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# *APOL1* Risk Variants, Acute Kidney Injury, and Death in Participants With African Ancestry Hospitalized With COVID-19 From the Million Veteran Program

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**IMPORTANCE** Coronavirus disease 2019 (COVID-19) confers significant risk of acute kidney injury (AKI). Patients with COVID-19 with AKI have high mortality rates.

**OBJECTIVE** Individuals with African ancestry with 2 copies of apolipoprotein L1 (*APOL1*) variants G1 or G2 (high-risk group) have significantly increased rates of kidney disease. We tested the hypothesis that the *APOL1* high-risk group is associated with a higher-risk of COVID-19–associated AKI and death.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective cohort study included 990 participants with African ancestry enrolled in the Million Veteran Program who were hospitalized with COVID-19 between March 2020 and January 2021 with available genetic information.

**EXPOSURES** The primary exposure was having 2 *APOL1* risk variants (RV) (*APOL1* high-risk group), compared with having 1 or 0 risk variants (*APOL1* low-risk group).

**MAIN OUTCOMES AND MEASURES** The primary outcome was AKI. The secondary outcomes were stages of AKI severity and death. Multivariable logistic regression analyses adjusted for preexisting comorbidities, medications, and inpatient AKI risk factors; 10 principal components of ancestry were performed to study these associations. We performed a subgroup analysis in individuals with normal kidney function prior to hospitalization (estimated glomerular filtration rate ≥60 mL/min/1.73 $m^2$).

**RESULTS** Of the 990 participants with African ancestry, 905 (91.4%) were male with a median (IQR) age of 68 (60-73) years. Overall, 392 (39.6%) patients developed AKI, 141 (14%) developed stages 2 or 3 AKI, 28 (3%) required dialysis, and 122 (12.3%) died. One hundred twenty-five (12.6%) of the participants were in the *APOL1* high-risk group. Patients categorized as *APOL1* high-risk group had significantly higher odds of AKI (adjusted odds ratio [OR], 1.95; 95% CI, 1.27-3.02; $P = .002$), higher AKI severity stages (OR, 2.03; 95% CI, 1.37-2.99; $P < .001$), and death (OR, 2.15; 95% CI, 1.22-3.72; $P = .007$). The association with AKI persisted in the subgroup with normal kidney function (OR, 1.93; 95% CI, 1.15-3.26; $P = .01$). Data analysis was conducted between February 2021 and April 2021.

**CONCLUSIONS AND RELEVANCE** In this cohort study of veterans with African ancestry hospitalized with COVID-19 infection, *APOL1* kidney risk variants were associated with higher odds of AKI, AKI severity, and death, even among individuals with prior normal kidney function.

Supplemental content

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A recent study of US veterans hospitalized with COVID-19 showed that acute kidney injury (AKI) was more common in non-Hispanic Black veterans compared with non-Hispanic White veterans.[1] Importantly, AKI in non-Hispanic Black veterans was also associated with a higher risk of death.[1] Studies suggest that African ancestry-specific kidney risk genetic variants may play a role in the risk of AKI in patients infected with COVID-19.[2,3]

Clinically relevant risk variants in the gene encoding for apolipoprotein L1 (*APOL1*) are common in individuals with African ancestry in the US, where approximately 45% carry at least 1 high-risk variant (RV) and 12% to 13% carry 2 RVs.[4-9] The 2 RVs, termed G1 and G2, are common in individuals of West African descent owing to positive genetic selection. Individuals with at least 1 RV are resistant to lethal *Trypanosoma brucei* infections.[9-12] However, having 2 RVs is associated with chronic kidney disease (CKD). The *APOL1* RVs partially explain the disparities observed in the risk of end-stage kidney disease (ESKD) among individuals with African ancestry.[13-15] In addition, *APOL1* RVs are associated with several forms of nondiabetic kidney disease.[16] Whether *APOL1* RVs are associated with AKI in general has not been established.[17-19]

The pathophysiology of AKI in individuals with COVID-19 is poorly understood and likely multifactorial, particularly with respect to patients with *APOL1* risk variants. Expression of *APOL1* in kidney cells is upregulated by inflammation,[3,10,20,21] which has been observed in several forms of kidney disease, including focal segmental glomerulosclerosis (FSGS), now well described in the COVID-19 literature.[22-25] However, it appears that most cases are owing to acute tubular injury during critical illness, where the exaggerated inflammatory response and robust immune activation may be a second hit.[3,20,26,27]

In this study, we leveraged a national cohort of US veterans hospitalized with COVID-19 with genetic information and with African ancestry through the VA Million Veteran Program (MVP)[28] to evaluate the association of *APOL1* high-risk group (2 RVs) in African ancestry participants with AKI. Because AKI is a strong predictor of mortality in patients with COVID-19,[1] our secondary goal was to evaluate the association of *APOL1* genotypes with the risk of death.

