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Clinical Research Article

Primary Aldosteronism and COVID-19-related Management, Disease Severity, and Outcomes: A Retrospective Cohort Study

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Abstract

Context: The SARS-CoV-2 virus is dependent on components of the renin-angiotensin-aldosterone system for infectivity. Primary aldosteronism (PA) is a form of secondary hypertension mediated by autonomous aldosterone production. The intersection of COVID-19 and PA, both which may involve components of the renin-angiotensin-aldosterone system, remains unknown.

Methods: We assessed PA as a risk factor for COVID-19 infection and compared management, severity of disease, and outcomes during COVID-19 with a matched population of patients with essential hypertension (EH) by conducting a retrospective observational cohort study.

Results: Of the patients with PA, 81 had a negative PCR test for COVID-19, whereas 43 had a documented positive PCR test for COVID-19. Those patients with PA who tested positive for COVID-19 tended to be female ($P = .08$) and the majority of those with COVID-19 infection identified as non-White race ($P = .02$) and Hispanic ethnicity ($P = .02$). In a subanalysis, 24-hour urine aldosterone on initial PA diagnosis tended to be higher those in the PA group who developed COVID-19 compared with those in the PA group who did not develop COVID-19 [median (interquartile range): 36.5 (16.9, 54.3) vs 22.0 (15.8, 26.8) mcg, $P = .049$] and was an independent predictor of COVID-19 infection controlling for sex, race, and ethnicity. Angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, and mineralocorticoid receptor antagonist use did not differ between those patients with PA who did and did not have COVID-19 infection. Comparing those patients with PA and matched patients with EH (n = 286) who were COVID-19 PCR positive, there was a significantly higher incidence of cardiovascular complications (12 vs 2%, $P = .004$) in the PA vs EH group.

Conclusion: These data begin to inform us as to whether PA should be a newly identified subpopulation at risk for COVID-19-related cardiovascular disease sequelae.

Key Words: primary aldosteronism, COVID-19, SARS-CoV-2, renin-angiotensin-aldosterone system, essential hypertension

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACEi, angiotensin-converting enzyme inhibitor; CAD, coronary artery disease; CV, cardiovascular; CVA, cerebrovascular accident; EH, essential hypertension; EHR, electronic health record; ICD, International Classification of Diseases; ICU, intensive care unit; MGB, Mass General Brigham; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; RAAS, renin-angiotensin-aldosterone system; RPDR, Research Patient Data Registry.

COVID-19, an infection caused by SARS-CoV-2, has significantly affected a large proportion of the world's population, resulting in an ongoing global pandemic. A large meta-analysis of 42 studies demonstrated that chronic medical conditions, including lung disease, obesity, diabetes, and cancer, place individuals at a higher risk of mortality because of COVID-19 infection [1–3]. In addition, there is literature to suggest that hypertension should be included as a medical condition with associated risk for COVID-19 [4–6].

Hypertension is classified into essential (primary) or secondary causes. Primary aldosteronism (PA) is a type of secondary hypertension resulting from autonomous production of excess aldosterone usually caused by bilateral adrenal hyperplasia or an aldosterone-producing adenoma [7]. Detection of PA as the underlying cause of hypertension is clinically relevant as those with PA have higher rates of cardiovascular (CV) complications compared with those with essential hypertension (EH) [8–11].

COVID-19 and PA have known associations with a key hormonal axis, the renin-angiotensin-aldosterone system (RAAS), and are linked to increased CV morbidity and mortality [12]. SARS-CoV-2 enters the host cell via the angiotensin-converting enzyme 2 (ACE2) receptor, and internalization of the ACE2 receptor decreases availability of soluble ACE2. Circulating ACE2 works along the RAAS pathway to cleave angiotensin I into angiotensin (1-9) and angiotensin II into angiotensin (1-7), thereby shunting substrates away from angiotensin II and aldosterone production. It could be postulated that a relative ACE2 deficiency subsequently leads to an increase in aldosterone [13]. Taken together, excess aldosterone may conceivably have vasoconstrictive, hypertrophic, and fibrotic effects that drive CV complications

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in both COVID-19 and PA. In this regard, little is known about PA coupled with COVID-19 and whether there may be neutral or enhanced CV risk because of interactions with the RAAS as well as pro-inflammatory pathways.

In the Primary Aldosteronism and COVID-19-related Management, Disease Severity and Outcomes/COVID-19 study, we sought to (1) understand clinical demographics and characteristics among patients with PA with and without COVID-19 and (2) compare COVID-19-related management, disease severity, and complications among patients with PA vs EH and COVID-19 through a retrospective chart review to better understand the clinical relationship between COVID-19 and PA. Given that both COVID-19 and PA are commonly linked by their association with RAAS dysregulation, which could have important CV implications, we hypothesized that patients with PA would have a worse COVID-19 disease presentation and more clinical complications when compared with patients with EH, though there could be neutral effects because of the known autonomy of the RAAS in PA.

Methods

Query for Patients With PA and With and Without COVID-19

The Research Patient Data Registry (RPDR) is a centralized clinical data registry for Mass General Brigham (MGB), the largest academic hospital system in the greater Boston area. In October 2021, we identified the electronic health records (EHRs) of patients aged 18 to 84 years with an International Classification of Diseases (ICD) code for PA and a COVID-19 PCR test. COVID-19 PCR tests were obtained for all those who had a documented test in the MGB RPDR. Two separate queries were performed: one for those with PA and a positive COVID-19 PCR test and one for those with PA and a negative COVID-19 PCR test. COVID-19 PCR testing was identified from October 2021 retrospectively to March 2020 (Fig. 1A). This search yielded a total of 308 patients with COVID-19 PCR tests: 72 with a positive COVID-19 PCR test and 236 with a negative COVID-19 PCR test in the EHR (Fig. 2A). We confirmed that those with a negative COVID-19 PCR test had no known positive COVID-19 PCR result in the EHR. If patients had multiple positive COVID-19 PCRs tests, the first encounter was used in the analysis.

