Journal of Microbiology, Immunology and Infection 56 (2023) 1158–1168

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

# Assessing the cardiovascular events and clinical outcomes of COVID-19 on patients with primary aldosteronism

Vin-Cent Wu [a,1], Jui-Yi Chen [b], Yen-Hung Lin [a,1], Cheng-Yi Wang [c,*], Chih-Cheng Lai [d,e,**]

[a] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan*
[c] *Department of Internal Medicine, Cardinal Tien Hospital and School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan*
[d] *Division of Hospital Medicine, Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan*
[e] *School of Medicine, College of Medicine, National Sun Yat-sen University, Kaohsiung, Taiwan*

Received 23 July 2023; received in revised form 12 September 2023; accepted 20 September 2023
Available online 27 September 2023

**KEYWORDS**
Primary aldosteronism;
Critical care;
Mortality;
MACE;
MAKE;
COVID-19;
TAIPAI

**Abstract** *Background:* Primary Aldosteronism (PA) is a common subtype of hypertension that increases the risk of adverse cardiovascular and kidney events. The impact of COVID-19 on patients with PA is not well understood.

This study aimed to investigate the impact of COVID-19 on patients with PA and compare their outcomes with hypertensive patients with essential hypertension.

*Methods:* A cohort study was conducted using data from the Trinetx platform, including 9,817,307 participants enrolled between January 1, 2020, and July 31, 2022. The study group consisted of participants who tested positive for PCR SARS-CoV-2. The primary outcome was critical care and all-cause mortality, while the secondary outcomes were major adverse cardiac events (MACE) or major adverse kidney events (MAKE). The study included 4814 patients with PA and 4814 hypertensive controls.

*Results:* Patients with PA had a higher risk of critical outcomes than the hypertensive control group (adjusted hazard ratio [aHR] 1.14, $p = 0.001$). Moreover, they had higher risks of MACE (aHR 1.32, $p < 0.001$) and MAKE (aHR 1.36, $p < 0.001$) for up to 180 days after COVID-19. The

*Abbreviations:* Af, atrial fibrillation; CHF, congestive heart failure; EH, essential hypertension; HR, hazard ratio; IHA, idiopathic hyperaldosteronism; MRA, mineralocorticoid receptor antagonist; MACE, major cardiovascular events; MAKE, major kidney events; PA, Primary Aldosteronism; PAC, Plasma aldosterone concentration; PRA, Plasma renin activity; aHR, adjusted hazard ratio.

* Corresponding author. Department of Internal Medicine, Cardinal Tien Hospital and School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, 23148, Taiwan.
** Corresponding author. Division of Hospital Medicine, Department of Internal Medicine, Chi Mei Medical Center, Tainan, 71004, Taiwan.
*E-mail addresses:* cywang@mospital.com (C.-Y. Wang), dtmed141@gmail.com (C.-C. Lai).
[1] TAIPAI, Taiwan Primary Aldosteronism investigator group and Primary aldosteronism center at National Taiwan University Hospital, Taipei, Taiwan.

https://doi.org/10.1016/j.jmii.2023.09.005

analysis of the aHR as a horizon plot after discharge showed that patients with pre-existing PA and COVID-19 had the highest risk of critical outcomes at 7 months (aHR = 1.21), MACE (aHR = 1.35) at 9 months, and MAKE (aHR = 1.47) at 10 months compared to those with EH. *Conclusions:* This study provides a comprehensive analysis of the cardiovascular impact of the COVID-19 pandemic on individuals with PA. The findings underscore the increased risk of mortality, critical care, MACE, and MAKE among patients with PA and COVID-19. The study highlights the need for continued optimization of strategies for follow-up care for patients with PA after SARS-CoV-2 infections.


## Introduction

Dealing with coronavirus disease 2019 (COVID-19) focused medical attention on several sensitive population groups. In addition to viral pneumonia, COVID-19 can also cause extrapulmonary complications, such as cardiovascular, kidney or cerebrovascular diseases.[1,2] According to a recent meta-analysis, patients with hypertension are at a higher risk for mortality and severity of COVID-19, with pooled risk ratios of 1.80 and 1.780, respectively.[3] Especially, the renin-angiotensin-aldosterone system (RAAS), a metabolic cascade modulating pressure and circulating blood volume, has been considered the main system involved in the pathogenesis of severe lung and organ injury in COVID-19 patients.[4,5] The virus SARS-CoV-2 responsible for the COVID-19 uses an important renin-angiotensin system (RAS) element-angiotensin-converting enzyme 2 (ACE2)-as a receptor protein for entry into target cells and, in consequence, disturbs the function of the main (circulating) renin-angiotensin-aldosterone system (RAAS) and the local renin-angiotensin system in various tissues and organs.[6] Currently, there are no reports on the clinical outcomes of patients with endocrine hypertension, particularly those with primary aldosteronism (PA), after contracting COVID-19. Along with its regulatory role in body fluid and electrolyte balance, prolonged exposure to hyperaldosteronism can lead to cardiac and kidney injuries independent of high blood pressure levels.[7] Patients with PA have been reported to be at a higher risk of cardiovascular events across multiple organs, which is more severe when compared to patients with essential hypertension (EH) who have similar blood pressure levels.[8—10]

A comprehensive assessment of post-acute COVID-19 sequelae targeting organs affected in PA patients is currently not available. Furthermore, there is a lack of studies comparing post-acute COVID-19 sequelae between patients with PA and those with EH.

Here, we aimed to investigate the subsequent critical admission and cardiovascular and kidney outcomes in COVID-19 survivors after SARS-CoV-2 based on a collaboration among 76 healthcare organizations (HCOs) in the TriNetX Research Network.

## Methods

### Data sources and study population

This retrospective, observational cohort study was conducted using the TriNetX research network, a global federated administrative database with real-time updates of electronic medical records (EMRs). It holds data from 76 HCOs, totaling 85 million patients across seven countries, with the majority of centers based in the United States. Other participating countries are Germany, the United Kingdom, Italy, Taiwan, Singapore and Israel,[11] which holds the largest global COVID-19 dataset.

A detailed description of the database is provided in the paper by Topaloglu et al. and can be found at the website: https://trinetx.com/company-overview/(eMethods in the Supplement).[11]

The index date for these patients was set as the date of their positive PCR test. Additionally, only the most recent laboratory values from the index date within the designated time frame were analyzed.

Among them, we used a validated algorithm to detect patients with PA, recruiting only patients aged ≥18 years old (10th International Classification of Diseases (ICD-10) code: E26.0) (Supplemental Fig. 1).[12] We also intended to find an algorithm with a high positive predictive value, and enrolled only PA patients who ever used mineralocorticoid receptor antagonist (MRA) at index time (belonging to the ATC class C03D, RXNORM:9997/298869, VA Class Code: CV704) because our main study aim was to construct a reliable PA sample according to our validation.[12] Patients who had ever been diagnosed with Bartter's syndrome, secondary hyperaldosteronism, end-stage kidney disease were excluded. In this study, we utilized a control group composed of hypertensive patients who tested positive for COVID-19 but did not have hyperaldosteronism. To increase the specificity of our findings, patients who received ventilator support, chronic dialysis, or adrenalectomy prior to the index date were excluded from the analysis. Our analysis incorporated additional covariates and identified algorithmically from extensive data sources encompassing diagnoses, medications, and laboratory test results, to supplement our pre-defined covariates.