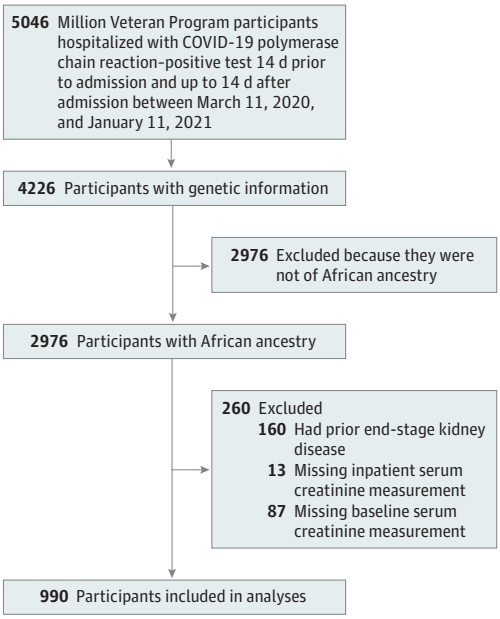
### Key Points

**Question** Are *APOL1* high-risk genotypes observed in individuals with African ancestry associated with acute kidney injury (AKI) and death following hospitalization for COVID-19?

**Findings** In this cohort of 990 veterans with African ancestry hospitalized with COVID-19, 1 in 8 had *APOL1* high-risk genotypes. Of those with high-risk genotypes, 51.2% had AKI, and 19.2% died, suggesting that high-risk genotype may be associated with a 2-fold increase in the odds of severe AKI and death; this increased risk was observed even in patients with normal kidney function prior to COVID-19.

**Meaning** *APOL1* high-risk genotypes were associated with increased odds of AKI, AKI severity, and death in individuals with African ancestry hospitalized with COVID-19.

Figure 1. Flowchart for Patient Eligibility




## Methods

### Study Population and Design

We identified 5046 MVP participants hospitalized with COVID-19 between March 11, 2020 and January 11, 2021. Of these, 4226 had genetic information. *APOL1* RVs, our exposure of interest (individuals with 2 RVs were considered high-risk group), are found in individuals of recent West African ancestry.[29,30] Consistent with this knowledge, we examined but found no participants without African ancestry who carried a high-risk *APOL1* genotype. Hence, the cohort consisted of (1) MVP participants hospitalized with COVID-19, (2) those with genetic information available, and (3) those with African ancestry.[28] After applying other exclusion criteria needed for AKI assessment as specified, our study sample size was 990 individuals (**Figure 1**).

Data were obtained from the VA Corporate Data Warehouse (CDW), the MVP Study Mart, the Observational Medical Outcomes Partnership version 5, and the COVID Share Data Resources.[31-33] COVID-19 was diagnosed based on a positive polymerase chain reaction test result for SARS-CoV-2 from a nasopharyngeal specimen between March 1, 2020 and January 11, 2021 (eFigure 1 in Supplement 1). Participants entered the cohort if they had positive SARS-CoV-2 testing results and were hospitalized 14 days prior or 14 days after the positive test result. The distribution of the date of admission with regard to test positivity are presented in eFigure 2 in Supplement 1. Overall, 934 (95%) of the individuals had a positive test within the first 3 days of hospitalization or prior to the admission date. The MVP received approval by the VA Central institutional review board (IRB), the IRB of each site, and the MVP COVID-19 Scientific Steering Committee. Written informed consent was obtained from all participants. Data analysis was conducted

between February 2021 and April 2021. This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines for observational research.[34]

## Cohort Exclusion Criteria

Participants were excluded if they had a preadmission history of ESKD, defined as previous dialysis or kidney transplant and those with a baseline estimated glomerular filtration rate (eGFR) lower than 15 mL/min/1.73 $m^2$ (n = 160) (eTable 1 in Supplement 1) or did not have serum creatinine levels measured during hospitalization (n = 13). We also excluded patients with no baseline outpatient serum creatinine level measurement used to characterize AKI, defined as the mean outpatient creatinine levels within the 7 to 365 days prior to hospitalization (n = 87)[35] (Figure 1). Participant AKI assessment was restricted to the first qualifying hospitalization during the study period.

## Outcomes and Follow-up

The primary outcome was AKI, defined using a modified Kidney Disease Improving Global Outcomes (KDIGO) creatinine-based criterion as a 0.3 mg/dL or 50% increase in serum creatinine levels from baseline using the peak serum creatinine during hospitalization (eTable 2 in Supplement 1).[36]

Our secondary outcomes included a modified KDIGO AKI severity stages result (stage 1, 0.3 mg/dL or 50% increase from baseline; stage 2, 100% increase from baseline; and stage 3, 200% increase from baseline or acute kidney replacement therapy [KRT]) or death. In this study, KRT was identified by diagnostic and procedural codes[37] (eTable 3 in Supplement 1). Dates of death were obtained from the VA vital status files of the CDW.[38,39]

Because our goal was to capture AKI events that were proximally related to COVID-19 infection, participants were followed until discharge or up to 30 days because late AKI occurring after 30 days may be more likely owing to hospital complications. For the death outcome, participants were followed for up to 30 days after admission, consistent with other VA studies.[39-41]

Exploratory analysis included dipstick proteinuria and hematuria measurements at baseline and on admission,[42] mechanical ventilation, and vasopressors.

