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Interaction of ACEI antihypertensive agent's administration with the inflammatory status at admission concerning COVID-19 clinical stay outcomes

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A B S T R A C T

Interactions between anti-hypertensive agents (ACEI), comorbidities, inflammation, and stress status may impact hospital stay duration in COVID-19 patients. This retrospective study analyzed epidemiological data, comorbidities, metabolic/inflammatory markers, and clinical information from 165 SARS-CoV-2 positive patients. In a multiple linear regression model, an IL-6 higher than 100 mg/L, glucose at admission (baseline levels at the hospital entry), and the interaction between ACEI administration and LDH predicted the days of hospital admission ($P < 0.001$). In conclusion, hypertensive patients suffering more severe inflammatory condition assessed by LDH levels clinically benefited more and reduced the hospital stay when prescribed ACEI agents than those with lower systemic baseline inflammation at admission.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), outreached in China at the end of 2019, with a later rapid worldwide extension, and a later surge in the case lethality ratio, pathogenesis and transmissibility, in most countries [1]. The viral infectious incidence and severity depend on the presence of associated comorbidities or metabolic and inflammatory-related diseases [2,3]. In this context, obesity and hypertension (HT) are associated with unfavorable evolution of the COVID-19 disease, with a high probability to develop severe pneumonia and impaired inflammatory reactions, in addition to organ and tissue damage. These outcomes were also related to increases in stay length, intensive care unit (ICU) stay, and mortality, as described elsewhere [4,5]. Covid-19 patients display inflammatory complications that have been related to a “cytokine storm” involving exacerbated blood interleukin 6 (IL-6), C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), neutrophil/lymphocyte index (NLI), D-Dimer, and red cell distribution width (RDW) levels. Furthermore, consistent associations

between hospital stay days and ICU admission implications concerning prescribed therapies and clinical outcomes were found as described elsewhere [6]. During the COVID-19 pandemic, several therapeutic approaches have been tested to fight against this viral disease [7], including the frequent administration of drugs belonging to Angiotensin-converting enzyme inhibitors (ACEI) group. Given the high prevalence of hypertension in severe cases of COVID-19 and the known clinical associations of pathogenic and inflammatory mechanisms accompanying SARS-CoV-2 infection, which may interfere with the administration of anti-hypertensive pharmacological agents (i.e. ACEI), the current research targeted in analyzing interactions of stay duration days at the hospital (dependent variable) with obesity, hypertension, the inflammatory status at admission based on IL-6 and LDH measurements and the metabolic stress status based on glycemia values (independent variables).

2. Materials and methods

This retrospective study was based on a series of 165 subjects

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consecutively admitted at the Puerta de Hierro Majadahonda University Hospital (Madrid, Spain) between March 15 and April 15, 2020. The following inclusion criteria were considered: patients >18 years old with positive PCR for SARS-CoV-2, moderate/severe pneumonia according to WHO guidelines, oxygen saturation rate < 94%, and respiratory rate > 22 breaths per minute. Patients with COVID-19 at 90 days before or those with incomplete clinical/metabolic information were excluded from the analyses. The variables recorded included administrative and epidemiological data, comorbidities, diagnosis examinations and information about the evolution of the disease following accepted standards [8]. Comorbidities and complications during hospital stay were defined as diagnoses included in the clinical history at admission and at discharge. Systolic and diastolic blood pressures (SBP and DBP, respectively) were recorded by the center's triage system upon arrival at the emergency room. HT was established as: SBP >140 mmHg and DBP >90 mmHg. Baseline blood cholesterol, glucose, inflammatory markers (IL-6, CRP, LDH), and liver enzymes (AST: aspartate aminotransferase; ALT: alanine transaminase) were collected from the first analysis performed during hospital admission. Height and weight were self-reported in all cases, with subsequent calculation of the Body Mass Index (BMI: kg/m²). Obesity was setup as BMI ≥30 kg/m². The data record was developed through information collected in the electronic medical record (SELENE System, Cerner Iberia, S.L.U, Madrid, Spain) filling in a template form previously established by the main investigators of this study. The laboratory analyzes were carried out by the Biochemistry Service of the center, according to validated analytical protocols. Triage was performed according to the Manchester scale [9], as a standard procedure in our center. Implementation was reviewed by two expert investigators to ensure the validity of the protocol. The Research Ethics Committee of the Puerta de Hierro Majadahonda University Hospital approved the study (PI 94/20). All the participating subjects gave their informed consent prior to its inclusion. This work respects the guidelines of Spanish and European Laws, as well as the Declaration of Helsinki, declaring no conflicts of interests or external sources of funding concerning this investigation. Quantitative variables are expressed as means and standard deviations, while qualitative variables are expressed as frequencies and proportions. Clinical and phenotypical characteristics of COVID-19 patients were compared by categorical variables or by the median values of continuous variables. For this last purpose, the reference values of IL-6 and LDH considered in our design are compatible with previous reports exploring laboratory predictors and prognostic factors of severe COVID-19 disease concerning respiratory functions