The data utilized in this study was secured in January 2023, and the study period spanned from January 2020 to July 31st, 2022, with a follow-up period until January 31st 2023. The inclusion of algorithmically identified covariates enhances the statistical power of our analysis, contributing to a more comprehensive understanding of the relationship between COVID-19 and hyperaldosteronism.

#### Ethical statement

The TriNetX platform is acquiescent of the Health Insurance Portability & Accountability Act and General Data Protection Regulation. The Institutional Review Board has granted

TriNetX a waiver of informed consent since this platform only aggregated counts and statistical results of de-identified information. The analysis of TriNetX for the current study was approved under the authority of the Institutional Review Board of Chi-Mei Hospital (No: 11202—002).

### Cohort

A flowchart of the cohort construction from the 9,817,307 participants enrolled between 1st January 2020 and 31st July 2022 is provided in Fig. 1, with those who tested positive for PCR marked. Of this cohort, 8080 had a diagnosis of hyperaldosteronism, while the remaining 701,714 did not.

### Prespecified outcomes

The primary focus of our investigation centered on critical care and all-cause mortality as the key indicators at 6 months after COVID-19. Meanwhile, we also delved into secondary outcomes, namely major adverse cardiac events (MACE) and major adverse kidney events (MAKE). For a comprehensive understanding, MACE encompassed acute myocardial infarction, cardiac arrest, ventricular tachycardia, cerebral infarction, cerebral hemorrhage, heart failure, and mortality within 180 days of the initial COVID-19 diagnosis.

To ensure a robust analysis and prevent any biases, we took several steps. First, we included all-cause mortality and admission to critical care units as part of our secondary outcomes. Additionally, MAKE comprised incident renal replacement treatment, kidney functional progression, acute kidney injury, and mortality. To mitigate the potential impact of protopathic or ascertainment biases, we meticulously excluded any occurrences of secondary outcomes before the index date. We also conducted propensity score matching (PSM) multiple times, enhancing the reliability of our findings. (See Supplementary Table).

### Statistical analyses

Student's t-tests and chi-squared tests were used to compare the PA patients and those identified to have EH. The built-in TriNetX function was employed for this purpose. In the Demographics category, patients were matched based on age at Index, gender, and ethnicity (not Hispanic or Latino). In the Diagnosis category, patients were matched on overweight/obesity, diabetes mellitus, ischemic heart disease, cerebrovascular disease, dementia, other chronic obstructive pulmonary disease, diseases of the liver, peptic ulcer, malignancy/lymphoma, chronic obstructive pulmonary disease, and autoimmune diseases. In the Medication category, patients were matched on antihypertensive drugs, statins, and aspirin. In the Laboratory category, patients were matched on serum creatinine level, body mass index (BMI), systolic blood pressure, diastolic blood pressure, cholesterol levels (LDL), and glucose levels. After propensity score matching was conducted with a 1:1 sampling ratio between PA and EH patients, standardized mean differences (SMDs) less than 0.2 indicated that they were well-matched.[13] Adjusted hazard ratios (aHRs) were used to evaluate the outcomes of interest; Cox proportional hazard models were employed to calculate HRs and assess proportionality. The generalized Schoenfeld approach built into the TriNetX network was used to test for proportional hazard assumptions; Kaplan—Meier methods were used to calculate survival probabilities. A two-sided p-value $<0.05$ was considered statistically significant.

## Results

### Patient characteristics

During the study period, there were a total of 9,817,307 patients who tested positive for SARS-CoV-2 via PCR. After excluding patients with PA, with secondary hypertension, such as those with Bartter's syndrome, end-stage renal disease, and those who had ever been on a ventilator or undergone adrenalectomy before the index date, 4822 patients with PA (mean age 63.0 years, 44.6% men) and 614,543 EH controls (mean age 59.7 years, 44.5% men) were enrolled based on our diagnosis algorithm due to their first positive PCR test for COVID-19 (Fig. 1). After propensity score matching, there were 4814 patients with PA (mean age 63.0 years, 44.6% men) and 4814 hypertensive patients (mean age 63.4 years, 45.1% men) as controls (Table 1).

### Critical care

Within 180 days of follow-up after COVID-19, 1269 (26.4%) patients with PA and 1143 (23.7%) patients with pre-existing EH had critical outcomes ($p = 0.013$). Furthermore, the PA group had a higher all-cause mortality rate (19.4% vs. 16.6%, $p = 0.001$) [adjusted hazard ratio (aHR), 1.21 (95% CI $= 1.10—1.32$, $p < 0.001$)] compared to the EH group after COVID-19.

The hazard ratio test revealed an aHR of 1.17 (95% CI $= 1.02—1.35$, $p = 0.021$), indicating that PA patients had a greater risk of critical outcomes than EH patients (Fig. 2A).

### Incidence of MACE

After excluding records of prior myocardial infarction, stroke, or heart failure before the index date, we further analyzed the risk of incident MACE in two groups: 3510 patients with PA and 3510 patients with EH. Results showed that 1150 (32.8%) patients with PA and 706 (20.1%) patients with EH experienced MACE within 180 days after contracting COVID-19 (sTable 2). The Kaplan-Meier survival analysis demonstrated a significant difference in the probability of MACE between the two groups (log-rank test, $p < 0.001$; Fig. 2B). Furthermore, patients with PA had a higher risk of MACE with an aHR of 1.32 (95% CI, 1.12—1.54; $p < 0.001$) compared to those with EH. (sTable 3, Fig. 2B).

### Incidence of MAKE

Following the exclusion of patients with incident AKI prior to the index date, 3373 patients with PA and 3373 with EH were analyzed. Of the two groups, 394 (11.7%) patients with PA and 289 (8.76%) patients with EH developed incident MAKE within 180 days after the first occurrence of the COVID-19 positive event ($p = 0.001$) (sTable 3). The Kaplan-Meier survival analysis revealed a statistically significant difference in probability between the two groups (log-rank test $p < 0.001$). Adjusted HR revealed that the PA group had a higher MAKE HR of 1.36 (95% CI, 1.05—1.58, $p < 0.001$) compared to the EH group (sTable 4, Fig. 2C). Notably, the observed disparity in the starting points at day 0 between the two groups in Fig. 2B can be attributed to the prompt

