Archives of Cardiovascular Disease 115 (2022) 96—105

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LETTERS TO THE EDITORS

Echocardiography and renin-aldosterone interplay as predictors of death in COVID-19

Interaction entre échocardiographie et système rénine-aldostérone comme prédicteurs de mortalité pour le COVID-19

Keywords COVID-19; Echocardiography; Aldosterone; Biomarkers; Prognosis
Mots clés COVID-19 ; Aldostérone ; Échocardiographie ; Biomarqueurs

Coronavirus disease 2019 (COVID-19) has spread worldwide and has resulted in millions of deaths, mainly caused by inappropriate systemic inflammatory reaction to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and evolution to refractory hypoxaemia, leading to acute respiratory distress syndrome [1]. It has also been shown that cardiac injury, including an increase in biomarkers (troponin, N-terminal prohormone B-type natriuretic peptide [NT-proBNP]), pulmonary embolism and alteration of ventricular function on echocardiography are associated with increased mortality [2,3]. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor to enter cells, and modulates the renin-angiotensin-aldosterone system (RAAS), a major factor in adverse cardiac remodelling [1]. The interplay between RAAS, systemic inflammation and lung and cardiac involvement in COVID-19 is unknown, and was the focus of the present work (ClinicalTrials.gov Identifier: NCT04320017; Institutional Review Board approval: CER-2020-14-JOCOVID). The main objectives of this study were to delineate how these variables are associated with each other, and to identify among them independent predictors of 30-day mortality.

A total of 127 non-intensive care patients with COVID-19 (no inotropes or mechanical ventilation) were included consecutively between March and May 2020 in a French tertiary care hospital (Pitié-Salpétrière Hospital, Paris, France). Upon admission, patients were systematically evaluated with transthoracic echocardiography, performed as soon as possible, and measurement of serial cardiac and inflammatory plasma biomarkers (troponin, NT-proBNP, C-reactive protein [CRP], lymphocyte count). COVID-19 infection was defined by at least one positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test (93%) or compatible thoracic scan and symptoms during the first 2020 French pandemic wave. Thoracic scans were performed to assess the magnitude of lung parenchymal involvement and rule out pulmonary embolism, as clinically indicated. Renin, aldosterone and ACE-2 circulating concentrations were measured in a subgroup of patients because of the time delay in setting up these methods after the start of the pandemic. Severity of oxygen (O_2) requirement at the time of echocardiography was defined by oxygen saturation (SpO_2)/fraction of inspired oxygen (FiO_2), with FiO_2 derived from nasal O_2 delivery (L/min). Medical history of chronic heart, respiratory failure or thromboembolic event before the COVID-19 event was assessed. Information regarding new-onset venous thromboembolism and acute coronary syndrome concomitant to COVID-19 was collected prospectively. Normal echocardiographic values (left and right ventricular dimensions and function, left ventricular filling pressures) were derived from the most recent guidelines [4,5]. All echocardiography was performed by the same trained operator (J.-E. S.; Vivid S5; General Electric Co., Boston, MA, USA), and analysed by a blinded operator (N. H.). Intraobserver values for our core laboratory for echocardiographic measurements have been detailed elsewhere [6,7]. Qualitative values are expressed as numbers and percentages, and quantitative variables as medians (interquartile ranges). Comparisons between qualitative and quantitative variables were performed using χ^2 and non-parametric tests (Wilcoxon: two groups; Kruskal-Wallis: three groups), respectively. Correlations between variables were computed by Spearman's test. *P* values were adjusted for multiple testings (Benjamini-Hochberg's method) with adjusted $P \leq 0.05$ deemed significant. A multivariable model (logistic regression, with and without imputation of missing data) was used to examine factors associated with death.