A diagnosis of PA was confirmed either through biochemical confirmation on chart review or in cases in which laboratory data were not available through the EHR, documentation by a provider confirming a medical history of PA was required (Table 1). In a few cases in which incomplete laboratory data were available and biochemical confirmation could not be confirmed, the diagnosis was made based on documentation in the EHR by a specialist. The diagnosis of PA was obtained before COVID-19 infection. Biochemical evaluation followed published guidelines by the Endocrine Society, which recommends screening for an increased aldosterone to renin ratio [14]. A paired plasma aldosterone concentration (PAC) of $\geq$10 ng/dL and plasma renin activity of <1.0 ng/mL/h were required. If all the following criteria were met: PAC > 20 ng/dL, plasma renin activity (PRA) suppressed, and spontaneous hypokalemia, then no further confirmation was necessary. Otherwise, the diagnosis was confirmed by looking for a confirmatory oral salt loading test or saline suppression test. A diagnosis of PA was made if the urine sodium was >200 mEq/24 h and the urine aldosterone was >12 mcg/24 h following an oral salt loading test. For the saline suppression test, a diagnosis of PA was made if the PAC was >10 ng/dL [15]. Of the 72 patients with PA with a positive COVID-19 PCR test, 28 were excluded who did not meet criteria for PA and 1 was excluded because the EHR was unable to be accessed. Of the 236 patients with PA with a COVID-19-negative test, 141 were excluded who did not meet the criteria for PA and 14 were excluded whose EHR were unable to be accessed. Ultimately, we identified 43 patients with PA with COVID-19 and 81 patients with PA without COVID-19.

Query for Matched Patients With EH

After the completion of the PA query, we identified a population of patients who both had an ICD code for EH and a positive COVID-19 PCR test using the RPDR in January 2022. Only those patients for whom the ICD code for EH was recorded >9 times in the medical record were included. COVID-19 PCR testing was identified from January 2022 retrospectively to March 2020 (Fig. 1B). Patients with EH were then matched 3:1 (accounting for the entire cohort of patients with PA) using the following 3 criteria permitted through the RPDR: age ($\pm$10 years), race/ethnicity, and sex. A diagnosis of EH was confirmed by chart review and hypertension attributed to secondary causes were excluded. A total of 314 matches was found; 1 was excluded because of a documented false-positive COVID-19 PCR test. Of the remaining 313 patients, 27 were excluded who did not have a confirmed diagnosis of EH (4 had no known EH at the time of COVID-19 diagnosis and 23 were characterized as secondary hypertension or non-EH). This resulted in 286 patients with EH with a positive COVID-19 PCR test (Figure 2B).

Data Collection

Two independent reviewers conducted a formal review to assess for eligibility. Each EHR was reviewed by a single investigator using standardized criteria. Approximately 20% of charts were rereviewed by the other investigator to ensure uniformity in chart extraction. A database was established for standardized data collection. This study was approved by the MGB Human Research Committee.

Outcomes

Sex, race, and ethnicity were obtained from the EHR based on self-report. For the COVID-19 PCR-negative group, the most recent data were extracted at the time of chart inspection. For the COVID-19 PCR-positive group, comorbidities and risk factors relating to medical history were reported as noted before the COVID-19 PCR test based on a confirmed ICD code or documentation in clinical notes on review by the investigators. Current outpatient medication use was extracted at the time of the most recent COVID-19 PCR test.

For those with a positive COVID-19 PCR test, information pertaining to symptomatology, management, and outcomes of COVID-19 infection, as well as biochemistry, were obtained during the acute COVID-19 encounter that was associated with the positive COVID-19 PCR test (which could have occurred between March 2020 and October 2021 for patients with PA and between March 2020 and January 2022 for patients with EH). Telemedicine visits instituted during the

