Table 1 (Continued)

Patient characteristics according to systolic strain phenotype in the polar map

Clinical, demographic, and echocardiography parameters	Overall population (n = 92)	RELAPS < 1 (n = 53)	RELAPS > 1 (n = 39)	P
AVG_{mean}, mmHg	51.9 ± 14.2	48.9 ± 13.2	55.9 ± 14.9	.020
AET, ms	333.3 ± 37.5	340.2 ± 38.0	324.4 ± 35.3	.053

AET, aortic ejection time; AF, atrial fibrillation; apical LS, average peak systolic longitudinal strain of the apical segments; AVG_{max}, peak aortic valve gradient; AVG_{mean}, mean aortic valve gradient; AVA, aortic valve area; basal LS, average peak systolic longitudinal strain of the basal segments; BMI, body mass index; CKF, chronic kidney failure; COPD, chronic obstructive pulmonary disease; DL, dyslipidemia; DM, diabetes mellitus; DT, E-wave transmitral deceleration time; E/E', ratio of early mitral inflow E-wave to pulsed-wave tissue Doppler mitral annular E' wave; ECC IND, eccentricity index (IVSd/PWTd ratio); GLS, global longitudinal strain; HF, prior admission due to heart failure; HTN, hypertension; IVSd, interventricular septal thickness at end diastole; LAVi, indexed left atrial volume by biplane area-length method; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; MCF, myocardial contraction fraction (ratio of stroke to myocardial volume, ie, LV mass ratio/1.05) (myocardial density); mid LS, average peak systolic longitudinal strain of the medial segments; MI, history of myocardial infarction; MWT, maximum wall thickness; PWTd, posterior wall thickness at end diastole; RWT, relative wall thickness (2×PWT/LVEDD); S', S' wave of the lateral mitral annulus with pulsed-wave tissue Doppler; stroke, history of ischemic stroke; V_{max}, peak aortic jet velocity.

Data are expressed as No. (%) or mean ± standard deviation.

Table 1 lists the baseline characteristics of the entire cohort analyzed with myocardial deformation parameters and the differences between the RELAPS < 1 and > 1 subgroups.

In patients able to undergo strain analysis (n = 92), average GLS was –15.1%; 39 patients (42%) showed RELAPS value > 1; 82 (89%) patients had an SAB ratio > 2.1, and 39 (42%) had EFSR > 4.1. Figure 1B shows patient distribution according to these 3 LS-based indices.

No differences in clinical or demographic variables were found between the groups with RELAPS < 1 or > 1. The echocardiography variables showed that the RELAPS > 1 group had significantly more severe AS and increased LV hypertrophic remodeling. No differences were found in the conventional parameters used to evaluate systolic function; however, myocardial contraction fraction was significantly lower in the group with normal apical strain. No differences were found in diastolic function parameters.

In the multivariate analysis, predictive echocardiography variables for strain with an apical sparing pattern were LV mass (OR, 1.02; 95%CI, 1.01-1.03; P = .002), LV end-systolic volume (OR, 0.97; 95%CI, 0.94-0.99); P = .014), aortic valve area (OR, 0.10; 95%CI, 0.01-0.38; P = .018), and aortic ejection (OR, 0.98; 95%CI, 0.96-0.99; P = .010). The c-statistic was 85.6% (95%CI, 76.6%-94.7%).

In our series, patients with severe symptomatic AS without CA were highly likely to exhibit strain with an apical sparing phenotype and EFSR similar to that described in CA. These findings could have relevant clinical implications, as they would not be applicable in regular clinical practice for CA screening in patients with a condition as common as severe AS.