[10,11] as well as pharmacological prescription making decision criteria [12]. Moreover, Chi-square and unpaired Student's *t*-tests were applied for the univariate analysis. Multivariate regression analyses were used to predict stay duration days at the hospital, which were adjusted for baseline characteristics of the population and the day of extraction and including appropriate product terms. Eventual statistical interactions between clinical, inflammatory, and pharmacological markers were evaluated by multivariate regression analyses using product-term variables in the model. Statistical analyses were performed in the STATA software (version 12.1 for Windows, Texas, USA). P values (two-tailed) below 0.05 were considered statistically significant. P values (two-tailed) below 0.10 were considered as marginal significance.

3. Results

The clinical and phenotypical characteristics of COVID-19 patients based on the presence or absence of obesity, HT, and ACEI administration are reported (Table 1). As expected, patients with obesity underwent higher frequencies of ICU stay/mortality as well as greater blood levels of glucose at admission than their lean counterparts (Table 1). Moreover, statistical tendencies ($P < 0.10$) to display elevated levels of LDH, CRP and higher frequencies of increased IL-6 were found in subjects with obesity, although these were at a marginal significance ($P < 0.10$). Meanwhile, patients with diagnosed HT were statistically older and had a higher AST:ALT ratio as well as marginally greater serum levels of total cholesterol, CRP, DBP, ALT, and elevated IL-6 than normotensive individuals (Table 1). Instead, no statistical differences were found in liver markers neither inflammatory features when compared HT patients with ACEI prescription that those who were not under this treatment.

The demographic, clinical and biochemical characteristics of the total COVID-19 sample based on cutoffs of IL-6 (clinical criteria) and median values of LDH (statistical criteria) are reported (Table 2). Patients with blood levels of IL-6 greater than 100 mg/L had significantly shorter days of admission, but higher frequencies of ICU stay/mortality than those with IL-6 concentrations equal or lower than 100 mg/L (Table 2). In addition, increased levels of glucose at admission, CRP and ALT were identified in subjects with elevated IL-6 (Table 2). Similarly, older age and greater AST:ALT ratio were found in this same group, although at marginal ($P < 0.10$) significance (Table 2). Patients with LDH values above the median (332.5 IU/L) presented higher levels of LDH, AST, AST:ALT ratio as well as a tendency ($P < 0.10$) to have

Table 1

Clinical and phenotypical characteristics of COVID-19 patients based on obesity, hypertension and ACEI administration.