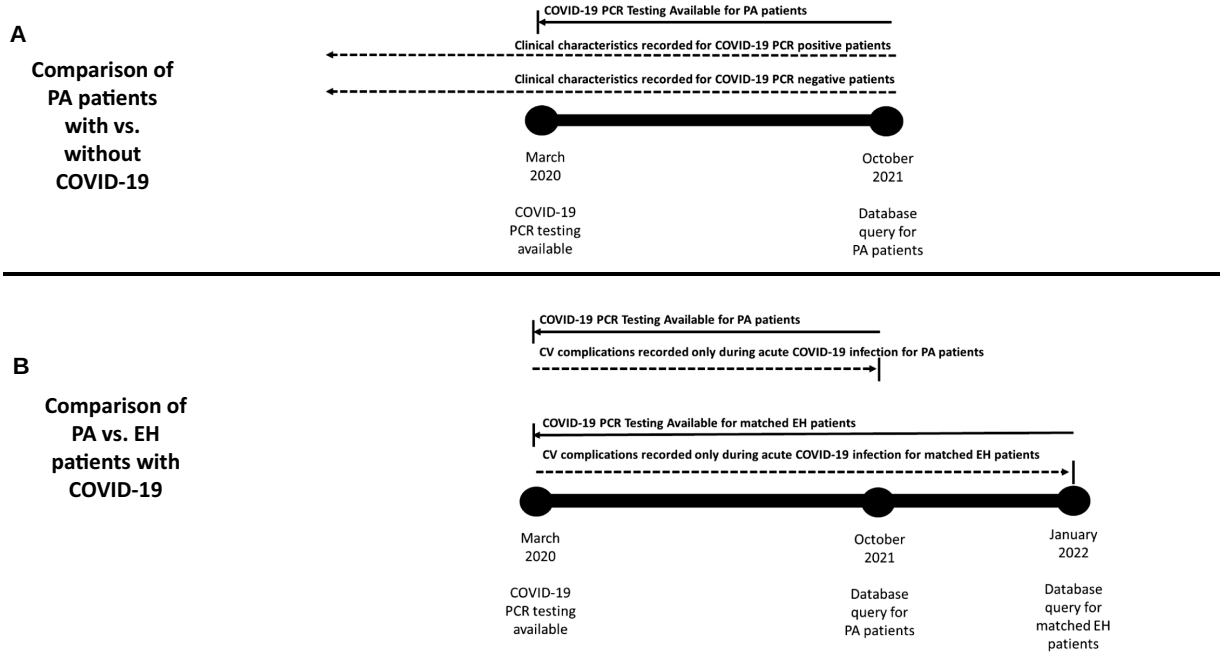

Figure 1. Timeline of queries and evaluation for primary aldosteronism and essential hypertension patients. (A) For the initial evaluation comparing primary aldosteronism (PA) patients with vs without COVID-19, the query was performed in October 2021. The COVID-19 PCR testing result was identified between March 2020 and October 2021 for patients with PA. Clinical characteristics were extracted at the time of chart inspection before October 2021. (B) For the second evaluation comparing patients with PA with those with essential hypertension (EH) with COVID-19, the query for matched EH patients was performed in January 2022. The COVID-19 PCR test result was identified between March 2020 and January 2022 for patients with PA. CV complications were obtained during the acute COVID-19 encounter that was associated with the positive COVID-19 PCR test (which could have occurred between March 2020 and October 2021 for patients with PA and between March 2020 and January 2022 for patients with EH). Abbreviation: CV, cardiovascular.

pandemic were useful to permit continued access to care [16]. If a virtual encounter was conducted through the MGB system, any ordered COVID-19 PCR testing would have been captured in the EHR.

The COVID-19 encounter was considered outpatient if the patient did not seek care through the emergency department, urgent care, or have a documented hospital admission. The highest level of encounter was recorded for patients who accessed more than 1 level of care. Baseline biochemistry was extracted from the most recent data within 12 months before a positive COVID-19 PCR test. Data related to hospitalization were only reported for those with an inpatient encounter. Medical therapy was reported for all COVID-19 encounters. CV complications (encompassing acute coronary syndrome, acute heart failure, arrhythmia, myocarditis, or cerebrovascular accident) and deaths were recorded only if attributed to COVID-19 infection. CV events were attributed to COVID-19 if they occurred as an acute event in relation to the positive COVID-19 PCR test and if there was no more likely secondary cause unrelated to COVID-19 through documentation in the medical chart by a provider. Diagnostic abnormalities were recorded for acute findings. Laboratory parameters during the acute COVID-19 encounter were documented as initial values. Hemoglobin A1c following the acute COVID-19 infection was recorded as the first value taken within 12 months of the positive COVID-19 PCR test.

Statistical Analysis

Data are reported as mean ± SD for normally distributed variables and median (interquartile range) for variables that were not normally distributed. Normality was determined after applying the Shapiro-Wilk test. Categorical variables were reported as the number of patients and percentages. Comparisons between groups were assessed using the Student *t* test or Wilcoxon rank sums test for normal and nonnormally distributed variables, respectively. Analyses are reported for data available. Continuous variables for which more than 10% of observations were missing are indicated. A P value $< .05$ was considered statistically significant. Analyses were performed using JMP version 16.

Results

Comparison of Demographics, Risk Factors, and Diagnostics Among Patients With PA and With and Without COVID-19

From the initial search, 124 patients met criteria for PA and had COVID-19 PCR testing available between March 2020 and January 2022. Of this group, 81 (65%) had a negative PCR test for COVID-19, whereas 43 (35%) patients had a documented positive PCR test for COVID-19. Almost all patients had a suppressed PRA documented. In the few cases in which the PRA was not suppressed, a diagnosis was obtained through documentation by a specialist. Serum aldosterone and potassium were not significantly different between the 2 groups. The 24-hour urine aldosterone tended to be higher in those in the PA group who developed COVID-19 compared with those in the PA group who did not develop COVID-19 [median (interquartile range): 36.5 (16.9, 54.3) vs 22.0 (15.8, 26.8) mcg, $P = .049$]. There was no difference between the groups in terms of nodule(s) present on imaging and the subtype of PA as confirmed by adrenal vein sampling (unilateral, bilateral, or inconclusive) (Table 1).