The clinicodemographic, biological, echocardiographic and thoracic scanner findings as a function of O_2 need at the time of echocardiography (classified into three groups: ambient air; O_2 0.5—4.5 L/min; and $O_2 \geq 5$ L/min) and mortality 30 days after hospital admission are shown in Table 1. In this cohort, median age was 77 (61—83) years, and 57% of patients were male. Echocardiography was performed 3 (2—5) days after hospital admission for COVID-19, and 47% (60/127) required O_2 at the time of echocardiography, with 27% (16/60) of these requiring ≥ 5 L/min. O_2 requirement at the time of echocardiography was asso-

Abbreviations: ACE-2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; O_2, oxygen; RAAS, renin-angiotensin-aldosterone system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1 Clinicodemographic, biological, echocardiographic and thoracic scanner findings as a function of oxygen need at the time of echocardiography and 30-day mortality after hospital admission for COVID-19 in 127 patients; association between aldosterone and renin circulating concentrations and these latter variables.

	Oxygen need at the time of echocardiography				Correlation (rho)		Vital status at day 30 of admission for COVID-19		
	Ambient air	O^2 0.5—4.5 L/min	$O^2 \geq 5$ L/min	Unadjusted *P*	Renin	Aldo	Alive	Dead	Unadjusted *P*
	(*n* = 67)	(*n* = 44)	(*n* = 16)		(*n* = 50)	(*n* = 62)	(*n* = 114)	(*n* = 13)	
Demographics before COVID-19									
Age (years)	74 (60—82)	72 (58—81)	83 (80—88)	0.001[a]	0.22	−0.02	74 (59—82)	83 (77—88)	0.02
Male sex	42 (63)	22 (50)	9 (56)	0.41	0.11	−0.02	65 (57)	8 (62)	0.99
Active tobacco user	22 (33)	11 (25)	4 (25)	0.62	0.13	−0.19	37 (32)	0 (0)	0.04
Hypertension	42 (63)	25 (57)	11 (69)	0.67	0.22	0.16	70 (61)	8 (62)	1
RAAS blocker use	27 (40)	18 (41)	7 (44)	0.97	0.40[a]	−0.06	48 (42)	4 (31)	0.62
Chronic diuretics	10 (15)	6 (14)	2 (12)	0.96	0.17	−0.08	18 (16)	0 (0)	0.26
Chronic corticosteroids	9 (13)	5 (11)	0 (0)	0.30	0.22	0.18	13 (11)	1 (7.7)	1
Ischaemic cardiomyopathy	16 (24)	8 (18)	4 (25)	0.74	0.22	0.02	23 (20)	5 (38)	0.25
Known heart failure	10 (15)	5 (11)	6 (38)	0.05	0.16	0.00	18 (16)	3 (23)	0.78
Thromboembolic disease history	10 (15)	4 (9)	1 (6)	0.49	0.08	−0.10	14 (12)	1 (7.7)	0.97
Chronic respiratory failure	3 (5)	0 (0)	2 (12)	0.08	−0.03	−0.13	5 (4.4)	0 (0)	0.99
COVID-19 features during hospital stay									

Table 1 (*Continued*)

	Oxygen need at the time of echocardiography				Correlation (rho)		Vital status at day 30 of admission for COVID-19		
	Ambient air ($n = 67$)	O^2 0.5—4.5 L/min ($n = 44$)	$O^2 \geq 5$ L/min ($n = 16$)	Unadjusted *P*	Renin ($n = 50$)	Aldo ($n = 62$)	Alive ($n = 114$)	Dead ($n = 13$)	Unadjusted *P*
Acute coronary syndrome	2 (3)	1 (2)	2 (12)	0.17	0.20	−0.04	4 (4)	1 (8)	1
Acute venous thromboembolism	4 (6)	2 (5)	2 (12)	0.53	−0.18	0.18	6 (5)	2 (15)	0.41
Overall 30-day mortality	2 (3)	4 (9)	7 (44)	≤ 0.0001[a]	0.18	0.40[a]	NA	NA	NA
Clinical variables at time of echocardiography									
Corporeal surface (m^2)	1.8 (1.7—2)	1.8 (1.7—2)	1.7 (1.5—1.8)	0.07	−0.11	−0.01	1.8 (1.7—2)	1.8 (1.5—1.9)	0.12
Sinus rhythm	58 (87)	42 (95)	11 (73)[15]	0.06	0.00	−0.04	101 (89)	10 (83)[12]	0.95
Heart rate (beats/min)	78 (68—84)	86 (74—93)	92 (78—100)	0.001[a]	0.00	0.11	80 (70—90)	92 (86—110)	0.002[a]
Systolic blood pressure (mmHg)	120 (110—130)[65]	130 (110—130)	130 (110—140)	0.29	−0.14[49]	−0.03[61]	120 (110—130)[112]	140 (110—150)	0.29
Diastolic blood pressure (mmHg)	66 (60—72)[65]	74 (61—82)	70 (60—80)	0.24	−0.25[49]	0.06[61]	68 (60—79[112]	71 (66—82)	0.3
SpO_2 (%)	97 (95—99)[65]	96 (95—99)	92 (89—95)	≤ 0.0001[a]	0.09[49]	−0.15[61]	97 (95—99)[112]	93 (90—95)	≤ 0.0001[a]
O_2 (L/min)	0 (0—0)[65]	2 (1—3)	15 (7—15)	≤ 0.0001[a]	−0.02[49]	0.06	0 (0—2)	15 (1—15)	≤ 0.0001[a]
SpO_2/FiO_2	460 (450—470)[66]	350 (320—390)	140 (140—230)	≤ 0.0001[a]	0.08[49]	−0.07[61]	450 (350—460)[112]	150 (140—390)	≤ 0.0001[a]