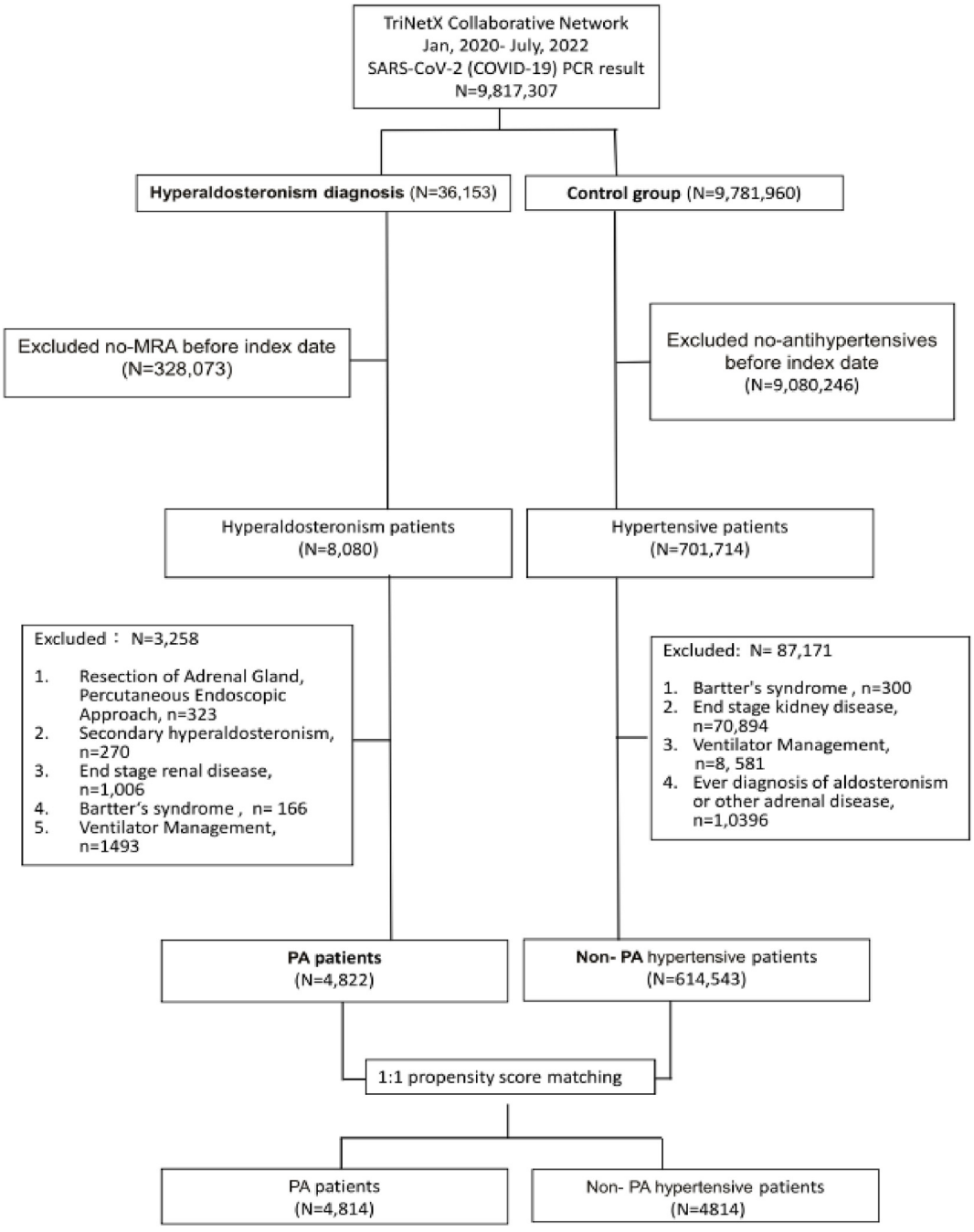


**Figure 1.** Enrollment algorithm for patients. **Abbreviation:** PA, primary aldosteronism.

diagnosis of MACE in PA patients following a positive COVID-19 PCR test (2.7%). This diagnosis occurred early and was more frequent compared to their EH counterparts (0.68%, $p < 0.001$), shortly after contracting COVID-19.

**Time sequential adjusted hazard ratios for the sequelae of PA versus EH**

An examination of the adjusted hazard ratio (aHR) as a horizon plot after discharge revealed that patients with pre-existing PA concomitant to COVID-19 had the highest risk of critical outcomes at 7 months (aHR = 1.21), MACE (aHR = 1.76) at 6 months and MAKE (aHR = 1.47) at 10 months compared to those with EH (Fig. 3).

**Specificity analysis**

We applied a doubly robust approach to the entire enrollee cohort, assessing the impact of pre-exposure to COVID-19 on outcomes in patients with PA and EH. Additionally, a focused analysis within the United States collaborative Network considered potential international variations in healthcare. These findings align with the primary methodology. A sensitivity analysis was conducted to evaluate the

**Table 1** Baseline characteristics comparison between patients with primary aldosteronism (PA) and essential hypertension (EH) after COVID-19.