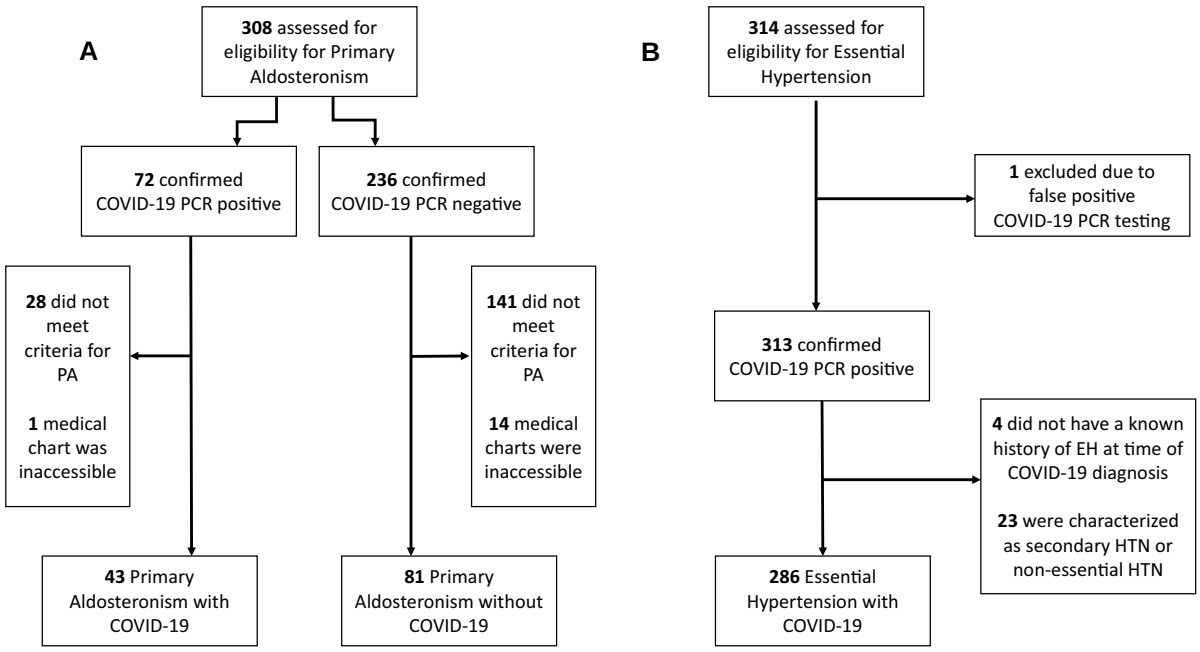

Figure 2. Flow chart of the participants in the study. The Research Patient Data Registry, a centralized clinical data registry for Mass General Brigham, was leveraged to obtain a primary aldosteronism cohort and an essential hypertension cohort. (A) The initial search for electronic health records (EHR) of patients with an International Classification of Diseases (ICD) code for primary aldosteronism (PA) and a COVID-19 PCR test yielded a total of 308 patients. This cohort was divided into those with a positive COVID-19 PCR test and those without a positive COVID-19 PCR test. A diagnosis of PA was confirmed by chart review using standardized diagnostic criteria. Overall, there were 43 patients with PA and a positive COVID-19 PCR test and 81 patients with PA and a negative COVID-19 PCR test used in the analysis. (B) After the completion of the PA evaluation, a search was performed for a cohort of patients who both had an ICD code for essential hypertension (EH) and a positive COVID-19 PCR test. The EH cohort was matched 3:1 (accounting for the entire cohort of patients with PA) using the following 3 criteria: age (±10 years), race/ethnicity, and sex. A diagnosis of EH was confirmed by chart review, and hypertension attributed to secondary causes were excluded. Overall, there were 286 matched patients with EH and a positive COVID-19 PCR test used in the analyses. Abbreviation: HTN, hypertension.

Table 1. Initial diagnostic evaluation of patients with primary aldosteronism with and without COVID-19

	Primary aldosteronism without COVID-19, N = 81	Primary aldosteronism with COVID-19, N = 43	Overall *P* value
Initial Diagnostic Evaluation			
Diagnosis PA, n (%)			.37
Confirmation by medical history	25 (31)	10 (23)	
Confirmation by biochemistry	56 (69)	33 (77)	
PRA <1.0 ng/mL/h, n (%)	76 (96)	41 (98)	.67
Aldosterone, ng/dL	24.0 (13.3, 32.0)	24.7 (16.0, 32.3)	.78
Potassium, mmol/L	3.4 ± 0.5	3.3 ± 0.4	.77
Underwent oral sodium loading or IV saline infusion for confirmatory sodium suppression test, n (%)	36 (46)	24 (57)	.22
24-h urine aldosterone test, mcg/24 h[a,b]	22.0 (15.8, 26.8)	36.5 (16.9, 54.3)	.049
Nodule(s) present on imaging, n (%)	48 (61)	22 (54)	.46
Underwent AVS, n (%)	24 (30)	11 (26)	.60
Subtype PA confirmed by AVS			.45
Unilateral, n (%)	23 (28.5)	8 (19)	
Bilateral, n (%)	35 (43)	20 (46)	
Inconclusive, n (%)	23 (28.5)	15 (35)	

Categorical variables were reported as the number of patients and percentages, normally distributed reported as mean ± SD, and nonnormally distributed variables are reported as median (interquartile range).
Abbreviations: AVS, adrenal vein sampling; PA, primary aldosteronism; PRA, plasma renin activity.
[a]Reported for data that was available, continuous variables for which >10% of values were missing are indicated.
[b]1 patient was removed from the analysis after it was determined the value was an outlier using the Tukey method.

Those who tested positive for COVID-19 tended to be female compared with those who did not test positive for COVID-19 (53 vs 37%, $P = .08$). Both groups were older and of similar age. Regarding race, the majority of patients with PA and without COVID-19 identified as White, and the majority of patients with PA and COVID-19 identified

Table 2. Baseline demographics and characteristics of patients with primary aldosteronism with and without COVID-19

	Primary aldosteronism without COVID-19, N = 81	Primary aldosteronism with COVID-19, N = 43	Overall *P* value
Demographics			
Male, n (%)	51 (63)	20 (47)	.08
Age, y	65 (55, 73)	62 (56, 72)	.61
Race, n (%)			.02
Asian	3 (4)	0 (0)	
White	44 (59)	16 (41)	
Black	22 (30)	14 (36)	
More than one race	2 (3)	1 (3)	
Other	3 (4)	8 (20)	
Ethnicity, n (%)			.02
Hispanic	10 (13)	13 (32)	
Not Hispanic	68 (87)	28 (68)	
Metabolic risk factors			
History of CAD, n (%)	22 (27)	8(19)	.28
History of CHF, n (%)	11 (14)	7(16)	.69
History of CVA, n (%)	15 (19)	6(14)	.51
History of arrhythmia, n (%)	12 (15)	6(14)	.90
History of diabetes, n (%)	33 (41)	14(33)	.37
History of asthma, n (%)	12 (15)	7(16)	.83
History of COPD, n (%)	4 (5)	4(9)	.36
BMI, kg/m^2	30.4 (27.4, 35.0)	30.7 (26.7, 34.6)	.63
Presence of obesity, n (%)	45 (56)	25 (58)	.78
Current aspirin use, n (%)	32 (40)	14 (33)	.44
Current statin use, n (%)	56 (69)	24 (56)	.14
Treatment regimens			
Postsurgical, n (%)	20 (25)	9 (21)	.64
On medical therapy, n (%)	65 (80)	37 (86)	.41
Current MRA use, n (%)	44 (54)	25 (58)	.68
Current ACEi use, n (%)	22 (27)	9 (21)	.44
Current ARB use, n (%)	15 (19)	9 (21)	.75