(*Continued*)

	Oxygen need at the time of echocardiography				Correlation (rho)		Vital status at day 30 of admission for COVID-19		
	Ambient air ($n = 67$)	O^2 0.5–4.5 L/min ($n = 44$)	$O^2 \geq 5$ L/min ($n = 16$)	Unadjusted *P*	Renin ($n = 50$)	Aldo ($n = 62$)	Alive ($n = 114$)	Dead ($n = 13$)	Unadjusted *P*
Respiratory rate (breaths/min)	20 (18–24)[62]	24 (20–26)	28 (24–31)	≤ 0.0001[a]	0.02[49]	0.00[61]	22 (18–24)[110]	25 (20–30)[12]	0.1
Diuretic use within 48 hours	11 (16)	9 (20)	3 (19)	0.86	0.20	0.01	21 (18)	2 (15)	1
RAAS blocker use within 48 hours	20 (30)	12 (27)	2 (12)	0.37	0.41[a]	−0.01	31 (27)	3 (23)	1
Biological variables at closest time to echocardiography[b]									
NT-proBNP (μg/L)	0.3 (0.1–0.7)[60]	0.4 (0.1–1.1)[40]	3.2 (2.1–13)[15]	≤ 0.0001[a]	0.31	−0.10	0.3 (0.1–0.9)[103]	4 (1.6–15)[12]	0.0003[a]
NT-proBNP > 0.45 μg/L < 50 years; > 0.9 μg/L 50–75 years; > 1.8 μg/L > 75 years	12 (20)[59]	11 (28)[40]	11 (73)[15]	0.0003[a]	0.40[a]	−0.10	26 (25)[102]	8 (67)	0.009
Troponin T (ng/L)	14 (7–33)[60]	18 (9–29)[41]	44 (22–95)	0.003[a]	0.45[a]	0.05	15 (8–29)[105]	78 (40–100)[12]	0.0002[a]
Troponin T > 14 ng/L	29 (48)[60]	24 (59)[41]	16 (100)	0.0009[a]	0.34	0.02	58 (55)[105]	11 (92)[12]	0.04
CRP (mg/L)	23 (7–64)	79 (45–120)	100 (57–150)	≤ 0.0001[a]	−0.03	−0.01	49 (14–87)	130 (64–280)	0.0002[a]
CRP > 5 mg/L	54 (81)	43 (98)	16 (100)	0.006[a]	0.04	−0.08	100 (88)	13 (100)	0.38
Lymphocyte count ($\times 10^9$/L)	1.2 (0.8–1.6)	0.9 (0.7–1.3)	0.7 (0.5–1.0)	0.01	−0.13	−0.02	1.1 (0.8–1.5)	0.6 (0.4–0.8)	0.0006[a]
Lymphocyte count < 1.5 × 10^9/L	47 (70)	37 (84)	15 (94)	0.06	−0.05	0.00	86 (75)	13 (100)	0.10

(*Continued*)