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | PA (n = 4822) | EH (n = 614,543) | Std | PA (n = 4814) | EH (n = 4814) | Std |
| Men (%) | 2150 (44.6%) | 273,482 (44.5%) | 0.002 | 2147 (44.6%) | 2169 (45.1%) | 0.009[a] |
| Age (years) | 63.0 ± 14.0 | 59.7 ± 18.6 | 0.196 | 63.0 ± 14.0 | 63.4 ± 15.4 | 0.030[a] |
| Not Hispanic or Latino (%) | 3985 (82.6%) | 507,476 (82.6%) | 0.002 | 3979 (82.7%) | 3998 (83.0%) | 0.010[a] |
| Laboratory[b] | | | | | | |
| Potassium, mEq/L | 4.1 ± 0.6 | 4.1 ± 0.5 | 0.137 | 4.1 ± 0.6 | 4.2 ± 0.5 | 0.181 |
| Creatinine, mg/dL | 1.1 ± 1.3 | 1.1 ± 1.1 | 0.075 | 1.1 ± 1.3 | 1.1 ± 0.6 | 0.080[a] |
| BMI, kg/m$^2$ | 31.5 ± 7.2 | 29.9 ± 7.1 | 0.217 | 31.5 ± 7.2 | 31.4 ± 7.3 | 0.011[a] |
| Blood pressure, systolic, mmHg | 123.2 ± 29.5 | 131.5 ± 23.4 | 0.312 | 123.2 ± 29.5 | 128.4 ± 24.8 | 0.188 |
| Blood pressure, ddiastolic, mmHg | 75.2 ± 16.5 | 75.8 ± 13.1 | 0.038 | 75.2 ± 16.4 | 74.9 ± 14.3 | 0.020 |
| Cholesterol, mg/dL | 158.2 ± 51.3 | 167.6 ± 47.1 | 0.191 | 158.3 ± 51.3 | 163.6 ± 49.0 | 0.107[a] |
| LDL, cholesterol, mg/dL | 89.5 ± 40.2 | 92.6 ± 38.0 | 0.078 | 89.6 ± 40.2 | 89.5 ± 38.2 | 0.002[a] |
| INR | 1.7 ± 3.6 | 1.3 ± 1.8 | 0.148 | 1.7 ± 3.6 | 1.5 ± 2.7 | 0.078[a] |
| Glucose, mg/dL | 125.7 ± 57.3 | 120.0 ± 54.2 | 0.103 | 125.7 ± 57.4 | 126.7 ± 59.9 | 0.016[a] |
| Plasma renin activity, ng/mL/h | 4.4 ± 11.5 | 6.8 ± 65.9 | 0.050 | 4.4 ± 11.6 | 3.9 ± 11.5 | 0.043 |
| Plasma aldosterone concentration, ng/dL | 28.4 ± 81.5 | 13.6 ± 20.6 | 0.249 | 28.4 ± 81.5 | 14.6 ± 15.8 | 0.236 |
| Hemoglobin, g/dL | 12.4 ± 2.3 | 12.7 ± 2.2 | 0.151 | 12.4 ± 2.3 | 12.6 ± 2.2 | 0.084[a] |
| Comorbidities, n (%) | | | | | | |
| Overweight | 2065 (42.8%) | 94,372 (15.4%) | 0.634 | 2057 (42.7%) | 2037 (42.3%) | 0.008[a] |
| Diabetes mellitus | 2321 (48.1%) | 121,290 (19.7%) | 0.629 | 2313 (48.0%) | 2378 (49.4%) | 0.027[a] |
| Rheumatoid arthritis | 122 (2.5%) | 8277 (1.3%) | 0.086 | 122 (2.5%) | 121 (2.5%) | 0.001[a] |
| Sepsis | 151 (3.1%) | 5396 (0.9%) | 0.161 | 150 (3.1%) | 155 (3.2%) | 0.006[a] |
| Ischemic heart diseases | 2004 (41.6%) | 96,362 (15.7%) | 0.598 | 1996 (41.5%) | 2025 (42.1%) | 0.012[a] |
| Cerebrovascular diseases | 1172 (24.3%) | 62,147 (10.1%) | 0.383 | 1166 (24.2%) | 1153 (24.0%) | 0.006[a] |
| Dementia | 130 (2.7%) | 10,869 (1.8%) | 0.063 | 129 (2.7%) | 143 (3.0%) | 0.018[a] |
| Peptic ulcer | 337 (7.0%) | 3679 (0.6%) | 0.339 | 329 (6.8%) | 289 (6.0%) | 0.034[a] |
| Lymphoma | 186 (3.9%) | 10,082 (1.6%) | 0.136 | 184 (3.8%) | 185 (3.8%) | 0.001[a] |
| Neoplasm | 369 (7.7%) | 10,721 (1.7%) | 0.282 | 364 (7.6%) | 362 (7.5%) | 0.002[a] |
| COPD | 934 (19.4%) | 45,060 (7.3%) | 0.36 | 928 (19.3%) | 958 (19.9%) | 0.016[a] |
| Liver Disease | 1321 (27.4%) | 36,489 (5.9%) | 0.601 | 1313 (27.3%) | 1242 (25.8%) | 0.033[a] |
| Diseases of the musculoskeletal system and connective tissue | 3545 (73.5%) | 279,889 (45.5%) | 0.595 | 3537 (73.5%) | 3626 (75.3%) | 0.042[a] |
| Antihypertensive medication, n (%) | | | | | | |
| Beta blockers | 3133 (65.0%) | 199,110 (32.4%) | 0.689 | 3126 (64.9%) | 2582 (53.6%) | 0.232 |
| Calcium channel blockers | 2254 (46.7%) | 136,951 (22.3%) | 0.532 | 2249 (46.7%) | 1778 (36.9%) | 0.199 |
| ACE inhibitors | 1515 (31.4%) | 92,395 (15.0%) | 0.395 | 1510 (31.4%) | 1378 (28.6%) | 0.060 |
| Alpha blockers | 771 (16.0%) | 69,408 (11.3%) | 0.137 | 769 (16.0%) | 867 (18.0%) | 0.054 |
| Angiotensin II inhibitor | 1691 (35.1%) | 84,495 (13.7%) | 0.512 | 1687 (35.0%) | 1179 (24.5%) | 0.232 |
| All antihypertensives | 1552 (32.2%) | 203,814 (33.2%) | 0.021 | 1552 (32.2%) | 1614 (33.5%) | 0.027[a] |
| Antiarrhythmics | 2607 (54.1%) | 187,932 (30.6%) | 0.489 | 2599 (54.0%) | 2630 (54.6%) | 0.013[a] |
| Aspirin | 2044 (42.4%) | 118,988 (19.4%) | 0.515 | 2036 (42.3%) | 2083 (43.3%) | 0.020[a] |
| Clopidogrel | 602 (12.5%) | 34,738 (5.7%) | 0.240 | 600 (12.5%) | 645 (13.4%) | 0.028[a] |
| Enoxaparin | 1256 (26.0%) | 69,531 (11.3%) | 0.385 | 1249 (25.9%) | 1212 (25.2%) | 0.018[a] |
| Atorvastatin | 1853 (38.4%) | 108,576 (17.7%) | 0.475 | 1847 (38.4%) | 1910 (39.7%) | 0.027[a] |

[a] Items were put into propensity score matching.
[b] Biochemistry data were available near the index date.
Data are mean (SD) and n (%).
**Abbreviation:** ACE, angiotensin-converting enzyme, ARB, angiotensin receptor blocker, BMI, body mass index, COPD, Chronic obstructive pulmonary disease, INR, international normalized ratio, LDL, Low-density lipoprotein, Std: standardized mean differences.

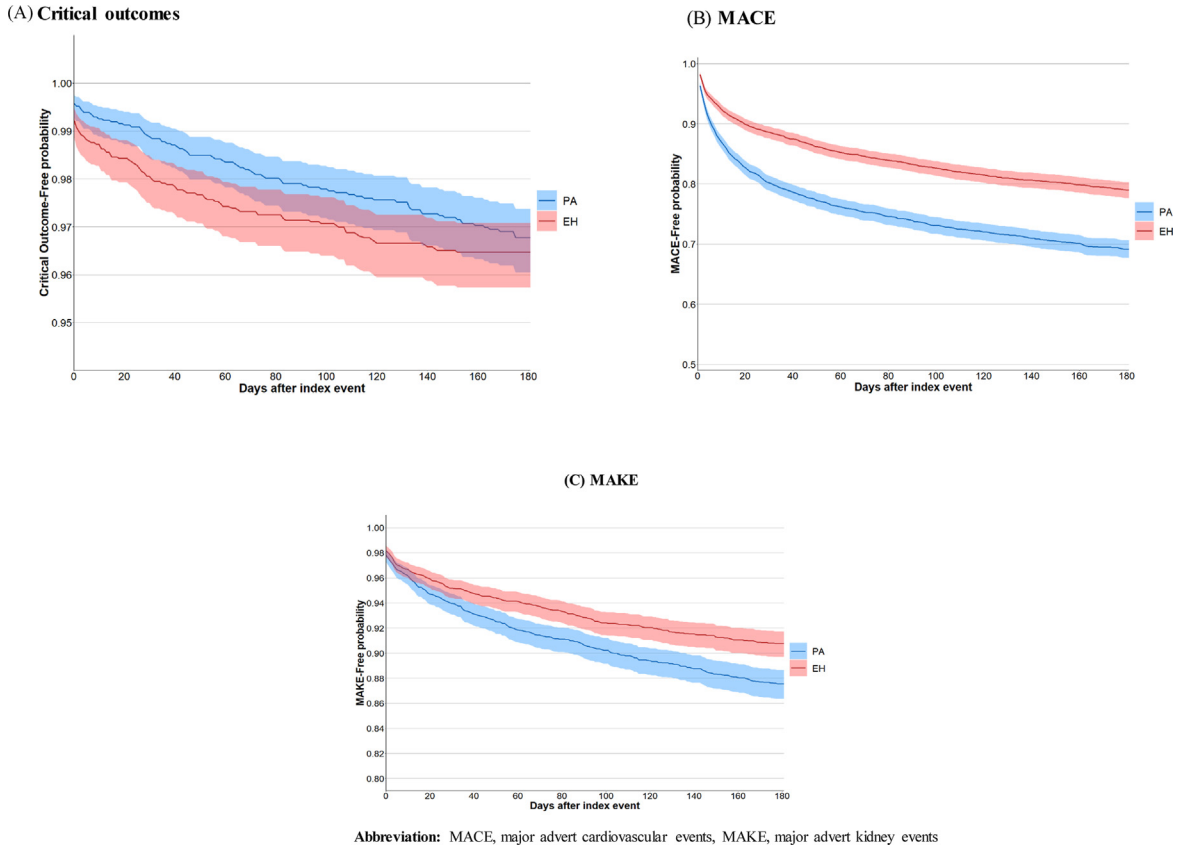


**Figure 2.** Kaplan-Meier curves showing the 6-month follow-up for (A) critical outcome ($p = 0.021$), (B) MACE ($p < 0.001$), (C) MAKE ($p < 0.001$), and any first outcome after COVID-19 in propensity-score matched cohorts. The green line represents essential hypertension, and the purple line represents primary aldosteronism. **Abbreviation:** MACE, major advert cardiovascular events, MAKE, major advert kidney events.