## *APOL1* Genotype Exposure

*APOL1* RVs G1 (rs73885319 p.S342G; rs60910145 p.I384M) and G2 (rs71785313, a 6-base pair deletion that removes amino acids N388 and Y389) were directly genotyped on the Affymetrix Axiom Biobank Array on DNA extracted from whole blood.[4] Participants were defined as 2 RV carriers if they were homozygotes for G1/G1, homozygotes for G2/G2, or compound heterozygotes for G1/G2. The genotyping was completed by the MVP Genomic Core.[43] The G1 and G2 genotypes were in Hardy-Weinberg equilibrium.

## Subgroup Analysis

A subgroup analysis was planned for all outcomes, restricted to the population with baseline eGFR levels of 60 mL/min/1.73 $m^2$ or higher, to evaluate if the effect of *APOL1* high-risk genotypes in the risk of AKI in the context of COVID-19 was independent of CKD.

## Covariates

Characteristics reported include demographics, comorbidities, hospitalization characteristics, laboratory tests, and medications. Determination of ancestry was based on a unified classification algorithm developed by MVP.[44] This algorithm integrates genetically inferred ancestry based on the top 30 principal components of ancestry (PCs) with self-identified race/ethnicity (SIRE). The HARE (Harmonizing Genetic Ancestry and Self-identified Race/Ethnicity) algorithm classifies an MVP participant as "African" if their genetic ancestry is consistent with "African ancestry" and it informs ancestry in those with missing SIRE information.[44] In MVP African ancestry assignment is population level and is derived from projecting the genetic PCs of MVP to those in the 1000 Genomes Project reference panel.[43]

Baseline comorbidities were obtained up to 730 days before the SARS-CoV-2 positive test. In-hospital risk factors for AKI were collected during the hospitalization prior to peak AKI. Drug exposures associated with high-risk of AKI were documented if they were administered prior to the peak creatinine using the bar-coded medication administration (BCMA) in the inpatient setting. Outpatient ACE inhibitors or ARB exposure was defined as a prescription fill within 180 days prior to admission by assessing outpatient VA pharmacy files. Diagnoses were defined using the *International Classification of Diseases, Ninth Revision, Tenth Revision (ICD-9, ICD-10)* procedures codes ICD-9/ICD-10 and Current Procedural Terminology (CPT) codes (eTable 3 in Supplement 1). Levels of eGFR were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[45]

## Statistical Analyses

The primary exposure variable was *APOL1* variable high-risk group defined by the presence of 2 RVs (recessive model of inheritance). Logistic regression models were used to study the association of the exposure and the outcomes of interest. We also used a partial proportional odds (PPO) regression model to study the association of the *APOL1* high-risk group and increasing severity stages of AKI.[46] Nested multivariable models included (a) model 1, minimally adjusted (demographics, baseline eGFR and 10 PCs of ancestry) and (b) model 2, fully adjusted, also adjusted for preexisting comorbid conditions and inpatient risk factors. All logistic regression models passed the Goodness of fit test by the Hosmer-Lemeshow test (eTable 4 in Supplement 1). When conducting proportional odds regression analyses, proportional odds were assumed for all variables except for baseline eGFR, diastolic blood pressure, and remdesivir, as suggested by the Brant test and addressed by the PPO model[46,47] (eTable 5 in Supplement 1). Nonlinear terms and secular effects were tested (eTable 6 and eTable 7 in Supplement 1). A subgroup analysis was done restricting the analytical file to individuals with a baseline eGFR level of 60 mL/min/1.73 $m^2$ or higher. Sensitivity analyses restricted the outcome to AKI stages 2 and 3 (eTable 8 in Supplement 1).

Exploratory analysis included other models of inheritance (codominant and dominant) (eTable 9 in Supplement 1) and dipstick proteinuria and hematuria. All statistical tests were 2-sided, where a $P = .05$ or a 95% CI that did not contain unity were considered statistically significant for the primary outcome. All analyses were conducted using R statistical software (version 3.6.1.; R Foundation, Inc).

## Results

### Baseline and Clinical Characteristics for the Participants

We studied 990 veterans enrolled in the MVP hospitalized with COVID-19 infection between March 2020 and January 2021, genotyped for *APOL1* risk variants, who were of African ancestry and satisfied cohort entry criteria for AKI assessment (Figure 1). Baseline cohort characteristics by *APOL1* genotype risk-group were summarized (**Table 1**). Clinical characteristics were similar across the different *APOL1* risk groups, including baseline eGFR levels and the proportion of individuals with eGFR levels lower than 60 mL/min/1.73 $m^2$, diabetes, and hypertension.

Demographics and participant characteristics overall and by AKI status were summarized (**Table 2**). Overall, 905 (91.4%) were men, median (IQR) age was 68 (60-73) years, 701 (71%) had a GFR level of 60 mL/min/1.73 $m^2$ or higher, with 493 (51%) of the participants hospitalized September 2020 or later (Table 2; eFigure 1 in Supplement 1).