Variable	Obesity		P	HT		P	HT + ACEI		P
	No (n = 103)	Yes (n = 51)		No (n = 99)	Yes (n = 66)		No (n = 17)	Yes (n = 49)	
Age	63.7 ± 11.5	61.4 ± 11.9	0.259	59.1 ± 11.2	68.4 ± 9.9	<0.001	69.4 ± 9.0	68.0 ± 10.3	0.612
Sex (F/M)	36/67	18/33	0.967	39/60	17/49	0.070	5/12	12/37	0.689
Days of admission	3.90 ± 2.76	3.42 ± 2.53	0.307	3.76 ± 2.60	3.98 ± 2.87	0.616	4.31 ± 3.16	3.87 ± 2.79	0.599
No ICU/No mortality	88 (85.4)	35 (68.6)	0.014	80 (80.8)	50 (75.8)	0.437	13 (76.5)	37 (75.5)	0.937
ICU/mortality	15 (14.6)	16 (31.4)		19 (19.2)	16 (24.2)		4 (23.5)	12 (24.5)	
Glucose at admission (mg/dL)	118.7 ± 48.6	145.2 ± 64.7	0.007	124.9 ± 56.8	137.5 ± 61.7	0.200	125.1 ± 65.7	141.7 ± 60.5	0.355
Total cholesterol (mg/dL)	138.1 ± 31.4	145.4 ± 34.2	0.270	144.5 ± 34.7	132.9 ± 25.8	0.053	133.4 ± 34.9	132.7 ± 23.2	0.942
LDH (IU/L)	346.1 ± 134.0	378.1 ± 148.8	0.097	352.3 ± 153.4	366.3 ± 117.6	0.539	387.0 ± 128.1	358.8 ± 114.1	0.402
CRP (mg/L)	120.4 ± 109.4	158.2 ± 205.6	0.073	118.1 ± 106.2	155.4 ± 186.2	0.055	159.5 ± 69.6	154.1 ± 210.5	0.923
IL-6 (0–100 mg/L)	74 (71.8)	31 (60.8)	0.083	70 (70.7)	40 (60.6)	0.089	10 (58.8)	30 (61.2)	0.861
IL-6 (>100 mg/L)	29 (28.2)	20 (39.2)		29 (29.3)	26 (39.4)		7 (41.2)	19 (38.8)	
SBP (mmHg)	138.9 ± 21.3	137.7 ± 22.4	0.748	136.7 ± 20.4	139.6 ± 23.9	0.402	145.7 ± 19.3	137.5 ± 25.2	0.224
DBP (mmHg)	79.3 ± 14.2	79.0 ± 13.9	0.895	80.3 ± 13.4	77.3 ± 15.2	0.094	79.0 ± 10.9	76.7 ± 16.4	0.593
D-dimer (µg/mL)	1.86 ± 6.85	1.55 ± 2.01	0.757	1.93 ± 7.00	1.43 ± 1.78	0.580	1.28 ± 0.77	1.48 ± 2.03	0.683
AST (IU/L)	53.4 ± 35.2	46.9 ± 19.4	0.223	52.5 ± 33.0	48.9 ± 25.8	0.456	53.0 ± 28.1	47.5 ± 25.2	0.467
ALT (IU/L)	42.9 ± 34.4	37.7 ± 21.1	0.333	43.6 ± 32.3	35.9 ± 25.4	0.055	36.8 ± 21.9	35.6 ± 26.6	0.879
AST:ALT ratio	1.46 ± 0.84	1.40 ± 0.56	0.640	1.35 ± 0.45	1.61 ± 1.02	0.029	1.49 ± 0.31	1.64 ± 1.17	0.609

Values are expressed as means ± standard deviations. P values were calculated by Student's T-tests. Bold numbers indicate P value lower than 0.05. F: female; M: male; HT: hypertension; ACEI: Angiotensin Converting Enzyme Inhibitors; LDH: lactate dehydrogenase; IL-6: interleukin 6; CRP: C-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate aminotransferase; ALT: alanine transaminase.

Table 2

Clinical and phenotypical characteristics of COVID-19 patients based on cut-offs of IL-6 and median values of LDH.