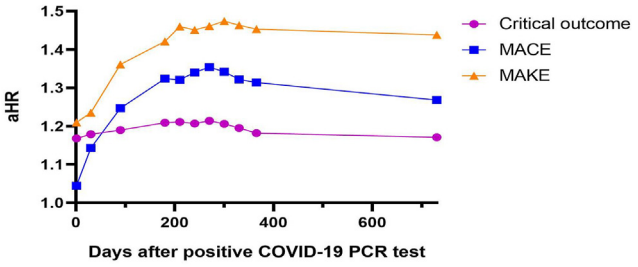


**Figure 3.** Time-varying adjusted hazard ratios for the sequelae of primary aldosteronism (PA) versus essential hypertension (EH) after COVID-19, in the propensity-score matched population, from one month to two years. **Abbreviation:** MACE, major advert cardiovascular events, MAKE, major advert kidney events.

reliability of our results related to the subcomponent outcomes of critical care, MACE, and MAKE (Fig. 4A).

Patients with PA were found to have a higher risk of all-cause mortality, critical care (aHR, 1.37; 95% CI, 1.17–1.60, $p < 0.001$), MACE (aHR, 1.61; 95% CI, 1.45–1.78, $p < 0.001$) and MAKE (aHR, 1.70; 95% CI, 1.55–1.86, $p < 0.001$).

Subgroup analyses revealed that patients with PA were associated with a significantly higher risk of all-cause mortality (aHR, 1.21; 95% CI, 1.10–1.32; $p = 0.001$), usage of critical unit (aHR, 1.18; 95% CI, 1.10–1.32; $p = 0.001$), kidney function progression (aHR, 1.40; 95% CI, 1.14–1.71; $p = 0.001$), AMI (aHR, 1.40; 95% CI, 1.01–1.93; $p = 0.040$), and congestive heart failure (aHR, 2.14; 95% CI, 1.92–2.39; $p < 0.001$) compared to EH patients. In contrast, no significant difference was observed in the risk of incident stroke or redialysis between the two groups.

### Sensitivity, subgroup analysis

In this study, a cohort of individuals was analyzed to determine the risks and burdens of pre-specified outcomes based on their obesity status, hypokalemia, presence of aldosterone-producing adenoma, use of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) and use of corticosteroid (Supplementary Fig. 5). The analysis was consistent with the primary analysis results (Fig. 4B).

Moreover, a subgroup analysis was conducted to assess the impact of COVID-19 vaccination on the outcomes of interest. Specifically, the subgroup analysis focused on individuals who were ever hospitalized in terms of disease severity. The results of this analysis were consistent with those of the primary analysis.

The study found that patients with diabetes mellitus and chronic kidney disease were at increased risk of critical care and MACE (Fig. 4B).

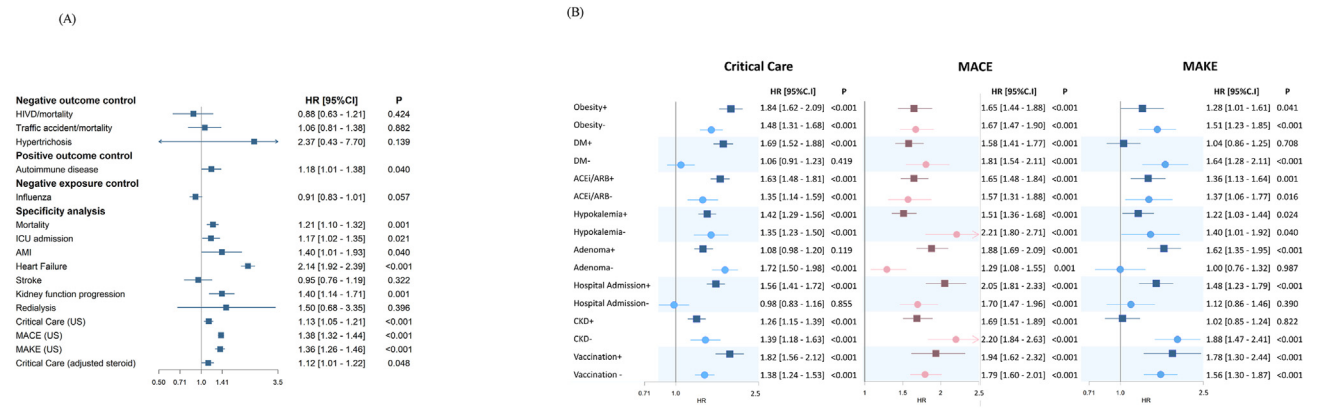


**Figure 4.** Forest plot of adjusted hazard ratios for patients with primary aldosteronism (PA) versus essential hypertension (EH) after COVID-19 regarding the 6-month risk of (A) negative/positive specificity for critical care and (B) sensitivity analysis for critical care, MACE, and MAKE. The hazard ratio was adjusted for age, gender, and race due to their potential interactions with COVID-19.[48] Adjusted HRs and 95% CIs (error bars) are presented. The vertical line indicates an HR of 1.00; lower limits of 95% CIs with values greater than 1.00 indicate significantly increased risk.

### Positive and negative-outcomes

Our results indicate that PA concomitant to COVID-19 could be associated with a heightened risk of autoimmune disease (aHR, 1.18, 95% CI, 1.01—1.38, p = 0.040). We found that patients with prior infections (PA) had similar risks of incident traffic accident (aHR, 1.06, 95% CI, 0.81—1.38), herniated intervertebral disc (HIVD) (aHR, 0.87, 95% CI, 0.60—1.26), and hypertrichosis (aHR, 2.53, 95% CI, 0.49—13.0) relative to those withEH after COVID-19. These results suggest limited systemic bias in our analysis between the PA and EH groups (Fig. 4B).

### Negative-exposure controls

To further assess the reliability of our data analysis, we developed and implemented a pair of negative-exposure controls. Under the hypothesis that PA patients after influenza infection would not increase the risk of developing critical care, MACE and MAKE, we compared associations between patients with PA (n = 3055) to those with EH (n = 358,911) concomitant influenza within the same study period (Fig. 4A). Utilizing the same data sources, cohort design, analytical approach (including covariate specification and matching method) and outcomes of interest, our results showed no significant association between PA patients concomitant influenza and any of the pre-specified critical care (aHR, 0.913, 95% CI, 0.831—1.012, p = 0.057), MACE (aHR, 0.938, 95% CI, 0.809—1.087, p = 0.394), or MAKE (aHR, 0.934, 95% CI, 0.818—1.065, p = 0.321) compared to EH patients with influenza.