The incidence of AKI was 392 (39.6%). Overall, AKI rates per month among study participants varied and are shown in eFigure 3 in Supplement 1. Of 392 individuals with AKI, 251 (25%) had stage 1, 59 (6%) stage 2, and 82 (8%) stage 3, including 28 (3%) who received dialysis due to AKI. Compared with individuals without AKI, individuals with AKI were older, and more likely to have eGFR levels lower than 60 mL/min, diabetes and hypertension, and positive baseline dipstick proteinuria.

Mechanical ventilation and vasopressors were required by 141 and 98 individuals, respectively. One-hundred twenty-two individuals died. Individuals with AKI were more likely than individuals without AKI to require mechanical ventilation (29% vs 5%, $P < .001$), vasopressors (22% vs 2%, $P < .001$), and to die (26% vs 3%, $P < .001$) (Table 2).

### *APOL1* Genotype

One-hundred twenty-five study participants (12.6%) carried 2 *APOL1* risk alleles, consistent with frequencies reported in other studies of individuals with African ancestry in the US.[4-7] However, 64 of 392 (16.3%) with AKI had 2 *APOL1* RVs compared with 61 of 598 (10.2%) without AKI ($P = .005$). Furthermore, we observed a dose relationship with more severe forms of AKI, with stages 2 and stage 3 having 22.0% and 20.7% high-risk genotypes, respectively, with only 13.5% with stage 1 AKI having the high-risk genotype (eFigure 4 in Supplement 1).

The *APOL1* high-risk genotype doubled the risk of severe stages 2 and 3 AKI, with incidences of stages 2 and 3 AKI in the *APOL1* high-risk group of 7 (13.6%) and 13 (10.4%), respectively, compared with 65 (7.5%) and 46 (5.3%) in the *APOL1* low-risk group. For stage 1, the incidence was 27.2% for the *APOL1* high-risk vs 25.1% for *APOL1* low-risk group (**Figure 2**) (Table 1).

### Association of *APOL1* With Incident AKI and AKI Severity

In the minimally adjusted model (model 1), individuals with the *APOL1* high-risk group had significantly increased odds of incident AKI (odds ratio [OR], 1.80; 95% CI, 1.21-2.69; $P = .004$). This association was also observed in the fully adjusted model (model 2) that included outpatient comorbidities and inpatient risk factors for incident AKI (OR, 1.95; 95% CI, 1.27-3.02; $P = .002$) (**Table 3**). For the association with AKI severity, we observed an increase of 88% in the odds of more severe stages of AKI (OR, 1.88; 95% CI, 1.30-2.71; $P = .001$) in model 1. The association was also observed in model 2 (OR, 2.03; 95% CI, 1.37-2.99; $P < .001$) (Table 3).

### Association of *APOL1* With AKI and AKI Severity in the Subgroup of Individuals With Normal Baseline Kidney Function

Among individuals with baseline eGFR levels of 60 mL/min/1.73 $m^2$ or higher (n = 701), participants in the *APOL1* high-risk group had significantly increased odds of experiencing AKI in both model 1 (OR, 1.88; 95% CI, 1.18-2.99; $P = .008$) and in model 2 (OR, 1.93; 95% CI, 1.15-3.26; $P = .01$) (Table 3). There was also an increase in the odds of more severe stages of AKI in model 1 (OR, 1.98; 95% CI, 1.28-3.06; $P = .002$) and in model 2 (OR, 2.11; 95% CI, 1.31-3.39; $P = .002$) (Table 3).

### Sensitivity Analysis

In the sensitivity analysis restricting the outcome to AKI stages 2 and 3, a 2-fold increase in the odds of AKI stages 2 and 3 in the *APOL1* high-risk group was also noted, consistent with the primary analyses, both for the entire cohort and the subgroup with normal eGFR levels (eTable 8 in Supplement 1).

### Association of *APOL1* Risk Variants With Death, Mechanical Ventilation, and the Use of Vasopressors

There were 122 (12.3%) deaths overall; 24 (19.2%) in the *APOL1* high-risk and 98 (11.3%) in the *APOL1* low-risk group. The *APOL1* high-risk group was associated with a 1.92 fold increase in the odds of death in model 1 (OR, 1.92; 95% CI, 1.13-3.17; $P = .01$) and in model 2 (OR, 2.15; 95% CI, 1.22-3.72; $P = .007$) (Table 3). This association was also present in the subgroup with normal eGFR levels, in model 1 (OR, 2.54; 95% CI, 1.32-4.72; $P = .004$) and model 2 (OR, 2.51; 95% CI, 1.21-5.05; $P = .01$). Overall, 102 (84%) individuals who died experienced AKI.

*APOL1* high-risk genotype was not associated with mechanical ventilation (OR, 1.51; 95% CI, 0.86-2.55; $P = .10$) or a vasopressor requirement (OR, 1.61; 95% CI, 0.85-2.89; $P = .10$) in the fully adjusted models.