Variable	All	IL-6		P	LDH		P
	n = 165	0–100 mg/L (n = 110)	>100 mg/L (n = 55)		<332.5 IU/L (n = 77)	≥332.5 IU/L (n = 77)	
Age	62.8 ± 11.6	61.5 ± 11.3	65.3 ± 11.9	0.051	63.1 ± 12.3	63.1 ± 10.9	0.983
Sex (F/M)	56/109	38/72	18/37	0.816	29/48	23/54	0.307
Days of admission	3.85 ± 2.70	4.27 ± 2.76	2.96 ± 2.35	0.004	3.74 ± 2.57	3.88 ± 2.88	0.758
No ICU/No mortality	130 (78.8)	101 (91.8)	29 (52.7)	<0.001	61 (79.2)	59 (76.6)	0.698
ICU/mortality	35 (21.2)	9 (8.2)	26 (47.3)		16 (20.8)	18 (23.4)	
Glucose at admission (mg/dL)	130.2 ± 59.1	119.9 ± 42.7	148.1 ± 77.0	0.004	121.2 ± 53.7	138.4 ± 64.1	0.087
Total cholesterol (mg/dL)	140.1 ± 32.1	142.6 ± 31.3	135.3 ± 33.2	0.246	141.5 ± 30.5	135.2 ± 32.0	0.298
LDH (IU/L)	358.1 ± 139.4	362.4 ± 150.2	350.1 ± 117.6	0.603	253.2 ± 57.3	463.1 ± 116.2	<0.001
CRP (mg/L)	132.8 ± 143.7	107.7 ± 73.9	182.1 ± 217.8	0.002	127.2 ± 193.9	150.0 ± 70.7	0.342
SBP (mmHg)	137.8 ± 21.9	137.2 ± 20.7	139.2 ± 24.2	0.578	136.4 ± 22.7	139.1 ± 21.2	0.439
DBP (mmHg)	79.1 ± 14.1	79.3 ± 14.0	78.6 ± 14.5	0.749	77.6 ± 14.4	80.6 ± 12.4	0.080
D-dimer (µg/mL)	1.71 ± 5.46	1.78 ± 6.58	1.60 ± 2.11	0.846	0.96 ± 0.98	2.53 ± 7.68	0.084
AST (IU/L)	51.1 ± 30.3	53.1 ± 34.4	47.2 ± 20.1	0.240	41.1 ± 23.3	59.7 ± 30.7	<0.001
ALT (IU/L)	40.6 ± 29.9	45.0 ± 34.5	32.0 ± 15.0	0.009	35.0 ± 25.6	43.6 ± 30.3	0.059
AST:ALT ratio	1.45 ± 0.74	1.38 ± 0.83	1.58 ± 0.53	0.057	1.31 ± 0.39	1.63 ± 0.97	0.009

Values are expressed as means ± standard deviations. P values were calculated by Student's T-tests. Bold numbers indicate P value lower than 0.05. F: female; M: male; LDH: lactate dehydrogenase; IL-6: interleukin 6; CRP: C-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate aminotransferase; ALT: alanine transaminase.

elevated glucose at admission, DBP, D-dimer, and ALT than individuals below the median value. About 75% of patients had been treated with corticoids at hospital admission, with an increasing proportional trend in those with higher IL-6 concentrations (about 63% in patients with 0–100 mg/dL and 96% in those with >100 mg/dL). Interestingly, regression analyses including corticoid therapy demonstrated the same statistical trends. The multiple linear regression model that predicted the days of admission in COVID-19 patients using clinical, inflammatory, and pharmacological variables is reported (Table 3). Noteworthy, increased IL-6 (>100 mg/L), glucose at admission, obesity (at a marginal significance), and the interaction between ACEI and LDH predicted the days of admission in approximately 27%. The LDH * ACEI interaction is depicted (Fig. 1). Patients who were under ACEI treatment and presented elevated LDH stayed lower days of admission, which was not observed in those without ACEI treatment (Fig. 1).