## Discussion

We provide the first evidence that, beyond the positive COVID-19 PCR test, people with COVID-19 exhibited increased risks and 6-month burdens of incident MACE, mortality, critical care, and MAKE. The risks were evident regardless of age, race, sex, and other cardiovascular risk factors, including obesity, aldosterone-producing adenoma, hospitalization, with or without vaccination, with or without ACEi/ARB users, and hypokalemia. This provides compelling evidence that these risks may indeed manifest in individuals with PA after COVID-19, particularly those at high risk of cardiovascular and kidney diseases. Our analyses of the risks and burdens of cardiovascular or kidney outcomes across aldosterone-related hypertensive settings after the acute infection revealed some important findings.

First, our study has significant implications for the management of patients with PA who have had a previous SARS-CoV-2 infection. Specifically, our findings highlight the need for continued optimization of follow-up strategies for such patients, as those with PA exhibited higher levels of end-organ injury compared to those with EH. Furthermore, these patients also experienced a higher incidence of MAKE that persisted for over 10 months.

Second, the increasing number of people worldwide who suffer from intractable hypertension, including those with PA,[16] means that the risks and 6-month burdens of major cardiovascular and kidney diseases identified in our study may have significant implications for a large number of individuals. Third, Specifically, we elaborate on how hyperaldosteronism could potentially exacerbate the risk of MACE shortly after COVID-19 infection, offering a more comprehensive understanding of the temporal dynamics of these complications.

Given the potential contribution of the COVID-19 pandemic to the rise in the burden of aldosterone-related hypertension, even for those with secondary hyperaldosteronism, it is crucial for endocrine and hypertension societies worldwide to be prepared to deal with this growing public health concern.

### PA deteriorated critical outcome and mortality

The effects of PA on patients are not solely persistent hypertension and electrolyte imbalance, but also a pro-inflammatory effect causing end-organ damage.[12,17] In clinical settings, patients with PA who underwent mineralocorticoid receptor antagonist treatment has increased risk of sepsis than EH.[18] Further plausible mechanisms are

aldosterone-related vascular stiffness, nephrosclerosis, and intractable hypertension, which are attributed to fragile vasculopathy as well as arterial stiffness.[19,20] Furthermore, the number and function of circulating endothelial progenitor cells were suppressed by aldosterone and could interfere with vascular endothelial integrity.[21] The strength of the correlation between generation probabilities and frequencies of T-Cell receptor repertoire clonotypes was significantly higher in the PA group than that in the EH group.[22] Consequently, aldosterone can modulate dendritic cells function by enhancing CD8(+) T cell activation and promoting Th17-polarized immune responses, which might contribute to the inflammatory injury attributed to hypertension and cardiovascular disease.[23] On the other hand, an increase in pro-inflammatory cytokine secretion, including interleukine-6 (IL-6) and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) leads to fibrosis-related factor expression and persistent, low-grade inflammation.[24] According to recent concepts, a chronic inflammatory disease could be attributed to sepsis.[25,26] Most importantly, the signaling milieu is likely very different after hypertensive endothelial injury in PA than in the hypertensive controls.[21] Furthermore, glucocorticoid co-secretion likely exists in patients with PA[27,28] can increase the secretion of proinflammatory cytokines, including TNF-$\alpha$ and IL-6,[29] which could promote the onset of respiratory distress in patients with SARS-CoV-2.[30]

## PA concomitant incident MACE

Many factors will attribute to the risk of incident cardiovascular disease beyond the acute phase of COVID-19. The recognized mechanism includes a putative mechanism for the downregulation of ACE2 and dysregulation of the renin—angiotensin—aldosterone system.[31,32] The binding of SARS-CoV-2 to ACE2 leads to the downregulation of this enzyme and, in the aftermath, to the excess of angiotensin II and aldosterone.[6]

Heart failure in patients with PA is attributed to the over-production of oxidative stress and pro-inflammatory cytokine augmented by Hyperaldosterone[33,34]; this phenomenon was reported to be promoted by aldosterone and related to dysfunction of innate and adaptive immunity.[35,36] Moreover, long-term excessive aldosterone concentrations have been accused of causing enduring hypertension due to increased arterial stiffness.[37]

It is hypothesized that the cumulative effects of excessive aldosterone may lead to vasoconstriction, hypertrophy, and fibrosis, which can contribute to the development of cardiovascular complications in both COVID-19 and PA. Long-term exposure to elevated aldosterone levels, in combination with hypertension, may eventually result in cardiovascular and kidney functional damage, including marked left ventricular hypertrophy (LVH), increased collagen deposition in the myocardium, renal hyperfiltration, and proteinuria.[38,39]

The observed trend provides support for the notion that MACE are more likely to manifest as early rather than long-lasting consequences of COVID-19 in PA patients, who receive a severe and early diagnosis compared to their EH counterparts. This temporal pattern can be attributed to several plausible mechanisms, particularly in patients with PA. These mechanisms may include various factors, such as the acute inflammatory response, hypoxia, thrombotic events, and myocardial injury induced by the virus, which have been well-documented and play significant roles.[1,40,41]

### PA concomitant incident MAKE

The incidence of AKI was increased in patients with COVID-19 compared with AKI attributed to bacterial sepsis, severe influenza infection, or in general hospitalized patients.[42] COVID-19 was associated with more severe acute tubular necrosis and microvascular thrombosis coupled with decreased microvascular flow, yet minimal inflammation.[43] Longer duration of hypertension among PA patients is positively associated with heavier proteinuria and higher kidney resistance index.[44] The activation of mineralocorticoid receptors injures podocytes and results in the disruption of the glomerular filtration barrier; leading to proteinuria and the progression of CKD.[45] Aldosterone aggravated large glomerular pore sizes and hyperfiltration in the residual glomeruli and worsened albuminuria.[46] We showed that first-time COVID-19 superimposed with hyperaldosteronism will increase the risk of incident ESKD.

### Subgroup analysis time sequential risks

The time-sequential risk plotting of the sequelae of PA and EH after COVID-19 has provided important insights into the risks associated with these medical conditions. The results demonstrate that adjusted hazard ratios are highest between 7 and 10 months after infection, indicating an additive effect of cardiovascular and kidney attributes to COVID-19 and hyperaldosterone that cannot be solely attributed to the traditionally high cardiovascular events common among PA patients.[8] Our study reported a Kaplan-Meier curve illustrating that most MACE in COVID-19 patients materialized within a span of two weeks subsequent to a positive COVID-19 test, with a median occurrence time of 9 days.[47] This trend does lend credence to the notion that MACE are more apt to manifest as early rather than enduring consequences of COVID-19.

These findings highlight the need for personalized healthcare strategies that account for individual patient characteristics and medical history. In particular, our data provide a unique perspective into cardiovascular events that occur in patients with PA during COVID-19, emphasizing the importance of tailored healthcare approaches in managing and treating patients with this condition. By leveraging these insights, healthcare providers can potentially improve overall health outcomes and reduce the burden of disease for patients with PA and other medical conditions.

