Primary Aldosteronism Screening Rates Differ with Sex, Race, and Comorbidities

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BACKGROUND: Primary aldosteronism (PA) is a common but under-recognized cause of secondary hypertension. Data directly comparing screening rates across single and overlapping indications are lacking.

METHODS AND RESULTS: We conducted a retrospective review of adults with hypertension seen in outpatient clinics at a tertiary referral academic center between January 1, 2017, and June 30, 2020. We included patients with hypertension plus at least one of the following: resistant hypertension; age<35 years; obstructive sleep apnea; hypokalemia; or an adrenal mass. We excluded patients with adrenal insufficiency, severe renal disease, or heart failure, and renovascular hypertension. Of 203,535 patients with hypertension, 86,044 (42.3%) met at least 1 PA screening criterion, and of these, 2,898 (3.4%) were screened for PA. Screening occurred in 2.7% of patients with resistant hypertension; 4.2% of those with obstructive sleep apnea; 5.1% of those <35 years; 10.0% of those with hypokalemia; and 47.3% of patients with an adrenal mass. Screening rates were higher in patients with multiple risk factors: 16.8% for ≥3, 5.7% for 2, and 2.5% for 1 criterion. Multiple logistic regression showed that the odds of PA screening were higher in patients with hypokalemia: odds ratio (95% CI): 3.0 (2.7–3.3); women: 1.3 (1.2–1.4); Black versus White: 1.5 (1.4–1.7); those with obstructive sleep apnea, chronic renal disease, stroke, and dyslipidemia.

CONCLUSIONS: Consideration for PA is given in a small subset of at-risk patients, and typically after comorbidities have developed.

Key Words: adrenal mass ■ aldosterone ■ hypertension ■ hypokalemia ■ primary aldosteronism ■ renin ■ screening

Primary aldosteronism (PA) is the leading cause of endocrine hypertension, with an estimated prevalence of at least 10% among patients with hypertension, and more than 20% of resistant hypertension cases.1–4 PA enhances the risk of renal and cardiovascular morbidity and mortality via direct insults to target organs, independently of hypertension.5, 6 Inappropriate activation of the mineralocorticoid receptors leads to myocardial fibrosis, endothelial dysfunction, and microalbuminuria.7–12 Prompt diagnosis of PA and targeted therapy with unilateral adrenalectomy or mineralocorticoid receptor antagonists can mitigate the excessive cardiovascular and renal risk.13–15

Expert guidelines recommend screening for PA in patients with resistant hypertension, hypertension and hypokalemia, and in those with early onset hypertension.16, 17 Additionally, the Endocrine Society guidelines recommend PA screening in patients with hypertension and obstructive sleep apnea (OSA) or an adrenal mass.2 Nevertheless, PA remains largely under-recognized. Across the U.S. Veterans Health Administration and in select academic institutions, screening for PA was reported in only ~3% of patients with resistant hypertension.18–20 Underestimation of PA prevalence, complex testing logistics, and lack of familiarity with results interpretation have been attributed to PA underdiagnosis.21, 22 Data comparing PA screening across at-risk populations are minimal. Several indications for PA screening, including resistant hypertension, OSA, and adrenal masses are common among...
the age group most often affected by PA. It remains unknown, however, if screening for PA occurs more often in patients with multiple risk factors. To further understand the gaps in PA recognition, we aimed to compare the patterns of screening among all major indications, alone and in combination, in a large tertiary referral center with nationally recognized adrenal expertise.

**METHODS**

**Study Design and Participants**

We conducted a retrospective study of adult patients (age ≥18 years) with hypertension seen at the University of Michigan outpatient clinics between January 1, 2017, and June 30, 2020. We first identified patients with a diagnosis of hypertension, based on International Classification of Diseases, Ninth and Tenth Revision (ICD-9, ICD-10) codes. We excluded patients with stage III and IV heart failure, adrenal insufficiency, congenital adrenal hyperplasia, chronic kidney disease (CKD) stages ≥4, renovascular hypertension, and those with a pre-existing diagnosis of PA. Among patients with hypertension included, we identified candidates for PA screening as patients who met at least one of the following criteria: (1) apparent resistant hypertension (defined by active hypertension while simultaneously taking ≥3 antihypertensive agents, or taking ≥4 antihypertensive agents); (2) hypertension onset at age ≤35 years old; (3) obstructive sleep apnea (OSA); (4) hypokalemia (based on any one of the following: a serum potassium below normal range; a diagnosis of hypokalemia; or having a potassium supplement prescription); or (5) an adrenal mass. The Institutional Review Board approved the study protocol, including a waiver of informed consent for the retrospective data collection (HUM00175789). The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Data Collection**