Categorical variables were reported as the number of patients and percentages, normally distributed reported as mean ± SD, and nonnormally distributed variables are reported as median (interquartile range).
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism.

as non-White ($P = .02$). Relatively more patients were of Hispanic ethnicity among those patients with PA and with COVID-19 vs those without COVID-19 (32 vs 13%, $P = .02$). (Table 2)

Risk factors including history of coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular accident (CVA), arrhythmia, diabetes, asthma, and chronic obstructive pulmonary disease (COPD) did not differ between the two groups. Prevalence of obesity was similar between both groups; it was present in more than approximately one-half of patients (Table 2).

Both groups were similarly managed for PA with surgical or medical treatments. For those who were receiving medical treatment, mineralocorticoid receptor antagonists (MRAs) (58 vs 54%), angiotensin-converting enzyme inhibitors (ACEi) (21 vs 27%), and angiotensin II receptor blockers (21 vs 19%) use was similar among patients regardless of COVID-19 infection (with vs without COVID-19, all $P = $ NS) (Table 2).

Comparison of Demographics, Risk Factors, and Biochemistry Among Patients With PA vs EH and With COVID-19

Comparing those patients whose COVID-19 PCR was positive, 43 had PA and 286 had EH. A matching algorithm was used, and participants were excluded as outlined in Fig. 1. There was a higher prevalence of female patients with PA and COVID-19 compared with female patients with EH with COVID-19 (53 vs 37%, $P = .047$), and the median age of patients with PA with COVID-19 tended to be lower. Race and ethnicity were not statistically different (Table 3).

Prevalence of other comorbidities (CHF, CVA, diabetes, asthma, COPD, and obesity) was not different between groups. Regarding medication use at the time of COVID-19 encounter, more patients with PA vs EH were on an MRA (58 vs 7%, $P < .0001$), whereas more patients with EH vs PA were on an ACEi (41 vs 21%, $P = .008$). Current aspirin and statin use tended to be higher in the EH group and angiotensin II receptor blocker use was similar between groups (Table 3).

COVID-19-specific Outcomes Among Patients With PA vs EH and With COVID-19

The proportion of individuals vaccinated before their documented COVID-19 PCR-positive test was low and did not differ among PA vs EH groups (13 vs 17%, $P = .58$). The majority of patients were symptomatic in both groups. The duration of COVID-19 symptoms did not differ among EH vs PA groups. More patients with PA were managed through outpatient encounters, whereas more patients with EH were managed through urgent care/emergency department or inpatient encounters ($P = .02$) (Table 4).

Of those patients who were hospitalized, there was a similar prevalence of those who required intensive care unit (ICU) care among the EH vs PA groups. Length of stay on the inpatient ward or in the ICU and specialized management (duration of ventilator use, inotropes, oxygen requirements, and specific COVID-19 therapy) were generally similar among the cohorts (Table 4).

Regarding COVID-19-related complications, there was a significantly higher incidence of cardiovascular complications in the PA group compared with the EH group (12 vs 2%, $P = .004$). Among the patients with PA and with COVID-19 who had a CV complication, 60% required ICU care and 100% had an abnormal chest radiograph. After excluding those patients with PA who underwent adrenalectomy before COVID-19 infection, CV risk remained significantly higher among the patients with PA compared with patients with EH and with COVID-19 (11 vs 2%, $P = .001$). After controlling for aspirin and statin use separately, the increased risk for CV complications remained significant in the PA group. COVID-19-related mortality was low, and the incidence did

Table 3. Demographics, risk factors, and baseline biochemistry of COVID-19 patients among PA vs EH groups

	PA/COVID-19, N = 43	EH/COVID-19, N = 286	Overall *P* value
Demographics			
Male, n (%)	20 (47)	179 (63)	.047
Age, y	62 (56, 72)	67 (58, 75)	.07
Race, n (%)			.25
Asian	0 (0)	2 (0.7)	
White	16 (37)	154 (54)	
Black	14 (33)	63 (22)	
More than one race	1 (2)	1 (0.3)	
Not reported	4 (9)	28 (10)	
Other	8 (19)	38 (13)	
Ethnicity, n (%)			.73
Hispanic	13 (30)	70 (25)	
Not Hispanic	28 (65)	201 (70)	
Not reported	2 (5)	15 (5)	
Metabolic risk factors			
History of CAD, n (%)	8 (19)	89 (31)	.08
History of CHF, n (%)	7 (16)	56 (20)	.60
History of CVA, n (%)	6 (14)	33 (12)	.65
History of arrhythmia, n (%)	6 (14)	72 (25)	.09
History of diabetes, n (%)	14 (33)	129 (45)	.12
History of asthma, n (%)	7 (16)	54 (19)	.68
History of COPD, n (%)	4 (9)	34 (12)	.61
BMI, kg/m^2	30.7 (26.7, 34.6)	30.6 (26.7, 34.6)	.88
Presence of obesity, n (%)	25 (58)	152 (53)	.55
Current aspirin use, n (%)	14 (33)	132 (46)	.09
Current statin use, n (%)	24 (56)	192 (67)	.15
Current MRA use, n (%)	25 (58)	20 (7)	<.0001
Current ACEi use, n (%)	9 (21)	118 (41)	.008
Current ARB use, n (%)	9 (21)	79 (28)	.34
Baseline biochemical parameters			
Total cholesterol, mg/dL[a]	160 (139, 193)	156 (129, 182)	.24
LDL, mg/dL[a]	86 (69, 114)	76 (57, 99)	.11
HDL, mg/dL[a]	52 (37, 60)	48 (40, 57)	.58
Triglycerides, mg/dL[a]	111 (73, 189)	122 (85, 181)	.61
Creatinine, mg/dL[a]	0.98 (0.87, 1.39)	0.98 (0.83, 1.24)	.32
eGFR, mL/min/1.73 m^2[a]	69 (48, 82)	71 (55, 88)	.26
Hba1c, %[a]	5.8 (5.6, 6.8)	6.4 (5.8, 7.6)	.01