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Renin-angiotensin system blockers and outcomes during hydroxychloroquine treatment in patients hospitalized for COVID-19 pneumonia

Inhibidores del sistema renina-angiotensina y pronóstico durante tratamiento con hidroxicloroquina en pacientes hospitalizados por neumonía por COVID-19

To the Editor,

SARS-CoV infection requires virus binding to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2). Hydroxychloroquine (HCQ) inhibits terminal glycosylation of ACE2 receptor, which may reduce the efficiency of its interaction with SARS-CoV spike protein.[1] Initial experiences during the COVID-19 pandemic supported the offlabel use of HCQ. However, its potential cardiotoxicity and still unclear benefit have eventually urged caution.[2]

High fatality rates have been reported in elderly individuals with COVID-19 and multiple cardiovascular comorbidities.[3] Concerns have arisen that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) might increase ACE2 receptor expression and patient susceptibility to viral entry into host cells, facilitating SARS-CoV-2 propagation.[4] Recent studies with different designs found no adverse effects associated with ACEIs/ARBs in various large populations with COVID-19 but did not report on HCQ coadministration.[5]

We analyzed 1031 patients admitted to the Hospital of Cremona, the epicenter of the COVID-19 outbreak in Italy, between February 22 and April 7, 2020, and followed up until May 3, 2020.

COVID-19 pneumonia was confirmed by chest computed tomography and a SARS-CoV-2-positive real-time reverse transcriptase-polymerase chain reaction assay from nasopharyngeal swabs. Treatment protocols were based on offlabel use of HCQ (400 mg twice a day on the first day and 200 mg twice a day thereafter for 10 days), as well as lopinavir/ritonavir or darunavir/ritonavir, intravenous methylprednisolone, empirical antimicrobial therapy, low-molecular-weight heparin, and supplemental oxygen.

From the hospital data warehouse, we extracted data on the admitting ward, cardiovascular risk factors and disease, drug therapies, and in-hospital outcomes. Demographic covariates (age, sex), cardiovascular covariates (smoking, hypertension, obesity, diabetes, atrial fibrillation, coronary heart disease, cerebrovascular disease, systolic dysfunction), and treatment covariates (antidiabetic agents, beta-blockers, calcium channel blockers, loop diuretics, antivirals, steroids) were tested by univariable Cox regression and those significantly associated ($P < .10$) with death or intensive care unit admission (combined end point) were entered in a multivariable model. Additionally, we performed weighted Cox regression using inverse probability of treatment weighted estimation with robust standard errors. A multivariable logistic regression model that included the same covariates as Cox regression was used to estimate the inverse probability of treatment weights for the individual propensities for ACEI/ARB receipt.

The institutional review board approved this retrospective analysis and waived the need for individual informed consent.

All 1031 patients received HCQ during hospitalization (table 1). Overall, 559 patients (54.2%) took $\geq$ 1 cardiovascular drugs (diuretics, beta-blockers, calcium channel blockers, or ACEIs/ARBs); of these, 278 (27%) received either an ACEI (135 [13.1%], 11 $\pm$ 4 mg/d enalapril equivalents) or an ARB (143 [13.9%], 64 $\pm$ 34 mg/d losartan equivalents) and 239 (86%) continued to take them throughout the hospitalization. Although patients treated with ACEIs/ARBs were older, had a higher cardiovascular comorbidity burden, and were more often taking antidiabetic agents and subject to cardiovascular polypharmacy, they had similar intensive care unit admission and mortality rates to patients not being treated with ACEIs/ARBs (table 1).

In total, 117 patients (11.3%) were admitted to the intensive care unit and 217 died (21%); 273 (27%) met the combined end point. After covariate adjustment (table 1), ACEIs/ARBs were independently associated with the combined outcome. ACEIs and ARBs conferred similarly lower risk (figure 1). The results were replicated in analysis restricted to mortality (adjusted hazard ratio [HR] for ACEIs/ARBs, 0.661; 95% confidence interval [95%CI], 0.490-0.890; $P = .006$) after further adjustment for the need for ventilatory support. The effects were consistent in the analysis weighted by inverse probability of treatment weighting (HR for ACEI/ARB use, 0.666; 95%CI, 0.445-0.997; $P = .048$).