### Study strengths and limitations

We tested the robustness of the results in multiple sensitivity analyses, and applied negative outcomes or exposure control to detect spurious associations and show that there were limited systemic or ascertainment biases. Patients with PA were found to have a higher risk of developing autoimmune disease.[14] This finding is corroborated by previous research, which has indicated that COVID-19 patients are associated with an increased risk for various autoimmune diseases.[15] In order to assess whether our data and analysis would be able to reproduce established

associations, we examined the association between PA with or without COVID-19 and the risk of autoimmune disease. In order to address potential concerns of health indication bias or ascertainment bias, we analyzed of the risk of incident traffic accident, herniated intervertebral disc (HIVD), and hypertrichosis among patients with prior coronavirus disease 2019 (COVID-19) infection, without any prior knowledge to suggest an association.[1] This study applied positive controls to test whether our approach would reproduce established knowledge. The results were consistently robust to challenges posed in several sensitivity analyses. These analyses included an examination of a positive outcome control, a battery of negative outcome controls, and a pair of exposure controls, all of which yielded results consistent with pre-test expectations. We measured the "outcome bias" to capture probabilistic dependence between variables and the outcome for cohort data. Our study utilized TRINETX data from multiple continents, which extended the generalizability of our findings.

However, there were some pitfalls in our studies. Although pre-defined outcomes were carefully selected and our analyses were adjusted for a large set of pre-defined and algorithmically selected variables, there could be misclassification bias and residual confounding. Potential confounding might also exist if there are substantial differences in unknown or unmeasured characteristics that might be associated with the risk of SARS-CoV-2 or PA, especially potential genetic susceptibility or environmental exposures. The rarity of PA among the study population was indeed a limitation we encountered, and we understand how it might raise concerns regarding the credibility of the results.

Furthermore, a specificity test evaluating traffic accidents and lumbosacral herniated intervertebral disc s revealed no difference between patients with PA or EH in our negative control analysis, aiding in the removal of selection bias that can be caused by existing knowledge of an individual's assignment. Importantly, we found that for patients with PA who had concomitant infections with influenza did not increase the risk of mortality. This suggests that other sources of error, including recall bias or analytic flaws, are unlikely to be significant.

In this study, we retrieved and examined federated electronic medical record data that do not provide the same level of control over diagnostic tests as could be achieved in single or multi-center clinical studies, such as the largest global COVID-19 registration. Despite this, the data are real-life and include completed medical records, allowing us to analyze long-term follow-up outcomes in PA patients coinciding with COVID-19 on a large scale.

## Conclusion

Our findings demonstrate that patients with PA are at a greater risk of detrimental outcomes, including increased incident MACE, mortality, critical care utilization, and MAKE, when it comes to COVID-19. This highlights the criticality of preventive measures and follow-up care for patients with PA amidst the COVID-19 pandemic. Moreover, further studies are needed to evaluate the optimal strategies for the prevention, diagnosis, and treatment of PA in the context of COVID-19. Such research could lead to improved clinical outcomes for patients with PA and help reduce the risk of deleterious outcomes associated with COVID-19.

## Author contributions

Dr. Vin-Cent Wu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design, Acquisition, analysis, or interpretation of data: Cheng-Yi Wang, Chih-Cheng Lai, Jui-Yi Chen, Yen-Hung Lin
Drafting of the manuscript: Chih-Cheng Lai
Administrative, technical, or material support: Chih-Cheng Lai, Vin-Cent Wu, Cheng-Yi Wang

## Financial disclosures

No competing interest was declared. No financial conflict of interest exists.

## Role of the funder/sponsor

The funders have no role on design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Funding

This study was supported by Taiwan National Science Council (grants NSC 101-2314-B-002-132-MY3, NSC100-2314-B-002-119, NSC 101-2314-B-002-085-MY3, MOST 104-2314-B-002 -125 -MY3) and NTUH 100-N1776, 101-M1953, 102-S2097.

## Twitter

Patients with Primary Aldosteronism and COVID-19 have a higher risk of adverse cardiovascular and kidney outcomes, highlighting the need for optimized follow-up care strategies. Our study sheds light on the impact of COVID-19 on individuals with PA. #hypertension #COVID19.

## Ethical statement

Our study received the proper ethical oversight. The TriNetX platform is acquiescent of the Health Insurance Portability & Accountability Act and General Data Protection Regulation. The analysis of TriNetX for the current study was approved under the authority of the Institutional Review Board of Chi-Mei Hospital (No: 11,202—002).

## Central illustration

Heightened Risk of Critical Care, MACE and MAKE After Covid-19 in Patients with Primary Aldosteronism.

## Declaration of competing interest

The authors have nothing to disclose.

## Acknowledgements

The authors thank the staff of the Second Core Lab in the Department of Medical Research of National Taiwan University Hospital for technical assistance.