Categorical variables were reported as the number of patients and percentages, normally distributed reported as mean ± SD and nonnormally distributed variables are reported as median (interquartile range).
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; EH, essential hypertension; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism.
[a]Reported for data that were available, continuous variables for which >10% of values were missing are indicated.

not differ based on the PA and EH phenotypes (7 vs 5%, *P* = NS) (Table 4).

C-reactive protein level was higher in patients with EH vs PA [median (interquartile range): 67.1 (16.8, 112.3) vs 11.3 (3.7, 84.7) mg/L, *P* = .04]. NT-proBNP tended to be higher in the PA group compared with the EH group [3445 (584, 16084) vs 419 (109, 1049) pg/mL, *P* = .007] (Table 4).

Exploratory Analyses to Evaluate Predictors of COVID-19 Infection and COVID-19-related Complications

We performed a subanalysis among those patients with PA who had 24-hour urine aldosterone collections (n = 43). One patient with PA was removed from the analysis after it was determined the value was an outlier using the Tukey method. A 24-hour urine aldosterone test at the time of PA diagnosis was an independent predictor of those who developed COVID-19 infection and remained an independent predictor after controlling for sex, race, and ethnicity in separate models (Table 5).

Among all those patients who were COVID-19 PCR-positive, those with PA were 7.39 (95% CI, 2.05-26.73; *P* = .002) times more likely to have a COVID-related CV complication when compared with patients with EH. In addition, group status (PA vs EH) remained an independent predictor for developing a CV complication (odds ratio = 15.48; 95% CI, 3.23-74.22; *P* = .0006) during COVID-19 after controlling for NT-proBNP (Table 6).

Discussion

In the current study, we assessed clinical characteristics that differed among patients with PA and with and without COVID-19 and sought to understand how the COVID-19-related disease course may differ among those with PA vs EH by comparing two subtypes of hypertension. In both PA and COVID-19, there may be a role for different components of the RAAS. To our knowledge, no prior studies have evaluated PA in COVID-19. Here, we demonstrate that those with PA were more likely to experience CV complications compared with those with EH during the acute COVID-19 disease course.

In addition to hypertension, individuals with PA are known to have cardiometabolic sequalae [8, 17], including CVD, arterial inflammation, stroke, and diabetes, which are all commonly themed as inflammatory-mediated processes. Excess aldosterone may activate both the innate and adaptive immune system, leading to infiltration of tissues with macrophages and T cells, promoting inflammation, remodeling, and ultimately fibrosis and end-organ damage [18]. Interestingly, those that were susceptible to COVID-19 infection had higher levels of aldosterone on diagnosis of PA when assessed among a limited set of patients who had 24-hour urine aldosterone. Such individuals with a higher aldosterone level may have a relatively greater inflammatory milieu that could make them more susceptible to COVID-19 or, alternatively, these individuals may have had a longer duration of uncontrolled disease before diagnosis. The aldosterone levels were obtained as part of the diagnostic workup for PA, and we were unable to assess aldosterone levels at the time of COVID-19 because aldosterone levels are not routinely evaluated during acute management of COVID-19. When comparing other unique factors that are important to PA, for example, subtype of primary aldosteronism (unilateral vs bilateral