	Oxygen need at the time of echocardiography				Correlation (rho)		Vital status at day 30 of admission for COVID-19		
	Ambient air	O^2 0.5—4.5 L/min	$O^2 \geq 5$ L/min	Unadjusted *P*	Renin	Aldo	Alive	Dead	Unadjusted *P*
	(*n* = 67)	(*n* = 44)	(*n* = 16)		(*n* = 50)	(*n* = 62)	(*n* = 114)	(*n* = 13)	
D-dimers (μg/mL)	0.7 (0.5—1.6)[38]	0.8 (0.6—1.1)[25]	1.5 (1.1—1.6)[6]	0.24	0.02[48]	−0.09[58]	0.9 (0.6—1.6)[65]	1 (0.5—1.6)[4]	0.94
D-dimers > 0.5 μg/mL	28 (74)[38]	22 (88)[25]	6 (100)[6]	0.17	0.15[48]	−0.03[58]	53 (82)[65]	3 (75)[4]	1
Renin (pg/mL)	9.4 (5.3—14)[28]	5.5 (1—18)[17]	19 (7.3—41)[7]	0.32	NA	NA	8.7 (3.4—16)[47]	19 (13—130)[3]	0.23
Aldosterone (pg/mL)	29 (18—39)[35]	31 (14—67)[20]	43 (19—84)[7]	0.66	NA	NA	29 (17—43)[57]	98 (71—110)[5]	0.002[a]
ACE-2 (pg/mL)	1.8 (1.4—2.8)[23]	1.5 (0.9—3.4)[11]	1.4 (1.3—1.5)[2]	0.42	0.08[30]	0.23[36]	1.7 (1.3—3.1)[35]	1.6 (1.6—1.6)[1]	0.89
Creatinine clearance (mL/min/m^2)	79 (63—96)	74 (56—88)	100 (80—150)	0.02	0.37	−0.08	76 (61—94)	110 (82—160)	0.01[a]
Creatinine clearance < 60 mL/min/m^2	14 (21)	13 (30)	2 (12)	0.33	−0.32	−0.12	28 (25)	1 (8)	0.31
Echocardiographic findings									
LVEF (%)	63 (59—68)	64 (62—68)	59 (58—70)	0.23	−0.13	0.00	63 (60—69)	58 (55—63)	0.03
LVEF < 52% males; < 54% females	7 (10)	0 (0)	1 (6.2)	0.09	0.32	0.00	7 (6.1)	1 (7.7)	1
LV strain (−%)	17 (14—19)[60]	18 (14—20)[36]	16 (16—20)[9]	0.74	−0.49[a][38]	0.10[48]	18 (14—20)	16 (16—20)[9]	0.96
LV strain below—20%	49 (82)[60]	26 (72)[36]	6 (67)[9]	0.42	0.16[38]	−0.04[48]	75 (78)[96]	6 (67)[9]	0.71
LVIDd (mm/m^2)	27 (24—29)	26 (24—29)	28 (24—30)	0.89	0.27	−0.22	27 (24—29)	27 (25—29)	0.26
LVIDd > 30 mm/m^2 males; > 31 mm/m^2 females	9 (13)	7 (16)	2 (12)	0.92	0.23	−0.02	16 (14)	2 (15)	1
LV mass (g/m^2)	88 (72—100)	80 (64—110)	88 (77—100)	0.77	0.18	−0.13	84 (70—100)	95 (88—110)	0.26
LV mass > 115 g/m^2 males; > 95 g/m^2 females	20 (30)	10 (23)	2 (12)	0.32	0.07	−0.17	29 (25)	3 (23)	1

(*Continued*)