Using the provided inclusion and exclusion criteria, medical records were queried by the University of Michigan Data Office. For patients included in the study, PA screening was recorded if plasma aldosterone concentration (PAC) and either plasma renin activity or direct renin concentration were measured simultaneously at any time in the available electronic medical records (since year 2000). Patients with a diagnosis of PA documented prior to the initial aldosterone and renin measurements available in our system (N=220) were excluded, as those cases are typically outside referrals who present to our clinics for subtyping or therapy. For patients who underwent PA screening, demographics, and clinical data, including laboratory studies, comorbidities, and medications, were collected from the office visit associated with PA screening. For patients who did not have PA testing, demographics and clinical data were collected from the most recent clinical encounter.

**Statistical Analysis**

Data analysis was conducted using Stata (Version 17.0 BE, StataCorp LP, College Station, TX) and R-3.4.3 (Foundation for Statistical Computing, Vienna, Austria). Comparison between patients screened and those not screened was performed using the Student’s t test for continuous variables, and the Chi-Squared test for categorical variables. Univariate and multivariate logistic regression were used to assess the association between various factors and PA screening. LASSO regression was used to select important factors associated with PA screening. We defined significance as a two-tailed P<0.05.
RESULTS

Rates of PA Screening

Of a total of 203,535 patients with hypertension seen in our outpatient clinics during the study period, a total of 86,044 (42.3%) patients met at least one criterion for PA screening, including 66,146 (76.9%) with apparent resistant hypertension, 30,602 (36.6%) with hypertension and OSA, 5,964 (6.9%) with hypertension and hypokalemia, 9,027 (10.5%) with early onset hypertension, and 9,551 (11.1%) with hypertension and an adrenal mass (Figure 1). Primary aldosteronism screening occurred in 2.2% (1,813) of patients with resistant hypertension; 4.2% (1,297) of those with hypertension and OSA; 5.1% (461) of those with early-onset hypertension; 10.0% (599) of those with hypertension and hypokalemia; and 47.3% (452) of patients with hypertension and an adrenal mass (Figure 1).

Most patients only met 1 screening criterion (79.1%), although 19.3% met 2, and 1.6% met 3 or more screening criteria (Figure 2 and Table 1). Screening for PA was performed in 2.5% of patients with 1 screening criterion, in 5.7% of patients with 2 screening criteria, in 15.8% of patients with 3 screening criteria, and in 51.4% of patients meeting 4 screening criteria (Figure 1).

Of the 2898 patients screened, 14.3% had a recorded diagnosis of PA (Figure 1). Screening was most often positive among patients with hypertension and hypokalemia (28.5%), followed by those with and adrenal mass (25.0%), and resistant hypertension (16.1%), while patients with early onset hypertension had the lowest positivity rate (6.1%).

Factors Associated With PA Screening

PA screening was conducted most often by internists or primary care physicians (35.2%), followed by endocrinologists (23.7%), nephrologists (14.8%), and cardiologists (12.8%).

Patient demographics and clinical characteristics are presented in Table 2. Compared with patients not screened for PA, screened patients were younger (58.3±14.2 years versus 66.5±13.2 years) and more often women (52.7% versus 44.2%, P<0.001 for both). While most patients in the study were White (82.9%), the proportion of Black patients was almost twice as high among patients who were screened versus those never screened for PA (23.1% versus 12.1%, P<0.001). Additionally, patients screened had higher rates of CKD (39.2% versus 25.7%), stroke (17.1% versus 12.9%), OSA (50.4% versus 39.8%), dyslipidemia (66.6% versus 59.3%), and diabetes (45.4% versus 40.2%, P<0.001 for all).