## References

1. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;**28**:583—90.
2. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a Review. *JAMA Cardiol* 2020;**5**:831—40.
3. Cai L, He C, Liu Y, Sun Y, He L, Baranova A. Inflammation and immunity connect hypertension with adverse COVID-19 outcomes. *Front Genet* 2022;**13**:933148.
4. Cafiero C, Rosapepe F, Palmirotta R, Re A, Ottaiano MP, Benincasa G, et al. Angiotensin system polymorphisms' in SARS-CoV-2 positive patients: assessment between symptomatic and asymptomatic patients: a pilot study. *Pharmgenomics Pers Med* 2021;**14**:621—9.
5. Chan CK, Huang YS, Liao HW, Tsai IJ, Sun CY, Pan HC, et al. Renin-angiotensin-aldosterone system inhibitors and risks of severe acute respiratory syndrome coronavirus 2 infection: a systematic Review and meta-analysis. *Hypertension* 2020;**76**:1563—71.
6. Pawlikowski M, Winczyk K. Endocrine and metabolic aspects of COVID-19. *Endokrynol Pol* 2021;**72**:256—60.
7. Marney AM, Brown NJ. Aldosterone and end-organ damage. *Clin Sci (Lond)* 2007;**113**:267—78.
8. Wu VC, Wang SM, Huang KH, Tsai YC, Chan CK, Yang SY, et al. Long-term mortality and cardiovascular events in patients with unilateral primary aldosteronism after targeted treatments. *Eur J Endocrinol* 2021;**186**:195—205.
9. Wu VC, Chueh JS, Hsieh MY, Hu YH, Huang KH, Lin YH, et al. Familial aggregation and heritability of aldosteronism with cardiovascular events. *J Clin Endocrinol Metab* 2020:105.
10. Huang WC, Chen YY, Lin YH, Chen L, Lin PC, Lin YF, et al. Incidental congestive heart failure in patients with aldosterone-producing adenomas. *J Am Heart Assoc* 2019;**8**:e012410.
11. Topaloglu U, Palchuk MB. Using a federated network of real-world data to optimize clinical trials operations. *JCO Clin Cancer Inform* 2018;**2**:1—10.
12. Wu VC, Hu YH, Wu CH, Kao CC, Wang CY, Yang WS, et al. Administrative data on diagnosis and mineralocorticoid receptor antagonist prescription identified patients with primary aldosteronism in Taiwan. *J Clin Epidemiol* 2014;**67**:1139—49.
13. Andrade C. Mean difference, standardized mean difference (SMD), and their use in meta-analysis: as simple as it gets. *J Clin Psychiatry* 2020:81.
14. Er LK, Chen L, Tsai YC, Lin YH, Huang WC, Chang CC, et al. Risk of new-onset autoimmune diseases in primary aldosteronism: a nation-wide population-based study. *J Hypertens* 2020;**38**:745—54.
15. Chang R, Yen-Ting Chen T, Wang SI, Hung YM, Chen HY, Wei CJ. Risk of autoimmune diseases in patients with COVID-19: a retrospective cohort study. *EClinicalMedicine* 2023;**56**:101783.
16. Er LK, Wu VC, Group TS. Call for screening for primary aldosteronism: an underdiagnosed and treatable disease. *J Thorac Dis* 2018;**10**:557—9.
17. Savard S, Amar L, Plouin PF, Steichen O. Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. *Hypertension* 2013;**62**:331—6.
18. Chan CK, Hu YH, Chen L, Chang CC, Lin YF, Lai TS, et al. Risk of sepsis in patients with primary aldosteronism. *Crit Care* 2018;**22**:313.
19. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 2003;**63**:1468—74.
20. Rocha R, Funder JW. The pathophysiology of aldosterone in the cardiovascular system. *Ann N Y Acad Sci* 2002;**970**:89—100.
21. Wu VC, Lo SC, Chen YL, Huang PH, Tsai CT, Liang CJ, et al. Endothelial progenitor cells in primary aldosteronism: a biomarker of severity for aldosterone vasculopathy and prognosis. *J Clin Endocrinol Metab* 2011;**96**:3175—83.
22. Chang CM, Peng KY, Chan CK, Lin YF, Liao HW, Chang JG, et al. Divergent characteristics of T-cell receptor repertoire between essential hypertension and aldosterone-producing adenoma. *Front Immunol* 2022;**13**:853403.
23. Herrada AA, Contreras FJ, Marini NP, Amador CA, Gonzalez PA, Cortes CM, et al. Aldosterone promotes autoimmune damage by enhancing Th17-mediated immunity. *J Immunol* 2010;**184**:191—202.
24. Chou CH, Hung CS, Liao CW, Wei LH, Chen CW, Shun CT, et al. IL-6 trans-signalling contributes to aldosterone-induced cardiac fibrosis. *Cardiovasc Res* 2018;**114**:690—702.
25. Del Vecchio L, Locatelli F, Carini M. What we know about oxidative stress in patients with chronic kidney disease on dialysis-clinical effects, potential treatment, and prevention. *Semin Dial* 2011;**24**:56—64.
26. Muniz-Junqueira MI, Braga Lopes C, Magalhaes CA, Schleicher CC, Veiga JP. Acute and chronic influence of hemodialysis according to the membrane used on phagocytic function of neutrophils and monocytes and pro-inflammatory cytokines production in chronic renal failure patients. *Life Sci* 2005;**77**:3141—55.
27. Arlt W, Lang K, Sitch AJ, Dietz AS, Rhayem Y, Bancos I, et al. Steroid metabolome analysis reveals prevalent glucocorticoid excess in primary aldosteronism. *JCI insight* 2017;**2**.
28. Wu VC, Chueh SJ, Chen L, Chang CH, Hu YH, Lin YH, et al. Risk of new-onset diabetes mellitus in primary aldosteronism: a population study over 5 years. *J Hypertens* 2017;**35**:1698—708.
29. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A. Complications of Cushing's syndrome: state of the art. *Lancet Diabetes Endocrinol* 2016;**4**:611—29.
30. Guarnotta V, Ferrigno R, Martino M, Barbot M, Isidori AM, Scaroni C, et al. Glucocorticoid excess and COVID-19 disease. *Rev Endocr Metab Disord* 2021;**22**:703—14.
31. Farshidfar F, Koleini N, Ardehali H. Cardiovascular complications of COVID-19. *JCI Insight* 2021:6.
32. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol* 2020;**17**:543—58.
33. Kotlyar E, Vita JA, Winter MR, Awtry EH, Siwik DA, Keaney Jr JF, et al. The relationship between aldosterone, oxidative stress, and inflammation in chronic, stable human heart failure. *J Card Fail* 2006;**12**:122—7.
34. Irita J, Okura T, Manabe S, Kurata M, Miyoshi K, Watanabe S, et al. Plasma osteopontin levels are higher in patients with

primary aldosteronism than in patients with essential hypertension. *Am J Hypertens* 2006;**19**:293—7.
35. Sun Y, Zhang J, Lu L, Chen SS, Quinn MT, Weber KT. Aldosterone-induced inflammation in the rat heart : role of oxidative stress. *Am J Pathol* 2002;**161**:1773—81.
36. Keidar S, Kaplan M, Pavlotzky E, Coleman R, Hayek T, Hamoud S, et al. Aldosterone administration to mice stimulates macrophage NADPH oxidase and increases atherosclerosis development: a possible role for angiotensin-converting enzyme and the receptors for angiotensin II and aldosterone. *Circulation* 2004;**109**:2213—20.
37. Strauch B, Petrak O, Zelinka T, Wichterle D, Holaj R, Kasalicky M, et al. Adrenalectomy improves arterial stiffness in primary aldosteronism. *Am J Hypertens* 2008;**21**:1086—92.
38. Wu VC, Yang SY, Lin JW, Cheng BW, Kuo CC, Tsai CT, et al. Kidney impairment in primary aldosteronism. *Clin Chim Acta* 2011;**412**:1319—25.
39. Rossi GP, Sechi LA, Giacchetti G, Ronconi V, Strazzullo P, Funder JW. Primary aldosteronism: cardiovascular, renal and metabolic implications. *Trends Endocrinol Metabol* 2008;**19**: 88—90.
40. Huang D, Yang H, Yu H, Wang T, Chen Z, Yao R, et al. A prediction model for major adverse cardiovascular events (MACE) in patients with coronavirus disease 2019 (COVID-19). *BMC Pulm Med* 2022;**22**:343.
41. McCurley A, Jaffe IZ. Mineralocorticoid receptors in vascular function and disease. *Mol Cell Endocrinol* 2012;**350**:256—65.
42. Moledina DG, Simonov M, Yamamoto Y, Alausa J, Arora T, Biswas A, et al. The association of COVID-19 with acute kidney injury independent of severity of illness: a multicenter cohort study. *Am J Kidney Dis* 2021;**77**:490—499 e1.
43. Volbeda M, Jou-Valencia D, van den Heuvel MC, Knoester M, Zwiers PJ, Pillay J, et al. Comparison of renal histopathology and gene expression profiles between severe COVID-19 and bacterial sepsis in critically ill patients. *Crit Care (London, England)* 2021;**25**:202.
44. Wu VC, Kuo CC, Wang SM, Liu KL, Huang KH, Lin YH, et al. Primary aldosteronism: changes in cystatin C-based kidney filtration, proteinuria, and renal duplex indices with treatment. *J Hypertens* 2011;**29**:1778—86.
45. Lam EY, Funder JW, Nikolic-Paterson DJ, Fuller PJ, Young MJ. Mineralocorticoid receptor blockade but not steroid withdrawal reverses renal fibrosis in deoxycorticosterone/salt rats. *Endocrinology* 2006;**147**:3623—9.
46. Ogata H, Yamazaki Y, Tezuka Y, Gao X, Omata K, Ono Y, et al. Renal injuries in primary aldosteronism: quantitative histopathological analysis of 19 patients with primary adosteronism. *Hypertension* 2021;**78**:411—21.
47. Calabuig JM, Garcia-Raffi LM, Garcia-Valiente A, Sanchez-Perez EA. Kaplan-meier type survival curves for COVID-19: a health data based decision-making tool. *Front Public Health* 2021;**9**:646863.
48. Thomas TS, Walpert AR, Shen G, Dunderdale C, Srinivasa S. Primary aldosteronism and COVID-19-related management, disease severit y, and outcomes: a retrospective cohort study. *J Endocrine Soc* 2023;**7**:bvad015.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.09.005.