Table 4. COVID-19 second specific parameters among PA vs EH groups

	PA/COVID-19, N = 43	EH/COVID-19, N = 286	Overall *P* value
COVID-19 symptoms			
Completed vaccination series before COVID-19, n (%)	5 (13)	47 (17)	.58
Symptomatic COVID-19, n (%)	41 (95)	253 (91)	.31
Duration of symptoms, d[a]	6 (3, 11)	7 (3, 13)	.13
COVID-19 encounter			
Type of encounter, n (%)			.02
Outpatient	29 (68)	142 (50)	
Urgent care/ED	1 (2)	37 (13)	
Inpatient	13 (30)	107 (37)	
COVID-19 management			
Duration of hospitalization of those admitted during COVID-19 infection, d	8(5, 18)	6(4, 14)	.47
ICU care for COVID-19, n (%)	5 (12)	24 (8)	.50
Duration of ICU care for those admitted to ICU during COVID-19, d	9 (6, 21)	12 (4, 23)	1.00
Inotrope/vasopressor use, n (%)	4 (9)	12 (4)	.19
Acute dialysis, n (%)	0 (0)	3 (1)	.36
Systolic BP at encounter, mm Hg[a]	144 (115, 166)	135 (120, 152)	.51
Diastolic BP at encounter, mm Hg[a]	80 ± 19	76 ± 13	.40
Required oxygen support (maximal), n (%)			.10
None	36 (84)	216 (75)	
Nasal cannula	2 (5)	48 (17)	
Facemask without reservoir	0 (0)	1 (0.5)	
Nonrebreather mask	1 (2)	1 (0.5)	
Noninvasive ventilation	0 (0)	5 (2)	
Invasive ventilation	4(9)	15(5)	
Duration of ventilator support of those requiring ventilation, d	13 (4, 21)	18 (11, 49)	.34
Administered medical therapy COVID-19, n (%)	9 (21)	86 (30)	.21
Type of medical therapy for COVID-19 for those administered medical therapy, n (%)			.70
Dexamethasone IV	1 (11)	3 (3)	
Other glucocorticoids	0 (0)	3 (3)	
Remdesivir	1 (11)	14 (16)	
Monoclonal antibody	2 (22)	18 (21)	
Combination therapy	5 (56)	43 (49)	
Other	0 (0)	7 (8)	
COVID-19 complications			
Cardiovascular complication, n (%)	5 (12)	5 (2)	.004[b]
Pulmonary embolism, n (%)	0 (0)	3 (1)	.36
Newly diagnosed diabetes, n (%)	0 (0)	0 (0)	–
HbA1c after COVID-19, %	5.9 (5.6, 6.7)	6.4 (5.8, 7.4)	.03
Deceased from COVID-19, n (%)	3 (7)	15 (5)	.65
Diagnostics obtained during COVID-19 encounter[c]			
CXR abnormality, n (%)	11 (69)	98 (72)	.82
Acute ECG abnormality, n (%)	4 (27)	33 (33)	.60
TTE abnormality, n (%)			.87
None	5 (62.5)	17 (68)	
RV abnormality	1 (12.5)	4 (16)	
LV abnormality	1 (12.5)	3 (12)	
RV and LV abnormality	1 (12.5)	1 (4)	
Laboratory values obtained during urgent care/ED or inpatient COVID-19 encounter			
WBC, K/μL	6.7 (5.6, 9.2)	6.0 (4.7, 7.9)	.24
LDH, U/L[a]	234 (162, 303)	272 (228, 368)	.06

(*continued*)

Table 4. Continued

	PA/COVID-19, N = 43	EH/COVID-19, N = 286	Overall *P* value
PT, s[a]	14.6 (13.2, 15.1)	14.0 (13.1, 16.0)	.93
INR[a]	1.2 (1.1, 1.2)	1.1 (1.0, 1.3)	.48
Fibrinogen, mg/dL[a]	455 (391, 722)	558 (422, 643)	.57
D dimer, ng/mL[a]	831 (310, 1390)	965 (509, 1733)	.30
CRP, mg/L[a]	11.3 (3.7, 84.7)	67.1 (16.8, 112.3)	.04
hs-TnT, ng/L[a]	27 (11, 78)	19 (11, 41)	.52
NT-proBNP, pg/mL[a]	3445 (584, 16084)	419 (109, 1049)	.007
CPK, U/L[a]	86 (47, 216)	137(76, 295)	.25
Creatinine, mg/dL	1.43 (0.80, 3.15)	1.15 (0.94, 1.63)	.50
eGFR, mL/min/1.73 m^2	49 (20, 79)	57 (40, 79)	.25

Categorical variables were reported as the number of patients and percentages, normally distributed reported as mean ± SD, and nonnormally distributed variables are reported as median (interquartile range).
Abbreviations: ASA, aspirin; BP, blood pressure; CPK, creatine phosphokinase; CRP, C-reactive protein; CXR, chest X-ray; DBP, diastolic blood pressure; ED, emergency department; EH, essential hypertension; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ICU, intensive care unit; INR, international normalized ratio; LDH, lactate dehydrogenase; LV, left ventricle; NT-proBNP, NT-proB-type natriuretic peptide; PA, primary aldosteronism; PT, prothrombin time; RV, right ventricle; SBP, systolic blood pressure; hs-TnT, high sensitivity Troponin T; TTE, transthoracic echocardiogram.
[a]Reported for data that were available, continuous variables for which >10% of values were missing are indicated.
[b]Remains statistically significant after controlling separately for current statin use and current ASA use.
[c]Reported for those who had the indicated imaging procedure.

Table 5. Multivariate model to assess determinants of COVID-19 PCR positive testing among patients with primary aldosteronism

Presence of COVID-19 PCR Positive								
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
	($R^2 = 0.15$; $P = .004$)		($R^2 = 0.22$; $P = .002$)		($R^2 = 0.28$; $P = .0005$)		($R^2 = 0.17$; $P = .008$)	
24-h urine aldosterone[a]	1.07 (1.01-1.13)	0.02	1.08 (1.01-1.14)	0.01	1.06 (1.01-1.12)	0.02	1.07 (1.01-1.13)	.03
Male			0.23 (0.05-1.03)	0.05				
White vs non-White					0.08 (0.01-0.66)	0.02		
Hispanic vs non-Hispanic							2.51 (0.57-11.11)	.22

R^2 represents the coefficient of determination and the proportion of variance explained by the model.
Abbreviation: OR, odds ratio.
[a]1 patient was removed from the analysis after it was determined the value was an outlier using the Tukey method.

disease), management of PA (surgical vs medical therapy), and other comorbidities, we did not see any differences based on COVID-19 infection. We may have expected a difference based on surgical vs medical therapy because data show that those with PA who are surgically managed have reduced cardiovascular events and all-cause mortality compared with those that are medically managed [19–21]. In our study, we were unable to confirm whether adrenalectomy was curative among those were surgically managed.

The RAAS has been a focus of study during the COVID-19 pandemic given the overlapping physiology, and some have suggested that RAAS dysregulation may be linked to the inflammatory storm, organ dysfunction, and worsened outcomes in COVID-19 infection [22]. However, most studies have evaluated ACE2 and angiotensin II levels, and limited studies have evaluated aldosterone. A single-center study showed no change in baseline and follow-up serum aldosterone levels in patients with and without COVID-19 [23]. In contrast, aldosterone levels may be linked to COVID-19 disease severity in smaller studies [24], and higher aldosterone in older patients with COVID-19 has been physiologically linked to immune dysregulation, leading to worsened CV outcomes [25] among studies in groups not specifically identified for PA. In addition, more common factors during a viral infection, such as dehydration and vasodilation, may contribute to RAAS activation need to be taken into account.