4. Discussion

The time of hospitalization in COVID patients diagnosed with hypertension and treated with ACE2 antagonists was dependent on the baseline inflammatory condition as assessed via IL-6 levels, and circulating glucose concentrations at admission. The most relevant finding of this study was that a negative interaction between LDH and ACEI prescription was statistically demonstrated concerning hospital stay, which means a protective role of these antagonists/blockers on those patients with high LDH values as a marker of tissue damage and inflammation. This information is compatible with the differential responses found in some patients and allow to understand and predict personalized outcomes concerning clinical stays of COVID-19 patients within precision medicine endeavors.

COVID-19 not only affects the pulmonary tissue, but also induces

Table 3

Multiple linear regression models deeming clinical, inflammatory, and pharmacological variables as important predictors of stay duration days at the hospital as the main outcome.

Variable	β coefficients (CI 95%)	P
IL6 (>100 mg/L)	5.1995 (2.8072, 7.5917)	<0.001
Obesity (yes)	0.4117 (−0.0168, 0.8402)	0.060
Glucose at admission	0.0353 (0.0002, 0.0703)	0.049
HT (yes)	2.2986 (−3.7035, 8.3006)	0.450
ACEI * LDH	−0.0361 (−0.0695, −0.0025)	0.035
Adjusted R ²	0.2683	<0.001

Bold numbers indicate P < 0.05.

harms in multiple organs, particularly the cardiovascular system [13]. This infectious condition may lead to myocardial injuries, endothelial dysfunctions and microvascular spasms, usually requiring preventive or pharmacological measures including ACE2 antagonist's administration [14]. These findings warrant specific analyses considering factors with potential impact on the clinical and stay outcomes. In this context, available mortality figures suggest that COVID-19 is more lethal in aged patients with comorbid conditions including hypertension [15]. The SARS-CoV-2 pathogenesis is initiated by the binding of viral spike protein with the target receptor ACE2 facilitating virus internalization within host cells [16]. Mechanistically, SARS-CoV-2, following serine protease cleavage of the S protein, binds to the transmembrane ACE2 to penetrate into type 2 pneumocytes, macrophages, perivascular pericytes, and cardiomyocytes, whose entry may be blocked by ACE2 antagonists/blockers [17]. Although there were a debate about whether the use of ACEI are useful or hazardous in patients with COVID-19, several reviews and analyses now suggest that ACEI and angiotensin receptor blockers (ARBs) administration should not be discontinued in COVID-19 patients with hypertension since that there was no evidence that both pharmacological agents affected the risk COVID-19 incidence and mortality [18–22]. However, it appears that phenotypical interactions and confounding factors such as the baseline inflammatory status, concurrent metabolic diseases and complications (obesity, diabetes dyslipidemia), hyperglycemia associated to morbid stress, age or sex need to be individually accounted for precision management. These features may explain clinical discrepancies concerning clinical outcomes and duration stays among COVID 19 patients administered ACE2 antagonists as found in current analyses, where inflammation markers (LDH/IL-6), circulating glucose and ACEI were involved concerning clinical outcomes.

Given that accumulating evidence suggests that SARS-CoV2 is associated with a hyperinflammation condition characterized by excessive release of pro-inflammatory cytokines, anti-viral agents alone will not provide the much required therapeutic effect [23]. Hence, the need to combine anti-inflammatory agents such as interferons, ACE2 inhibitors, IL-6, and Janus kinase (JAK) family inhibitors, anticoagulants and other agents involved in inflammation resolution needs to conjointly examine the inflammatory status in these patients by measuring inflammatory markers such as IL-6 or LDH [24]. Using meta-regression tests, neutrophils, lymphocytes, IL-6, ferritin, C-reactive protein, D-dimer and LDH demonstrated that hyperinflammation, blunted adaptive immune response and intravascular coagulation, playing key roles in the pathogenesis of COVID-19 [25]. Indeed, LDH and IL-6 are valid inflammation markers and reliable surrogates for inflammation categorization in