### Exploratory Analyses

#### Association of *APOL1* Risk Variants With Proteinuria and Hematuria

Urine dipstick proteinuria data were available in 614 participants at baseline. There was no association in the *APOL1* high-risk group with outpatient baseline proteinuria in those with available measurements (OR, 1.12; 95% CI, 0.68-1.80; $P = .60$).

Table 1. Participants Clinical Characteristics According to *APOL1* Genotype Risk Group

| Characteristic | No. | *APOL1*, No. (%) | | SMD[a] |
|---|---|---|---|---|
| | | Low-risk group (1 or 0 risk variants) | High-risk group (2 risk variants) | |
| No. | | 865 | 125 | |
| Baseline characteristics (outpatient) | | | | |
| Sex | | | | 0.13 |
| Female | 990 | 70 (8.0) | 15 (12.0) | |
| Male | 990 | 795 (91.9) | 110 (88.0) | |
| Age, median (IQR), y | 990 | 68.0 (60.0-73.0) | 68.0 (62.0-73.0) | 0.05 |
| Baseline | | | | |
| eGFR, median (IQR), mL/min/1.73 $m^{2b}$ | 990 | 72.4 (56.5-88.3) | 70.9 (59.7-86.3) | 0.02 |
| eGFR <60 mL/min/1.73 $m^2$ | 990 | 256 (29.6) | 33 (26.4) | 0.07 |
| Creatinine, median (IQR), mg/dL | 990 | 1.19 (1.00-1.43) | 1.18 (1.00-1.40) | 0.001 |
| BMI | 988 | 30.0 (25.6-34.8) | 28.7 (25.1-34.2) | 0.17 |
| Diabetes mellitus type 2 | 988 | 519 (60.1) | 73 (58.9) | 0.02 |
| Hypertension | 988 | 736 (85.2) | 104 (83.9) | 0.04 |
| Cardiovascular disease | 988 | 239 (27.7) | 42 (33.9) | 0.14 |
| Congestive heart failure | 988 | 165 (19.1) | 22 (17.7) | 0.04 |
| COPD | 988 | 236 (27.3) | 39 (31.5) | 0.09 |
| Liver disease | 988 | 90 (10.4) | 16 (12.9) | 0.08 |
| Human immunodeficiency virus | 990 | 4.3 (5) | 2 (0.2) | 0.19 |
| Outpatient dipstick proteinuria during the year prior | 614 | | | 0.06 |
| Negative or trace | | 341 (63.9) | 49 (61.3) | |
| 1+ | | 96 (18.0) | 15 (18.8) | |
| ≥2+ | | 97 (18.2) | 16 (20.0) | |
| Outpatient prescriptions | | | | |
| RAAS inhibition the 180 d prior Inpatient characteristicsto hospitalization | 990 | 440 (50.9) | 65 (52.0) | 0.02 |
| Admission values, median (IQR) | | | | |
| Serum albumin, g/dL | 821 | 3.60 (3.20-4.00) | 3.60 (3.20-3.90) | 0.15 |
| Serum creatinine, mg/dL | 922 | 1.30 (1.05-1.77) | 1.30 (0.98-1.80) | 0.03 |
| BP, mmHg | | | | |
| Systolic | 976 | 132 (117-148) | 133 (119-148) | 0.02 |
| Diastolic | 974 | 78.0 (69.0-87.0) | 78.0 (70.0-88.0) | 0.10 |
| Hemoglobin, g/dL | 853 | 13.2 (11.8-14.4) | 13.3 (12.0-14.5) | 0.11 |
| Lymphocyte count, cells/$mm^3$ | 835 | 5.65 (1.10-18.2) | 2.71 (0.90-17.9) | 0.02 |
| C reactive protein, g/L | 347 | 12.6 (5.40-68.5) | 20.6 (9.77-76.5) | 0.06 |
| Ferritin, ng/mL | 392 | 435 (226-833) | 454 (203-804) | 0.07 |
| Admission dipstick proteinuria | 357 | | | 0.4 |
| Negative or trace | | 94 (31.2) | 13 (23.2) | |
| 1+ | | 79 (26.2) | 8 (14.3) | |
| ≥2+ | | 128 (42.5) | 35 (62.5) | |
| Hospitalization characteristics | | | | |
| Acute kidney injury | 990 | 328 (37.9) | 64 (51.2) | 0.3 |
| AKI severity stages | 990 | | | 0.3 |
| 0 | | 537 (62.1) | 61 (48.8) | |
| 1 | | 217 (25.1) | 34 (27.2) | |
| 2 | | 46 (5.3) | 13 (10.4) | |
| 3 | | 65 (7.5) | 17 (13.6) | |
| Length of stay | 990 | 6 (3-13) | 7 (3-13) | 0.05 |
| Vasopressors | 990 | 81 (9.4) | 17 (13.5) | 0.13 |
| Mechanical ventilation | 990 | 119 (13.7) | 22 (17.5) | 0.11 |
| Death | 990 | 98 (11.3) | 24 (19.2) | 0.22 |

Abbreviations: AKI, acute kidney injury; *APOL1*, apolipoprotein L1; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR estimated glomerular filtration rate; RAAS inhibition, renin angiotensin-aldosterone inhibition (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers); SMD, standard mean difference.

