapy with ARB (angiotensin receptor blockers)/ACE inhibitor medications (Table 1). The mean level of renin plasma was lower in the survivor group and in the normal weaning group, as reported in Figure 1 with a *p*-value of 0.029*. Considering the low number of patients that the *p* value reported, only differences among groups are highlighted; however, the sample size does not allow clinical clear associations to be made.

Table 1. Features of patients enrolled and plasma renin levels.

Patient	Age (Year)	SAPS II % (Percentage)	Comorbidities	Plasma Renin pg/mL			SOFA SCORE (Points)			90-Day Survivors	Difficult Weaning
				T0	T1	T2	T0	T1	T2		
Id 001	59	7.9%	Hypertension	37.10	8.00	11.00	4	2	4	Yes	Yes
Id 002	21	2.0	Psychiatric, smoker	9.50	52.30	6.00	4	3	2	Yes	No
Id 003	63	7.9%	Prev. myocardial infarction (ACE receptors blocker)	18.60	19.70	40.40	4	2	2	Yes	Yes
Id 004	65	16.7%	Hypertension, hypothyroidism (ACE inhibitors)	107.50	40.50	31.50	4	3	2	No	Yes
Id 005	55	7.2%	None	23.10	9.00	25.40	3	3	3	Yes	Yes
Id 006	63	21.0%	None	1.90	2.10	3.70	4	4	2	Yes	No
Id 007	54	9.7%	Diabetes II, hypothyroidism	2.60	1.50	4.40	3	4	3	No	No
Id 008	61	9.7%	None	22.5	172.50	206.70	3	4	3	No	Yes

Plasma renin concentration in severe COVID-19 patients



	A	B	C	D
Hours	Normal Weaning (M, SD) (obs)	Difficult Weaning (M, SD) (obs)	Survivors (M, SD) (obs)	Not Survivors (M, SD) (obs)
Admission (0 Hours)	4.67 ± 4.20 (3)	23.16 ± 37.43 (5)	18.04 ± 13.44 (5)	44.20 ± 55.71 (3)
48 Hours	18.63 ± 29.15 (3)	35.34 ± 69.74 (5)	18.22 ± 20.08 (5)	71.50 ± 55.71 (3)
168 Hours	4.70 ± 1.17 (3)	33.73 ± 91.32 (5)	17.32 ± 15.41 (5)	105.56 ± 143.04 (3)
P value (AC Vs BD)				0.029*

Figure 1. Plasma renin levels in COVID-19; the figure shows the difference between the survivors and non-survivors, and between normal weaning and difficult weaning. The results are expressed as the mean (M), standard deviation (SD), and number of observations (obs). The difference in plasma levels over time was measured via a multiple-way ANOVA test; *p*-value was considered significant if it was * < 0.05.

3. Discussion

Several biomarkers have been proposed for evaluating the clinical severity of patients with COVID-19 with respiratory or neurological symptoms, such as interleukin 6, ferritin and LDH, or angiotensin levels [4,5]. However, their measurement is often not simple or easy to perform, or their accuracy is not entirely known, and many conditions can alter their values [6]. Furthermore, RAAS dysregulation in COVID-19 patients has a dangerous role in cardiovascular complications [7]. In eight patients, we observed a higher plasma renin concentration in patients with difficulty weaning and in non-survivors; only one patient with a low value of plasma renin died, due to a sudden cerebral disease one day before ICU discharge. No difference in the production of renin was discovered in patients previously treated with sartin or ACE blockers (ARB or ACE inhibitors). Indeed, this is a preliminary observation, and it is not sufficient to demonstrate a possible biomarker role of plasma renin level in COVID-19 patients. However, it is interesting to observe how an increased plasma renin level during hospitalization usually follows difficult weaning as a possible expression of the severity of the disease. The variation of plasma renin levels and angiotensinogen in septic conditions is known, but settings such as COVID-19 infection have recently been investigated, showing a correlation with ACE2 receptor expression and functionality [8,9]. This cascade seems to correlate with the pulmonary severity of the disease. The downregulation of these receptors may increase angiotensin II stimulation, contributing to the deleterious hyperinflammatory reaction induced by the virus. This mechanism could be responsible for variations in the plasma renin concentration levels in

this kind of patient. Furthermore, it is essential to underline the significant activation of the RAAS system in severe diseases as a physio-pathological phenomenon [10].

Study Limitations

These cases form a preliminary study designed during the first pandemic wave to evaluate a possible role of plasma renin concentration in COVID-19 patients. Later, from 30 May 2020 to October, we did not admit any new COVID-19 patients. From October 2020, we were again able to measure plasma renin in COVID-19 patients: this last study is still ongoing, and for that reason, we describe these initial results.

4. Conclusions

These are preliminary data, and it will be necessary analyze these associations with a larger cohort of patients. Observing the renin levels in each patient, the value of T0 and T2 could be marked as potential predictors of the evolution of the patients in terms of the need or not for mechanical ventilation, and whether they survive or not. Still, more patients would be needed to reach statistical significance. A possible early identification of the most critical subjects could be a valuable instrument for better allocation of resources and to improve quality of care. The value of plasma renin expression correlates with activation of the RAAS system; in the near future, it will be interesting to have more data about its variation and value in COVID-19 patients.

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Informed Consent Statement: Patient consent was waived due to critical admission in ICU during the first COVID-19 patient wave.

Data Availability Statement: Data are available upon request to the author.

Conflicts of Interest: The authors declare no conflict of interest.

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