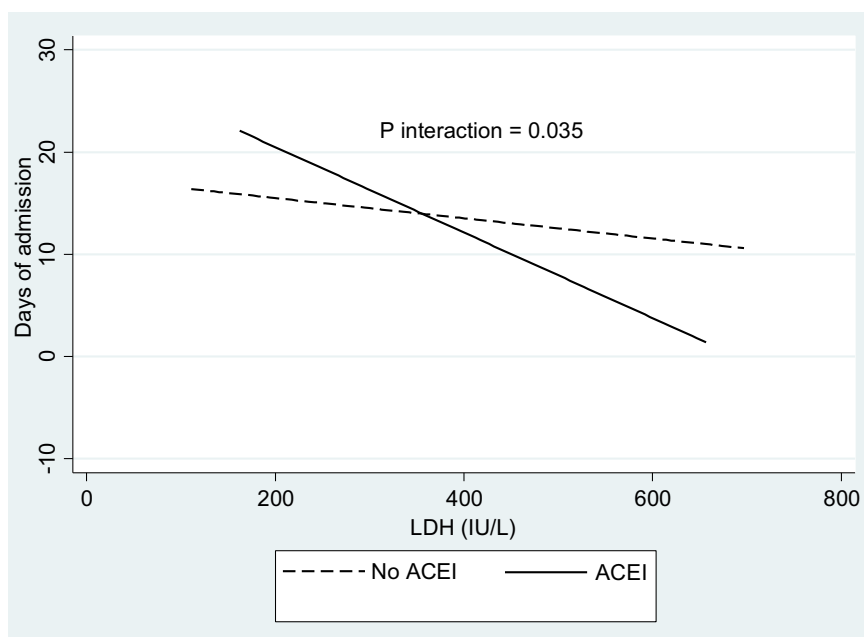


Fig. 1. Interaction between ACEI and LDH concerning days of admission in COVID-19 patients.

COVID-19 patients regardless of age or sex [24], and support the inclusion of these inflammation proxies in our regression analyses to explain the hospital stay duration implications. In fact, IL-6, LDH, C-reactive protein, and lymphocytes are key inflammatory markers in COVID-19 patients with hypertension receiving ACEI therapy, who had a lower rate of severe diseases and a trend toward a lower level of IL-6 in peripheral blood, which supports the benefit of using ACEIs to potentially contribute to the improvement of clinical outcomes of COVID-19 patients with inflammation features and hypertension [26].

A limitation of this analysis is the retrospective nature of the design, but the results were plausible according to available evidences and the hypothesis of this research. Although the analyzed sample was relatively small, it is comparable to larger series such as the COVID-DATA-SAFE-LIFES cohort [27]. Also, initial stages of COVID-19 hampered to collect some clinical information. This research should be considered as a proof of principle with valuable results and actual clinical applications, although type I and type II errors cannot be discarded given the relative small sample size. As positive strengths are that an interaction of ACE2 antagonist with the baseline LDH status has been demonstrated after adjusted by relevant inflammation variables and confounding factors. In this regard, alternative linear regression models with corticoids administration as covariable revealed that the use of corticoids did not affected the ACEI*LDH interaction (data not shown). Interestingly, those with higher IL-6 values were more prone to be treated with corticoids, which provide additional support to the need to appraise the inflammatory status in hypertensive patients.

5. Conclusion

In conclusion, the interaction between ACEI administration and the inflammatory marker LDH influenced the stay duration (days) at the hospital, which could contribute to improve the clinical/pharmacological management of COVID-19 disease under a personalized medicine approach, where patients with a more severe inflammatory status may probably benefit more specifically by ACEI treatment. This investigation allowed to define some factors that discriminate some divergent personalized clinical outcomes with emphasis on factors explaining clinical interindividual differences for a precision vascular pharmacology in COVID-19 patients.

Declaration of Competing Interest

We guarantee that there is no conflict of interest in our paper.

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