Multiple logistic regression showed that, across the entire cohort, the odds of PA screening were higher in women (odds ratio [OR], 1.30 [95% CI, 1.20–1.41]; Black versus White patients (OR, 1.52 [95% CI, 1.38–1.67]); patients with history of hypokalemia (OR, 3.00 [95% CI, 2.75–3.28]); OSA (OR, 1.40 [95% CI, 1.29–1.52]); stroke (OR, 1.44 [95% CI, 1.29–1.60]); CKD (OR, 1.73 [95% CI, 1.59–1.89]); dyslipidemia (OR, 1.42 [95% CI, 1.30–1.56]); and diabetes (OR, 1.15 [95% CI, 1.06–1.25], Table 3). Conversely, patients with congestive heart failure (OR, 0.79 [95% CI, 0.71–0.88]), and current or former smokers were less likely to be screened (Table 3).

Representing the largest group in the study, patients with apparent resistant hypertension displayed similar associations between PA screening and patient characteristics (Table S1). In addition, the odds of PA screening increased with the number of antihypertensive agents (OR, 1.93 [95% CI, 1.81–2.05]).

Comparably, in patients with hypertension and OSA, the odds of PA screening were higher in women (OR, 1.37; 1.22–1.55); Black versus White patients (OR, 1.67; 1.44–1.93); patients with history of hypokalemia (OR, 3.09; 2.68–3.56); stroke (OR, 1.39; 1.18–1.64); CKD (OR, 2.30; 2.01–2.64); dyslipidemia (OR, 2.07; 1.78–2.41); and diabetes (OR, 1.21; 1.07–1.38, Table S2).

In patients with hypokalemia, the odds of PA screening were higher in Black versus White patients (OR, 1.51; 1.22–1.87); patients with history of OSA (OR, 1.63; 1.32–2.00); CKD (OR, 1.50; 1.23–1.85); and dyslipidemia (OR, 1.37; 1.11–1.70). Conversely, the odds of PA screening were lower in women (OR, 0.81; 0.67–0.98), and in patients with history atrial fibrillation (OR, 0.63; 0.47–0.85) or congestive heart failure (OR, 0.67 [95% CI, 0.51–0.86]) (Table S3).

Unlike other indications for PA screening, race was not associated with screening among patients with hypertension and adrenal masses and patients with early onset hypertension. Nevertheless, PA screening remained higher in those with hypokalemia (Tables S4 and S5).

DISCUSSION

In this study of more than 200,000 patients with hypertension, we assessed the rates and patterns of PA screening across various indications in a large university center, with immediate access to world experts in the field and all resources needed for PA diagnosis and subtyping. Despite these rich resources, we found that PA screening rates were overall not higher than those reported in the general population, but they increased in patients with multiple indications for PA screening. Surprisingly, we found that PA screening targets more women than men, and Black versus White patients with hypertension. More importantly, we show that PA screening is more often pursued following the development of comorbidities known to be
associated with PA, including CKD and cerebrovascular accidents.

International expert guidelines uniformly recommend screening for PA in patients with resistant hypertension, hypertension and hypokalemia, and early onset hypertension. 17, 24–26 Additionally, the Endocrine Society guidelines suggest PA screening in patients with adrenal masses and those with OSA. 2 We found that of all indications, treatment-resistant hypertension is the least likely to trigger PA testing. Resistant hypertension affects roughly 10% of adults in the United States, 27, 28 and it increases the cardiovascular morbidity and mortality. 29 Over 20% of patients with treatment-resistant hypertension have PA, 4 and PA further amplifies the cardiovascular and renal morbidity index above that rendered by high blood pressure. 5, 13 In our cohort, 16.1% of patients with apparent resistant hypertension who underwent PA testing had a documented PA diagnosis, which indicates that, at least for this indication, screening was not necessarily conducted in patients with the highest pre-test probability of PA.

Patients with hypertension and OSA constitute the second largest group at risk for PA, yet also among those least frequently screened for PA. While both PA and OSA are independent risk factors for resistant hypertension, the association between OSA and PA has been debated. 30, 31 Primary aldosteronism is thought to contribute to OSA by nocturnal redistribution of the expanded intravascular volume in the peri-pharyngeal tissue. 32 Treatment with mineralocorticoid receptor antagonists has been shown to improve the apnea-hypopnea index in patients with both OSA and resistant hypertension. 33–35 In a small prospective study of unselected patients referred for OSA evaluation, PA was suspected in 30% of 40 patients with OSA and

Figure 1. Study population and rates of primary aldosteronism screening. HTN indicates hypertension; and OSA, obstructive sleep apnea.
We found that 14.5% of patients had both apparent resistant hypertension and OSA, and only 3.7% of these were screened for PA.