In our hospitalized cohort treated with HCQ for COVID-19 pneumonia, ACEIs/ARBs were independently associated with a lower hazard of mortality or severe disease requiring intensive care unit admission. ACEI or ARB receipt was balanced and both, administered at relatively high doses, had a similar impact on outcome. The findings were confirmed in the analysis weighted by inverse probability of treatment weighting.

Recent observational studies in geographically diverse populations found no differences in the need for invasive ventilation or death in patients with SARS-CoV-2 pneumonia treated with ACEIs/ARBs.[5] None of these studies reported on the coadministration of HCQ, which might represent a confounding factor. Moreover,

Table 1

Characteristics of the study cohort and associations with the combined end point (death or intensive care unit admission) by Cox regression analysis

	All		No ACEI/ARB		ACEI/ARB			Unadjusted			Adjusted		
	1031	%	773	(73.0)	278	(27.0)	P	HR	95%CI	P	HR	95%CI	P
Male sex	655	(63.5)	470	(62.4)	185	(66.5)	.244	1.602	1.224-2.097	.001	1.755	1.339-2.300	< .001
Age, y	67	± 14	65	± 14	72	± 11	< .001	1.042	1.030-1.052	< .001	1.046	1.035-1.057	< .001
Active smoker	100	(9.7)	43	(5.7)	57	(20.5)	< .001	1.234	0.872-1747	.235			
Hypertension	298	(28.9)	80	(10.6)	218	(78.4)	< .001	.883	0.682-1.145	.349			
Diabetes	190	(18.4)	111	(14.7)	79	(28.4)	< .001	1.389	1.064-1.814	.016			
Obesity	129	(12.5)	61	(8.1)	68	(24.5)	< .001	1.230	0.895-1.690	.201			
Atrial fibrillation	177	(17.2)	119	(15.8)	58	(20.9)	.056	1.386	1.051-1.826	.021			
CVD	70	(6.8)	24	(3.2)	46	(16.5)	< .001	.856	0.548-1.338	.495			
CHD	110	(10.7)	45	(6)	65	(23.4)	< .001	1.371	0.994-1.889	.054			
LVEF < 35%	82	(8)	24	(3.2)	58	(20.9)	< .001	1.037	0.704-1.527	.855			
Treatment													
Loop diuretics	157	(15.2)	97	(12.9)	60	(21.6)	.001	1.556	1.189-2.038	.001			
Beta-blockers	308	(29.9)	176	(23.4)	132	(47.5)	< .001	1.271	0.994-1.623	.055			
CCBs	190	(18.4)	106	(14.1)	84	(30.1)	< .001	1.039	0.777-1.390	.794			
ACEIs/ARBs	278	(27.0)			278	(27.0)	-	0.795	0.607.1.042	.096	0.630	0.480-0.827	.001
Antidiabetic agents	184	(17.8)	107	(14.2)	77	(27.7)	< .001	1.419	1.086-1.856	.010			
Antiviral agents	944	(91.6)	685	(91.0)	259	(93.2)	.313	0.858	0.577-1.277	.451			
Steroids	569	(55.2)	403	(53.5)	166	(59.7)	.078	1.321	1.016-1.719	.038			
Ventilatory support	263	(25.5)	196	(26.0)	67	(24.1)	.573	1.919	1.466-2.513	< .001*			
ICU admission	117	(11.3)	89	(11.8)	28	(10.1)	.507						
Mortality	217	(21.0)	156	(20.7)	61	(21.9)	.668						

95%CI, 95% confidence interval; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; CHD, coronary heart disease; CVD, cerebrovascular disease; HR, hazard ratio; ICU, intensive care unit; LVEF, left ventricular ejection fraction.