[a] SMDs are the absolute difference in means or percentage divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations.

[b] Baseline eGFR is the mean outpatient baseline eGFR level −7 days to −365 days prior to the admission date.

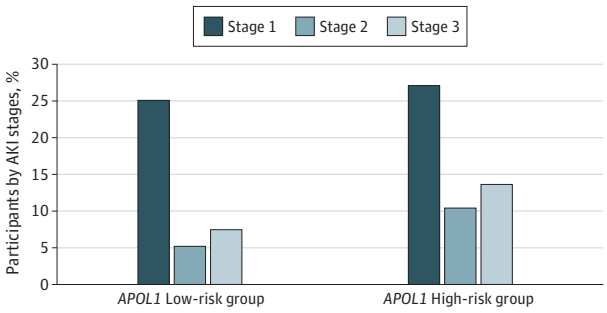
Table 2. Participants Clinical Characteristics According to Acute Kidney Injury (AKI) Status

| Characteristic | No. | No. (%) | | SMD |
|---|---|---|---|---|
| | | No AKI (n = 598) | AKI (n = 392) | |
| Baseline characteristics (outpatient) | | | | |
| Sex | | | | .23 |
| Female | 990 | 66 (11.0) | 19.0 (5.0) | |
| Male | 990 | 532 (89.0) | 373.0 (95.2) | |
| Age, median (IQR), y | 990 | 66.0 (59.0-73.0) | 69.0 (63.0-74.0) | .25 |
| Baseline eGFR, median (IQR), mL/min/1.73 $m^2$ | 990 | 77.0 (62.4-92.7) | 65.6 (48.8-80.8) | .52 |
| eGFR <60 mL/min/1.73 $m^2$ | 990 | 132 (22.1) | 157 (40.1) | .40 |
| Body mass index, median (IQR) | 988 | 29.8 (25.6-34.2) | 29.9 (25.6-35.5) | .06 |
| Comorbidities | | | | |
| Diabetes mellitus type 2 | 988 | 328 (54.9) | 264 (67.5) | .26 |
| Hypertension | 988 | 489 (81.9) | 351 (89.8) | .23 |
| Cardiovascular disease | 988 | 157 (26.3) | 124 (31.7) | .12 |
| Congestive heart failure | 988 | 104 (17.4) | 83 (21.2) | .10 |
| COPD | 988 | 158 (26.5) | 117 (29.9) | .08 |
| Cancer | 990 | 107(18.0) | 65(17.0) | .04 |
| Human immunodeficiency virus | 990 | 32 (5.0) | 13 (3.0) | .10 |
| Dipstick proteinuria, year prior | 614 | | | .41 |
| Negative or trace | | 261 (70.4) | 129 (53.1) | |
| 1+ | | 63 (17.0) | 48 (19.8) | |
| ≥2+ | | 47 (12.7) | 66 (27.2) | |
| Dipstick hematuria, year prior | 608 | | | .10 |
| Negative or trace | | 273 (74.2) | 187 (77.9) | |
| 1+ | | 65 (17.7) | 34(14.1) | |
| ≥2+ | | 30 (8.1) | 19 (7.9) | |
| Outpatient prescriptions | | | | |
| RAAS inhibition | 990 | 269 (45.0) | 236 (60.2) | .31 |
| Inpatient characteristics | | | | |
| Admission values, median (IQR) | | | | |
| Serum creatinine, median (IQR), mg/dL | 922 | 1.1 (0.9-1.3) | 1.8 (1.4-2.6) | .99 |
| Blood pressure, median (IQR), mm Hg | | | | |
| Systolic | 976 | 134.0 (121.0-150.0) | 128.0 (111.0-144.0) | .35 |
| Diastolic | 974 | 80.0 (72.0-89.0) | 74.0 (66.0-85.0) | .39 |
| Hemoglobin, median (IQR), g/dL | 853 | 13.1 (12.0-14.3) | 13.3 (11.7-14.7) | .04 |
| Lymphocyte count, median (IQR), cells/$mm^3$ | 835 | 5.40 (1.20-19.8) | 5.95 (0.9-16.7) | .02 |
| C reactive protein, median (IQR), g/L | 347 | 11.4 (3.9-64.7) | 18.4 (7.8-77.8) | .15 |
| D Dimer, median (IQR), µg/mL FEU | 444 | 2.4 (0.9-346.0) | 2.3 (0.9-284.0) | .03 |
| Dipstick proteinuria on admission | 357 | | | .47 |
| Negative or trace | | 74 (38.9) | 33 (19.8) | |
| 1+ | | 47 (24.7) | 40 (24.0) | |
| ≥2+ | | 69 (36.3) | 94 (56.3) | |
| Dipstick hematuria on admission | 351 | | | .44 |
| Negative or trace | | 117 62.9) | 72 (43.6) | |
| 1+ | | 47 (25.3) | 50 (30.3) | |
| ≥2+ | | 22 (11.8) | 43 (26.1) | |
| Inpatient medications[a] | | | | |
| RAAS inhibitors | 990 | 136 (22.7) | 57 (14.5) | .21 |
| NSAIDs | 990 | 49 (8.2) | 28 (7.1) | .04 |
| Vancomycin | 990 | 4 (0.7) | 15 (3.8) | .21 |
| Remdesivir | 990 | 182 (30.4) | 172 (43.9) | .28 |
| Dexamethasone, prior to peak creatinine | 990 | 131 (21.6) | 126 (32.1) | .23 |
| Steroids, anytime during hospitalization | 990 | 260 (43.5) | 237 (60.5) | .35 |
| Tocilizumab | 990 | 6 (1.0) | 24 (5.0) | .22 |
| Cefazolin | 990 | 47 (8.0) | 46 (12.4) | .19 |
| Beta-lactams | 990 | 8 (1.3) | 7 (1.9) | .12 |
| Inpatient characteristics | | | | |
| Length of stay, median (IQR), d | 990 | 5 (2.0-10.0) | 10 (5.0-17.0) | .26 |
| Mechanical ventilation | 990 | 29 (4.9) | 112 (28.6) | .67 |
| Vasopressors | 990 | 10 (1.7) | 88 (22.0) | .67 |
| Death | 990 | 20 (3.3) | 102 (26.0) | .68 |