	Oxygen need at the time of echocardiography				Correlation (rho)		Vital status at day 30 of admission for COVID-19		
	Ambient air	O^2 0.5—4.5 L/min	$O^2 \geq 5$ L/min	Unadjusted *P*	Renin	Aldo	Alive	Dead	Unadjusted *P*
	(*n* = 67)	(*n* = 44)	(*n* = 16)		(*n* = 50)	(*n* = 62)	(*n* = 114)	(*n* = 13)	
LV RWT	0.4 (0.35—0.43)	0.4 (0.36—0.42)	0.42 (0.4—0.47)	0.02	−0.10	0.31	0.4 (0.36—0.43)	0.42 (0.4—0.44)	0.05
LV RWT > 0.42	19 (28)	9 (20)	7 (44)	0.20	−0.03	0.31	30 (26)	5 (38)	0.55
E (m/s)	63 (54—74)	64 (54—78)	62 (48—69)	0.66	−0.04	−0.15	63 (55—77)	54 (42—68)	0.1
E/A ratio	0.8 (0.7—1.1)[57]	0.8 (0.7—0.9)[40]	0.7 (0.6—0.8)[12]	0.13	−0.15[44]	−0.12[54]	0.8 (0.7—1)[98]	0.7 (0.6—0.8)[11]	0.32
Septal e' (cm/s)	6.6 (5—9)[65]	7 (5—8)[43]	5.5 (4.5—5.8)	0.10	−0.16	−0.16	6 (5—8)[111]	5.6 (5—7)	0.52
Septal e' < 7 cm/s	33 (51)[65]	21 (49)[43]	13 (81)	0.06	0.20	0.15	60 (54)	7 (54)	1
Lateral e' (cm/s)	8 (7—11)[65]	8.5(7—10)	8.2(5.9—9)	0.47	−0.16	−0.13	8.3 (7—10)[112]	8.5 (7—9)	0.44
Lateral e' < 10 cm/s	41 (63)[65]	29 (66)	13 (81)	0.39	0.09	0.18	72 (64)[112]	11 (85)	0.25
E/e' (average septal/medial)	8.4 (6.8—11)[64]	8.9 (7.2—11)[42]	9.4 (7.9—11)	0.79	0.10[49]	−0.09[61]	8.7 (6.9—11)[109]	8.6 (5.7—10)	0.49
E/e' > 14 (average septal/medial)	7 (11)[64]	5 (12)[42]	2 (12)	0.98	0.20[49]	0.06[61]	13 (12)[109]	1 (7.7)	1
Left atrial volume (mL/m^2)	33 (23—45)	32 (26—41)[43]	33 (24—49)	0.81	0.13[49]	−0.06[61]	32 (24—44)[113]	35 (28—51)	0.25
Left atrial volume > 34 mL/m^2	29 (43)	18 (42)[43]	7 (44)	0.99	0.32[49]	−0.06[61]	46 (41)	8 (62)	0.25
Peak TR velocity (m/s)	2.3 (2.2—2.6)[58]	2.4 (2.2—2.5)[33]	2.7 (2.4—3)[15]	0.04	0.02	0.07[53]	2.4 (2.2—2.6)[95]	2.5 (2.3—2.7)[11]	0.33
Peak TR velocity > 2.8 m/s	7 (12)[58]	5 (15)[33]	5 (33)[15]	0.13	0.08	0.13[53]	15 (16)[95]	2 (18)[11]	1
Normal LV filling pressure[4]	57 (88)[65]	39 (91)[43]	13 (81)	0.61	0.17[49]	0.06[61]	97 (87)[111]	12 (92)	0.95

(*Continued*)

	Oxygen need at the time of echocardiography				Correlation (rho)		Vital status at day 30 of admission for COVID-19		
	Ambient air ($n = 67$)	O^2 0.5—4.5 L/min ($n = 44$)	$O^2 \geq 5$ L/min ($n = 16$)	Unadjusted *P*	Renin ($n = 50$)	Aldo ($n = 62$)	Alive ($n = 114$)	Dead ($n = 13$)	Unadjusted *P*
RV basal diameter (mm)	30 (27—34)[64]	28 (27—30)[40]	30 (27—33)[13]	0.15	0.09[49]	−0.18[61]	30 (27—33)[105]	28 (27—30)[12]	0.21
RVED/LVED	0.76 (0.73—0.83)	0.78 (0.71—0.82)[42]	0.78 (0.74—0.82)[15]	0.92	0.21[48]	0.02[60]	0.77 (0.72—0.82)[112]	0.8 (0.78—0.84)[12]	0.14
RV dilatation with RV basal diameter > 41 mm or RVED/LVED > 1	3 (4.5)	2 (4.5)	3 (19)	0.09	0.17	−0.06	7 (6.1)	1 (7.7)	1
TAPSE (mm)	22 (19—24)[64]	21 (20—23)[43]	18 (15—22)	0.05	−0.12	−0.14[61]	22 (19—24)[111]	18 (15—20)[12]	0.01[a]
TAPSE < 17 mm	8 (12)[64]	4 (9.3)[43]	5 (31)	0.09	0.06	−0.17[61]	13 (12)[111]	4 (33)[12]	0.1
Tricuspid s' (cm/s)	11 (10—13)	12 (10—13)	11 (7—12)	0.24	0.02	−0.17	12 (10—13)	10 (7—12)	0.07
Tricuspid s' < 9.5 cm/s	11 (16)	5 (11)	6 (38)	0.06	0.08	0.23	16 (14)	6 (46)	0.01[a]
Pericardial effusion	23 (34)	14 (32)	5 (31)	0.95	−0.06	0.11	38 (33)	4 (31)	1