* HR for mortality alone.
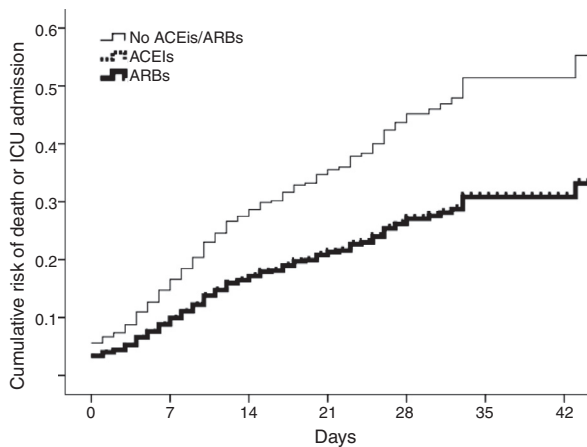
Figure 1. Cumulative risk of death or intensive care unit (ICU) admission in patients on angiotensin-converting enzyme inhibitors (ACEIs) (dotted line), angiotensin receptor blockers (ARBs) (thick line), or neither (thin line). Curves for ACEIs and ARBs overlap, indicating comparably lower risk.

evidence on the benefits and harm of the use of HCQ or chloroquine to treat COVID-19 is still weak and conflicting.[3,6]

Our patients were older and had a higher burden of cardiovascular risk factors and comorbidities than previous series, all factors that may have contributed to high event rates. Intriguingly, during HCQ coadministration, ACEIs/ARBs were associated with lower hazards of mortality and the need for invasive ventilation, reinforcing previous findings of their lack of detriment in COVID-19.[5]

In a setting similar to ours, Geleris et al.[6] found no association of HCQ treatment with a higher or lower risk of intubation or death. However, the study did not report the effects of ACEIs/ARBs, which were prescribed in rates similar to those of our cohort.

Our data do not allow confirmation of a possible synergy of ACEIs/ARBs and HCQ or a protective impact of ACEIs/ARBs on the potential cardiac adverse events of HCQ. In many cardiovascular diseases, ACEIs/ARBs exert beneficial effects on cardiac function and endothelial cell dysfunction, which might improve prognosis despite the use of cardiotoxic drugs.

The positive impact of ACEIs and ARBs in our aging patients with cardiovascular morbidities hospitalized for COVID-19, even during treatment with a potentially cardiotoxic agent, has particular relevance for cardiology practice and strengthens the recommendation to continue treatment with ACEIs/ARBs when indicated.

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D-dimer and right ventricular abnormalities as prognostic factors in critically ill COVID-19 patients

Dímero D y alteraciones del ventrículo derecho como factores pronósticos en pacientes críticos con COVID-19

To the Editor,

Coronavirus disease 2019 (COVID-19) seems to be associated with a higher risk of myocardial injury, especially in critically ill patients.[1] Previous definitions of acute COVID-19 cardiovascular syndrome[2] have been heterogeneous, and therefore its true incidence, clinical relevance and prognostic impact remain unclear. The aim of this study was to analyze echocardiographic abnormalities and biomarkers in COVID-19 patients requiring intensive care and their association with 30-day survival.

Observational, prospective cohort study of patients admitted to the intensive care unit (ICU) of *Hospital Universitario La Paz* (Madrid, Spain) with confirmed COVID-19 infection and acute respiratory distress syndrome between March 1 and April 8, 2020. We analyzed serum biomarkers in all patients. Following current recommendations,[3,4] a focused cardiac ultrasound study[3] was performed by accredited cardiologists. The main outcome was 30-day survival. Major cardiovascular events during follow-up were recorded, including myocarditis, pericarditis, pulmonary embolism (PE), and ventricular arrhythmias. The patients were followed up until hospital discharge or death. The study was conducted in compliance with the Declaration of Helsinki and was approved by the ethics committee of our institution.

Fifty-two patients were included (table 1), and the median follow-up was 46 [22-54] days. The most common findings in our study were right ventricular (RV) abnormalities, mainly RV systolic