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; RAAS inhibition, renin angiotensin-aldosterone inhibition (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers): SMD, standard mean difference.

[a] Unless otherwise specified, baseline eGFR level is the mean baseline eGFR −7 days to −365 days prior to the admission date.

Figure 2. Incidence of Acute Kidney Injury (AKI) and AKI Stages by *APOL1* Risk Group




Dipstick proteinuria data were available in 357 participants on admission. Ninety-six of 357 (27%) had new-onset proteinuria and 24 people had worsening dipstick proteinuria results. The *APOL1* high-risk group was associated with proteinuria of 1+ or more on admission (n = 357) (OR, 2.20; 95% CI, 1.21-4.10; *P* = .01). There was no association of *APOL1* high-risk group and hematuria defined as 1+ or more at baseline (n = 608) (OR, 0.95; 95% CI, 0.53-1.64; *P* = .90) or on admission (n = 351) (OR, 1.32; 95% CI, 0.74-2.31; *P* = .30).

### Other Models of Inheritance

Other models of *APOL1* inheritance were performed also as exploratory analyses. We observed significant associations with 2 RVs and AKI, AKI severity, and death in the codominant model, consistent with the recessive model. No associations were observed with a single RV (eTable 9 in Supplement 1).

## Discussion

We report a robust association between individuals in the *APOL1* high-risk group and AKI development and severity among participants with African ancestry hospitalized with COVID-19. Half of the participants with 2 *APOL1* high-risk group variants developed AKI and 24 (19%) died. Because 1 in 8 individuals with African ancestry have 2 *APOL1* kidney risk variants, this inherited genetic difference may in part explain the excess risk of AKI described in previous studies in veterans with African ancestry hospitalized owing to COVID-19.[1] This increased risk of AKI was present even among individuals without preexisting CKD and followed a recessive model of inheritance, consistent with other kidney phenotypes.[9,11,48] These associations were further accentuated among individuals with increasing AKI severity.

This study also identified an association of *APOL1* high-risk group and death in participants of African ancestry hospitalized with COVID-19. Study participants baseline characteristics were similar between the *APOL1* high-risk and low-risk groups. Recent studies report an association of *APOL1* with endothelial cell defects, sepsis severity, and COVID-19 severity.[3] Larger studies may further inform the association of *APOL1* with death in the context of COVID-19.

In the general population, the association of *APOL1* and AKI and *APOL1* and death has been controversial.[18,19,49,50] Potential explanations for the different findings include variation in the populations studied, outcome ascertainment, or the potential effects of a second hit in a given study setting.[27] For example, not all individual carriers of 2 RVs will develop kidney disease and a second hit, including environmental or genetic modifiers, have been considered as playing a role.[27,29] In the case of COVID-19, the heightened inflammatory response has been hypothesized to be a second hit. Similar hypotheses have been made in the contexts of uncontrolled HIV where the high levels of interferon are associated with the development of HIV-associated nephropathy and the risk of ESRD,[51] or that observed with the therapeutic administration of interferon (IFNs).[21]

The pathophysiological mechanisms of *APOL1* RVs remain incompletely characterized. Several studies have shown that *APOL1* RVs represent gain of function variants with cytotoxic effects.[52,53] When exposed to inflammatory triggers, podocytes and other specific cells overexpress *APOL1*, which compromises mitochondrial respiration, lysosome integrity, and autophagic flux resulting in cell death.[54-57] Animal studies suggest that *APOL1* variants impair mitophagy in endothelial cells, allowing the release of mitochondrial DNA that activates inflammasome.[3] A second hit could also involve other genetic modifiers that can diminish cytotoxicity.[48] The potential role of inflammation in the pathogenesis of AKI in the context of high-risk *APOL1* and its relative contributions to different subtypes of AKI warrants further study.