(*Continued*)

	Oxygen need at the time of echocardiography				Correlation (rho)		Vital status at day 30 of admission for COVID-19		
	Ambient air	O^2 0.5—4.5 L/min	$O^2 \geq 5$ L/min	Unadjusted *P*	Renin	Aldo	Alive	Dead	Unadjusted *P*
	(*n* = 67)	(*n* = 44)	(*n* = 16)		(*n* = 50)	(*n* = 62)	(*n* = 114)	(*n* = 13)	
Pericardial effusion ≥ 10 mm	3 (4.5)	1 (2.3)	1 (6.2)	0.74	0.33	0.07	4 (3.5)	1 (7.7)	1
Thoracic scanner findings at closest time to echocardiography[c]									
Proportion of lung parenchyma affected[d]	2 (1—2.5)[51]	3 (2—4)[37]	2 (1—4)[13]	0.002[a]	0.11[44]	0.12[56]	2 (1—3)[91]	2.5 (1—3.8)[10]	0.71
Pulmonary artery diameter (mm)	26 (25—29)[51]	26 (25—28)[37]	26 (25—30)[13]	0.40	−0.02[44]	0.05[56]	26 (25—29)[91]	26 (25—28)[10]	0.73

Data are expressed as median (interquartile range) or number (%). Quantitative and qualitative variables were compared using Wilcoxon's test (two groups) or the Kruskal-Wallis test (three groups) and the χ^2 test, respectively. Correlations (rho) were performed by Spearman's test. [N] indicates the number of evaluations available, if fewer than the maximum. *P* values were adjusted for multiple testings (Benjamini-Hochberg's method). A: late diastolic transmitral flow velocity; ACE-2: angiotensin-converting enzyme 2; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; E: early diastolic transmitral flow velocity; e': tissue Doppler mitral annular early diastolic velocity; FiO_2: fraction of inspired oxygen ($FiO_2 = 0.21 + 0.03*O_2$ in L/min); LV: left ventricular; LVED: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; LVIDd: left ventricular internal dimension in diastole; NA: not applicable; NT-proBNP: N- terminal prohormone of brain natriuretic peptide; O_2: oxygen; RAAS: renin-angiotensin-aldosterone system; RV: right ventricular; RVED: right ventricular end-diastolic dimension; RWT: relative wall thickness; s': tissue Doppler tricuspid annular systolic velocity; SpO_2: oxygen saturation; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

[a] Adjusted *P* value ≤ 0.05.

[b] The median (interquartile range) times between echocardiography and measurement of circulating concentrations of NT-proBNP, troponin-T, CRP, lymphocytes, D-dimers, renin, aldosterone and ACE-2 and creatinine clearance were 1 (0—1), 1 (0—1), 1 (0—1), 1 (0—1), 1 (0—3), 2 (1—2), 2 (1—2), 2 (1—2) and 2 (1—2) days, respectively.

[c] The median (interquartile range) time between echocardiography and thoracic scan was 3 (2—7) days.