Patients with early onset hypertension or hypokalemia were screened more often in our population (10%) than in other reports. In a retrospective population study of adults with hypertension and hypokalemia from Ontario, Canada, only 1.6% underwent testing for PA, while PA screening occurred in 5% of patients with apparent resistant hypertension and hypokalemia among US veterans. Considering that close to 30% of patients with hypertension and hypokalemia screened had a documented diagnosis of PA, it remains concerning that PA testing is not pursued in the vast majority of such patients.

Systematic evaluation of individuals with early onset hypertension for secondary causes of hypertension is lacking. In our population, 5.1% of patients with hypertension younger than 35 were screened for PA, and 6.1% of these had a PA diagnosis. Screening for secondary hypertension causes is widely accessible, and screening for PA has been shown to be cost-effective for patients with resistant hypertension. Considering the average lifetime span and the potential complications of unrecognized secondary hypertension, screening for curable forms, like PA, is likely to be particularly cost effective in young patients.

Of all at-risk groups, patients with hypertension and adrenal masses were most frequently tested for PA (44%), and about a quarter of those tested had positive screening results. The substantially higher rates of PA screening among patients with hypertension and adrenal masses versus all other at-risk groups is likely explained by the fact that many such patients are evaluated by endocrinologists. Prior studies reported a higher likelihood of PA testing by endocrinologists and nephrologists compared with internists and cardiologists. In our study, PA screening was conducted by endocrinologists and nephrologists (38.7%) more often than by internists or primary care physicians (37%). Considering that endocrinologists represent only ~0.85% and nephrologists ~1.21% of the active physician workforce in the US, these data suggest that strategies to encourage PA testing that target physicians at the forefront of hypertension treatment are highly needed.
Regarding clinical characteristics associated with PA screening, we found that beyond the expected association with hypokalemia, testing occurred more often in patients with multiple comorbidities known to be associated with PA, including CKD, dyslipidemia, stroke, and OSA, even after adjusting for age. Conversely, PA testing was less frequent in patients with history of coronary artery events or atrial fibrillation. These cardiovascular complications have also been associated with PA via aldosterone-mediated fibrosis, cardiac remodeling, and endothelial dysfunction. Despite this, our data confirm that most clinicians do not associate coronary artery disease and cardiac arrhythmias with PA.

Although men and White patients are typically overrepresented in PA cohorts, including from our institution, women versus men, and Black versus White patients underwent testing for PA more often. Black race was also associated with higher rates of PA testing among US veterans. Although Black individuals are known to have higher salt sensitivity, existing data suggest that the rates of hyperaldosteronism are similar in Black and White people. However, the prevalence of hypertension, including treatment-resistant hypertension, and related complications are higher among Black individuals, which could explain, at least in part, the higher rates of PA screening observed in this population. While there are well-recognized differences in aldosterone-driver mutation distributions between sexes, the true prevalence of PA among unselected men and women with hypertension remains unknown. Considering the higher age-specific rates of cardiovascular disease in men versus women, we expected to find that the disproportionate representation of men in published PA studies might reflect a bias towards higher PA screening rates in men. Surprisingly, we found that the adjusted likelihood of PA screening was 1.3-fold higher in women. Data from the Centers for Disease Control suggest that compared with men, women are 33% more likely to visit a doctor, and 100%
better at maintaining screening and preventive care, which could also explain the higher PA screening rates observed in women.

Our study has several limitations, including the retrospective aggregation of data, and lack of granular information. The large number of patients included made individual chart review unfeasible; thus, we ascertained PA screening based on concomitant plasma aldosterone and renin testing. Although these laboratory tests can be used for a variety of clinical reasons, we excluded all major indications other than suspected PA. Moreover, this approach could over- rather than under-estimate PA screening rates. Conversely, we could have missed testing done in outside institutions. Additionally, we excluded advanced CKD and congestive heart failure, because the renin-angiotensin-aldosterone system is severely altered in these disorders; it is conceivable, however, that a subset of these patients had undiagnosed PA. Future studies designed to conduct accurate PA testing in these populations would be of great value.