The strengths of our study include the use of a large national data set with genetic data on participants with African ancestry and carefully curated creatinine-based definitions of AKI and KRT. The use of longitudinal phenotype data prior to COVID-19 infection enabled rigorous adjustment for baseline conditions and inpatient exposures that might influence the risk of AKI and severe COVID-19. Our estimates were robust and consistent across nested multivariable models, subgroup and sensitivity analyses that included known comorbidities associated with worse outcomes in COVID-19 and AKI. Further, these results were consistent among individuals without known CKD.

### Limitations

Limitations of this study include reduced generalizability to women, the lack of quantitative proteinuria measurements, which precluded a subgroup analysis by proteinuria, or the detection of severe forms of nephrotic syndrome. The study lacked histologic data, with only 1 patient having a kidney biopsy during a COVID-19 hospitalization. Socioeconomic status (SES) indicators were not available, and some covariates were defined using diagnosis and procedure codes. However, covariate ascertainment should not be differential by genotype. Another limitation of our study is that we could not identify a comparable replication cohort, which most likely will be available in the near future. Finally, our limited follow-up period reduced the ability to examine longer-term consequences of COVID-19–associated AKI.

Table 3. Association of *APOL1* High-Risk Group, AKI, AKI Stages, and Death in Veterans With African Ancestry Hospitalized With COVID-19[a]

| | | Primary outcome, acute kidney injury | | Secondary outcomes | | | |
|---|---|---|---|---|---|---|---|
| | | | | AKI severity stages | | Death | |
| Variable | No. | Odds ratio (95% CI) | *P* value | Odds ratio (95% CI) | *P* value | Odds ratio (95% CI) | *P* value |
| **All patients** | | | | | | | |
| Minimally adjusted | | | | | | | |
| 2 Copies of *APOL1* RVs | 125 | 1.80 (1.21-2.69) | .004 | 1.88 (1.30-2.71) | .001 | 1.92 (1.13-3.17) | .01 |
| 1 Or 0 copies of RVs | 865 | 1 [Reference] | | 1 [Reference] | | 1 [Reference] | |
| Fully adjusted model | | | | | | | |
| 2 Copies of *APOL1* RVs | 121 | 1.95 (1.27-3.02) | .002 | 2.03 (1.37-2.99) | <.001 | 2.15 (1.22- 3.72) | .007 |
| 1 Or 0 copies of RVs | 812 | 1 [Reference] | | 1 [Reference] | | 1 [Reference] | |
| **Subgroup GFR ≥60 mL/min** | | | | | | | |
| Minimally adjusted | | | | | | | |
| 2 Copies of *APOL1* RVs | 92 | 1.88 (1.18-2.99) | .008 | 1.98 (1.28-3.06) | .002 | 2.54(1.32-4.72) | .004 |
| 1 Or 0 copies of RVs | 609 | 1 [Reference] | | 1 [Reference] | | 1 [Reference] | |
| Fully adjusted | | | | | | | |
| 2 Copies of *APOL1* RVs | 88 | 1.93 (1.15-3.26) | .01 | 2.11 (1.31-3.39) | .002 | 2.51(1.21-5.05) | .01 |
| 1 Or 0 copies of RVs | 569 | 1 [Reference] | | 1 [Reference] | | 1 [Reference] | |

Abbreviations: AKI, acute kidney injury; *APOL1,* apolipoprotein L1; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; RV, risk variants.

[a] A recessive model of inheritance was used for these analyses. Logistic regression was used to evaluate the association of *APOL1* high-risk group and AKI as a binary outcome. Partial proportional odds logistic regression was used to evaluate the association of *APOL1* high-risk groups and AKI stages (controls, stage 1, stage 2 and stage 3). Model 1 or minimally adjusted: adjusted for age, sex, baseline eGFR and 10 PCs of ancestry. Model 2 or fully adjusted = model 1 + BMI, diabetes, hypertension, COPD, CHF, liver disease, smoking, systolic blood pressure, diastolic blood pressure, ACE inhibitor /ARBs outpatient (180 days prior to admission). Inpatient vancomycin, inpatient NSAID, ACE inhibitor/ARB inpatient, Remdesivir, dexamethasone (definitions included in eTable 3 in Supplement 1). All drug administration exposures were accounted for if they occurred prior to development peak creatinine.

## Conclusions

In this cohort of participants with African ancestry hospitalized with COVID-19 infection, *APOL1* RVs were associated with an increased risk of AKI, severe AKI, and death, independent of CKD. Our findings suggest that genetic risk assessment can inform COVID-19 kidney risk prognostication in individuals with African ancestry. Because *APOL1* RVs are highly prevalent in the population with African ancestry, studies evaluating the role of existing and novel therapies are needed to reduce poor outcomes in this population.

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