[d] Six levels of lung parenchyma involvement secondary to COVID-19: 0, none; 1, < 10%; 2, 10—25%; 3, 25—50%; 4, 50—75%; 5, > 75%.

ciated with older age ($P \leq 0.01$), tachycardia ($P \leq 0.01$), tachypnoea ($P \leq 0.001$), increased cardiac biomarkers (troponin T [$P \leq 0.01$]; NT-proBNP [$P \leq 0.01$]) and inflammatory biomarkers (CRP [$P \leq 0.0001$]), proportion of lung infiltration on scan ($P \leq 0.01$) and mortality 30 days after hospital admission ($P \leq 0.0001$) (Table 1). Interestingly, echocardiographic surrogates of elevated left ventricular filling pressures or systolic function were not associated with intensity of O_2 requirement or mortality. Thirty-day total mortality (13/127, 10%) was also associated with tachycardia ($P \leq 0.01$), increased cardiac biomarkers (troponin T [$P \leq 0.001$]; NT-proBNP [$P \leq 0.01$]) and inflammatory biomarkers (CRP [$P \leq 0.001$]), lymphopoenia ($P \leq 0.01$), higher plasma creatinine concentration ($P \leq 0.05$), higher aldosterone concentration ($P \leq 0.01$) and right ventricular dysfunction (tricuspid annular plane systolic excursion in M-mode [$P \leq 0.05$]; tissue Doppler tricuspid annular systolic velocity [$P \leq 0.05$]) (Table 1) in univariate analysis. In multivariable analysis, with imputation of missing data (replacement by the mean), only aldosterone concentration ($\beta = 0.8$; $P = 0.01$), $O_2 \geq 5$ L/min ($\beta = 0.5$; $P = 0.05$ versus ambient air), CRP ($\beta = 0.9$; $P = 0.002$) and NT-proBNP ($\beta = 0.5$; $P = 0.01$) remained associated with 30-day mortality. Results were similar for the association between aldosterone concentration and 30-day mortality in the multivariable analysis with non-imputed data ($\beta = 0.73$; $P = 0.03$).

The association between RAAS and echocardiographic cardiac alteration is displayed in Table 1. Renin concentrations were moderately correlated with RAAS blocker intake within 24 hours ($r = 0.41$) and surrogate of volume overload, including increased NT-proBNP ($r = 0.4$) and, more marginally, left atrial volume ($r = 0.32$) and pericardial effusions ($r = 0.33$), but not 30-day mortality or severity of O_2 requirement (Table 1). Aldosterone concentrations were only associated with 30-day mortality, but not with any other echocardiographic or biological variables.

Our results show that right ventricular dysfunction in COVID-19 is independent of RAAS pathway alterations. Circulating aldosterone concentrations emerged as a potential novel predictor of COVID-19 mortality after adjustment for echocardiographic findings, cardiac biomarkers, systemic inflammation and extension of pulmonary lesions. Further prospective large-scale studies are needed to further confirm this exploratory result, and to evaluate any therapeutic potential for drugs that alter aldosterone pathways in COVID-19. Indeed, the main limitations of our study were the relatively limited sample size and the fact that aldosterone could only be evaluated in a subset of it.

Funding

None.

Acknowledgments

We thank Pr Xavier Girerd for his help in reviewing this manuscript.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Chung MK, Zidar DA, Bristow MR, et al. COVID-19 and cardiovascular disease: from bench to bedside. Circ Res 2021;128:1214—36.
[2] Lavie CJ, Sanchis-Gomar F, Lippi G. Cardiac injury in COVID-19-echoing prognostication. J Am Coll Cardiol 2020;76:2056—9.
[3] Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020;382:2431—40.
[4] Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277—314.
[5] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:14.
[6] Salem JE, Laveau F, Ceccaldi A, et al. Impact of negative inotropic drugs on accuracy of diastolic stress echocardiography for evaluation of left ventricular filling pressure. Sci Rep 2017;7:9537.
[7] Salem JE, Nguyen LS, Hammoudi N, et al. Complex association of sex hormones on left ventricular systolic function: insight into sexual dimorphism. J Am Soc Echocardiogr 2018;31:231—40.

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Received 17 September 2021;
accepted 18 November 2021
Available online 2 February 2022

https://doi.org/10.1016/j.acvd.2021.11.006