In summary, in this is study is of more than 200,000 patients with hypertension, we compared the rates of PA screening across various indications endorsed by international expert guidelines. We found that patients with resistant hypertension and those with hypertension and OSA account for the largest at-risk groups, yet they are rarely screened for PA. Conversely, patients with adrenal nodules and those with 3 or more risk factors for PA are offered screening more frequently. Our data suggest that screening for PA is triggered more often in patients with multiple risk factors and after cardiovascular and renal complications have occurred. To prevent such complications, initiatives to encourage PA screening among internists and primary care physicians, who are at the forefront of hypertension treatment, are critical.

ARTICLE INFORMATION
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Disclosures
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Supplemental Material
Tables S1–S5

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SUPPLEMENTAL MATERIAL
**Table S1.** Multivariable logistic regression assessing the effect of important demographic and clinical factors (selected using LASSO) on screening for primary aldosteronism in patients with resistant hypertension

| Factor                        | Odds ratio | 95% CI       | p-value |
|-------------------------------|------------|--------------|---------|
| Age                           | 0.96       | [0.95 - 0.96]| < 0.001|
| Sex (vs. men)                 |            |              |         |
| Women                         | 1.31       | [1.18 - 1.45]| < 0.001|
| Black                         | 1.45       | [1.29 - 1.64]| < 0.001|
| Race (vs. white)              |            |              |         |
| Asian                         | 1.10       | [0.79 - 1.53]| 0.567   |
| Other                         | 1.39       | [1.06 - 1.82]| 0.019   |
| Ethnicity                     |            |              |         |
| Non-Hispanic                  | 1.27       | [0.88 - 1.84]| 0.208   |
| Smoking status (vs. never smoker) | |              |         |
| Current smoker                | 0.62       | [0.52 - 0.75]| < 0.001|
| Former smoker                 | 0.82       | [0.74 - 0.92]| < 0.001|
| Body mass index               | 0.98       | [0.97 - 0.98]| < 0.001|
| Hypokalemia                   | 3.08       | [2.74 - 3.46]| < 0.001|
| Atrial fibrillation           | 0.88       | [0.76 - 1.01]| 0.062   |
| Myocardial infarction         | 0.84       | [0.72 - 0.98]| 0.029   |
| Congestive heart failure      | 0.61       | [0.54 - 0.70]| < 0.001|
| Obstructive sleep apnea       | 1.72       | [1.54 - 1.92]| < 0.001|
| Stroke                        | 1.46       | [1.28 - 1.66]| < 0.001|
| Chronic kidney disease        | 1.57       | [1.41 - 1.75]| < 0.001|
| Dyslipidemia                  | 1.39       | [1.24 - 1.56]| < 0.001|
| Diabetes mellitus             | 1.07       | [0.96 - 1.19]| 0.195   |
| Number of anti-hypertensive agents | 1.93     | [1.81 - 2.05]| < 0.001|
Table S2. Multivariable logistic regression assessing the effect of important demographic and clinical factors (selected using LASSO) on screening for primary aldosteronism in patients with hypertension and obstructive sleep apnea

| Variable                         | Odds ratio | 95% CI      | p-value |
|----------------------------------|------------|-------------|---------|
| Age                              | 0.94       | [0.94 - 0.95] | < 0.001 |
| Sex (vs. men)                    | 1.37       | [1.22 - 1.55] | < 0.001 |
| Race (vs. white)                 |            |             |         |
| Black                            | 1.67       | [1.44 - 1.93] | < 0.001 |
| Other                            | 1.11       | [0.81 - 1.53] | 0.511   |
| Smoking status (vs. never smoker)|            |             |         |
| Current smoker                   | 0.71       | [0.57 - 0.90] | 0.005   |
| Former smoker                    | 0.96       | [0.84 - 1.09] | 0.501   |
| Body mass index                  | 0.97       | [0.97 - 0.98] | < 0.001 |
| Hypokalemia                      | 3.09       | [2.68 - 3.56] | < 0.001 |
| Myocardial infarction            | 0.90       | [0.75 - 1.09] | 0.298   |
| Congestive heart failure         | 0.90       | [0.78 - 1.05] | 0.187   |
| Stroke                           | 1.39       | [1.18 - 1.64] | < 0.001 |
| Chronic kidney disease           | 2.30       | [2.01 - 2.64] | < 0.001 |
| Dyslipidemia                     | 2.07       | [1.78 - 2.41] | < 0.001 |
| Diabetes mellitus                | 1.21       | [1.07 - 1.38] | 0.003   |
Table S3. Multivariable logistic regression assessing the effect of important demographic and clinical factors (selected using LASSO) on screening for primary aldosteronism in patients with hypertension and hypokalemia