Among those with PA and COVID-19 infection, there were more females, fewer of White race, and more of Hispanic ethnicity compared with those without COVID-19 infection. The COVID-19 literature supports an increase in COVID-19 positivity rates in ethnic and racial minority groups, highlighting increased comorbidities, socioeconomic factors, and lack of access to medical care as key determinants of health [1]. These demographics factors are nondisease specific, independent of having PA, and are more generalized characteristics of poor health outcomes. The sex disparity could be in part from estrogen's effects to increase ACE2 levels and activate the immune system [26], which may have additive effects in PA, where there is excess aldosterone. The sex interaction between PA and COVID-19 should be investigated further, as should whether excess activation of the immune system could be a potential mechanism.

Table 6. Multivariate model to assess group status on CV and CVA complications among patients with PA vs EH

Presence of CV complication				
	Model 1		Model 2[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
	($R^2 = 0.09$; $P = .004$)		($R^2 = 0.23$; $P = .0006$)	
PA vs EH	7.39 (2.05-26.73)	.002	15.48 (3.23-74.22)	.0006

R^2 represents the coefficient of determination and the proportion of variance explained by the model.
Abbreviations: CV, cardiovascular; EH, essential hypertension; OR, odds ratio; PA, primary aldosteronism.
[a]Model 2 reported after controlling for NT-proBNP.

There was a greater incidence of CV complications attributed to acute COVID-19 infection among the PA vs EH as we hypothesized. Both groups had similar baseline comorbidities, although more EH patients tended to be older, have a history of CAD and DM, and have aspirin and statin use, suggesting the complications may have occurred regardless of traditional risk factors. Even after controlling for aspirin and statin use, we saw that the patients with PA were still at increased risk for CV complications. These findings mirror data from a large meta-analysis comparing patients with PA to individuals with EH outside the context of COVID-19 infection, showing increased odds of stroke, atrial fibrillation, heart failure, and coronary artery disease [8]. The risk of CAD was 1.77 times increased, and the risk of CVA was 2.58 times increased in these prior analyses conducted in the absence of COVID-19 infection [8]. To place this in context, we demonstrate a greater risk of CV complications in the PA group that is approximately 7 times higher than the EH group at the time of COVID-19. Our data may provide unique insight on CV events in patients with PA occurring at the time of COVID-19 infection. Although the data may suggest an additive effect of CV risk attributed to COVID-19, ultimately these data cannot be directly compared with previously published data evaluating CV risk in relation to the natural history of PA. In addition, it is not clear that the additive effect is attributed to the RAAS given the autonomy of the RAAS seen in PA. Our preliminary findings should be further confirmed in a prospective study comparing EH vs PA groups both without and with COVID-19 infection to understand how risk may differ in relation to COVID-19 and further whether inflammation may play a role. Interestingly, NT-proBNP levels were relatively higher in the PA vs EH group, though a diagnosis of PA seemed to be associated with the incidence of CV complications during COVID-19 independent of the NT-proBNP. The natriuretic peptide system is responsible for counterregulatory action of the RAAS and could serve as a marker of increased RAAS dysregulation and subsequent CVD.

As expected, patients with PA had more MRA use and EH patients more ACEi use, which is consistent with the first-line recommended therapies for each respective group. Few data are available from observational studies regarding RAAS-blocking medications in COVID-19 and have generally shown either neutral or reduced risk [27–29]. There may be potential benefit based on altered RAAS pathology in COVID-19. Use of MRA and ACEi did not differ based on COVID infectivity in the PA group alone, and we were unable to assess whether MRA or ACEi use was protective during COVID-19 with regard to complications and outcomes in the PA vs EH group because of the relatively small absolute number of CV events.

A strength of our study was the rigorous data collection, in which charts were carefully reviewed. We eliminated selection bias by using standardized diagnostic criteria to ensure diagnoses of PA and EH. We leveraged the medical record system from a large academic tertiary medical system, which enabled a large sample from which to study. There were some limitations. The literature suggests that PA may be more prevalent than reported. We could only account for the testing and documentation that was available within the medical record. Although we performed a thorough review for secondary forms of hypertension, there could have been undiagnosed cases within the EH group because of undertesting for PA, which has been reported in the general population [30, 31] Moreover, we could not clearly assess whether the degree of uncontrolled hypertension had an impact on the findings nor could we specifically discern those who were in remission following adrenalectomy. We could not account for health records that existed at other medical centers or missing data, and only those patients who sought COVID-19 PCR testing at our facility were included and stratified based on positivity from the available results. Nonetheless, key information was obtained in a specific population of patients with PA who may have cardiometabolic disease sequelae in relation to COVID-19 distinct from other patient populations.

In summary, there may be an increased risk of acute COVID-19-related CV complications in PA vs EH. It would be important to understand whether PA should be a newly identified subpopulation at risk for COVID-19-related cardiovascular disease sequelae and whether this may be due to a RAAS-dependent or RAAS-independent mechanism. Because COVID-19 is evolving from pandemic to endemic, fluctuating infection and vaccination rates may also impact complication rates as well. Prospective studies are needed to confirm and assess these findings further and will begin to inform us as to whether subtypes of hypertension should be further risk-stratified for COVID-19 infection and subsequent CV morbidity and mortality.

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Disclosures

T.S.T., A.R.W., G.S., and C.D. have nothing to declare. S.S. was the recipient of a Gilead Sciences Research Scholars award. All disclosures are unrelated to this manuscript.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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