|                                | Odds ratio | 95% CI   | p-value |
|--------------------------------|------------|----------|---------|
| Age                            | 0.96       | [0.95 - 0.96] | < 0.001 |
| Sex (vs. men)                  | 0.81       | [0.67 - 0.98] | 0.027   |
| Black                          | 1.51       | [1.22 - 1.87] | < 0.001 |
| Other                          | 1.35       | [0.80 - 2.29] | 0.259   |
| Ethnicity                      | 1.52       | [0.78 - 2.95] | 0.219   |
| Smoking status (vs. never smoker) |          |          |         |
| Current smoker                 | 0.66       | [0.49 - 0.89] | 0.007   |
| Former smoker                  | 0.64       | [0.52 - 0.79] | < 0.001 |
| Body mass index                | 0.99       | [0.98 - 1.00] | 0.045   |
| Atrial fibrillation            | 0.63       | [0.47 - 0.85] | 0.003   |
| Myocardial infarction          | 1.08       | [0.80 - 1.45] | 0.614   |
| Congestive heart failure       | 0.67       | [0.51 - 0.86] | 0.002   |
| Obstructive sleep apnea        | 1.63       | [1.32 - 2.00] | < 0.001 |
| Stroke                         | 1.30       | [1.01 - 1.67] | 0.044   |
| Chronic kidney disease         | 1.50       | [1.23 - 1.85] | < 0.001 |
| Dyslipidemia                   | 1.37       | [1.11 - 1.70] | 0.003   |
| Diabetes mellitus              | 1.14       | [0.94 - 1.40] | 0.191   |
Table S4. Multivariable logistic regression assessing the effect of important demographic and clinical factors (selected using LASSO) on screening for primary aldosteronism in patients with hypertension onset at age <35 years

| Factor                                | Odds ratio | 95% CI       | p-value |
|----------------------------------------|------------|---------------|---------|
| Age                                    | 0.86       | [0.84 - 0.87] | < 0.001 |
| Sex (vs. men)                          | 1.30       | [1.06 - 1.59] | 0.012   |
| Race (vs. white)                       | 1.26       | [0.76 - 2.07] | 0.373   |
| Ethnicity (vs. Hispanic)               | 1.36       | [0.82 - 2.27] | 0.237   |
| Smoking status (vs. never smoker)      |            |               |         |
| Current smoker                         | 0.70       | [0.49 - 1.00] | 0.051   |
| Former smoker                          | 1.18       | [0.90 - 1.54] | 0.227   |
| Body mass index                        | 0.98       | [0.97 - 0.99] | < 0.001 |
| Hypokalemia                            | 2.94       | [2.18 - 3.97] | < 0.001 |
| Obstructive sleep apnea                | 1.84       | [1.40 - 2.41] | < 0.001 |
| Chronic kidney disease                 | 1.20       | [0.92 - 1.56] | 0.17    |
| Dyslipidemia                           | 1.84       | [1.41 - 2.39] | < 0.001 |
Table S5. Multivariable logistic regression assessing the effect of important demographic and clinical factors (selected using LASSO) on screening for primary aldosteronism in patients with hypertension and adrenal nodules

| Factor                        | Odds ratio | 95% CI       | p-value |
|-------------------------------|------------|--------------|---------|
| Age                           | 0.95       | [0.93 - 0.96]| < 0.001|
| Sex (vs. white)               |            |              |         |
| Black                         | 1.23       | [0.78 - 1.93]| 0.365   |
| Other                         | 1.26       | [0.51 - 3.12]| 0.61    |
| Ethnicity (vs. Hispanic)      |            |              |         |
| Non-Hispanic                  | 0.78       | [0.21 - 2.98]| 0.72    |
| Smoking status (vs. never smoker) |         |              |         |
| Current smoker                | 0.74       | [0.50 - 1.08]| 0.114   |
| Hypokalemia                   | 2.15       | [1.45 - 3.19]| < 0.001|
| Myocardial infarction         | 0.69       | [0.42 - 1.13]| 0.141   |
| Obstructive sleep apnea       | 1.50       | [1.08 - 2.08]| 0.016   |
| Chronic kidney disease        | 1.26       | [0.89 - 1.78]| 0.189   |
| Diabetes mellitus             | 1.24       | [0.91 - 1.67]| 0.168   |