Autosomal Dominant Polycystic Kidney Disease Does Not Significantly Alter Major COVID-19 Outcomes among Veterans

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Introduction

According to the US Centers for Disease Control and Prevention (CDC), people of any age with CKD are at increased risk of severe illness from coronavirus disease 2019 (COVID-19) (1). CKD was found to be a risk factor for severe COVID-19–related illness and death in early studies from China (2), New York (3), and Mexico (4). CKD also increased the risk for hospital visits among 2 million users of a COVID-19 smart application (M. N. Lochlainn et al., unpublished observations). Among 17 million participants in the United Kingdom’s National Health Service, the estimated hazard ratio of CKD as a risk factor for COVID-19–related death was 1.33 (95% CI, 1.28 to 1.40) for an eGFR of 30–60 ml/min per 1.73 m2, and 2.52 (95% CI, 2.33 to 2.72) for an eGFR of <30 ml/min per 1.73 m2, after controlling for major comorbidities (5).

The assessment of the direct effects of CKD on COVID-19 outcomes is complicated by the interweaving of relationships among CKD causes and COVID-19 risk factors. For example, obesity is a risk factor for CKD onset and progression. It also increases the risk for other CKD risk factors, such as type 2 diabetes mellitus (T2DM), hypertension, and autoimmune disorders (reviewed in Kovessy et al. [6]). Notably, obesity, T2DM, and immunosuppression (a commonly used treatment for autoimmune disorders) are all risk factors of severe illness from COVID-19 (1). Therefore, it is difficult to delineate between the COVID-19 risks attributable to CKD, and the risks attributable to CKD’s underlying causes and their complications.

However, the fourth leading cause of CKD and ESKD, autosomal dominant polycystic kidney disease (ADPKD; Online Mendelian Inheritance in Man entries 173900 and 613095) (7,8), mainly affects the kidneys. Therefore, ADPKD may reveal CKD’s direct effects on major COVID-19 outcomes, with limited confounding effects by other medical complications.

To explore ADPKD’s effect on major COVID-19 outcomes (hospitalization, intensive care unit [ICU] admission, ventilator requirement, and mortality), we studied participants in the largest integrated US health system, the Veterans Health Administration (annually serves >9 million veterans). The goal of this study was to compare these major outcomes across groups of patients with ADPKD versus other cystic renal disease (e.g., simple renal cysts) or those with cystic liver disease only (without renal cysts) in veterans positive and negative for COVID-19.

Materials and Methods

We created a Veterans Affairs (VA) cystic kidney and liver cohort by extracting relevant data for all patients with cystic kidney disease (International Classification of Diseases, Tenth Revision [ICD-10] and ICD-9 codes Q61 and 753.1) and cystic disease of the liver (ICD-10 and ICD-9 codes Q44.6 and 751.62) from the VA Corporate Data Warehouse (restricted to January 1, 2000 to January 31, 2020). A subset of this cohort, an ADPKD–enriched group, was defined by the ICD-10 code for

Key Points

● Autosomal dominant polycystic kidney disease (ADPKD) was not a significant, independent risk factor for the four major outcomes studied among veterans with confirmed coronavirus disease 2019 (COVID-19).
● ADPKD did not significantly increase the risk for newly starting dialysis (after controlling for CKD) among veterans positive for COVID-19.
● The established risk factors for severe COVID-19 illness had significant effects in this cohort (e.g., type 2 diabetes and Black race).

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polycystic kidney, adult-type (Q61.2), and ICD-9 codes for ADPKD and polycystic kidney disease (753.13 and 753.12). We assigned the remaining patients to the control (“other cystic kidney” group). Patients with the cystic disease of the liver who were not assigned into any of the cystic kidney disease groups served as another control (the “cystic liver–only” group). Patients with multiple ICD codes were included in only one group, with priority given to the ADPKD-enriched group, followed by the other cystic kidney group. We used this strategy to identify patients with relevant diagnoses. However, the studies presented in this manuscript stem strictly from the overlap (on patient identifier) of this diagnosis data, with the data extracted from the VA COVID-19 shared resources.

Specifically, we extracted the COVID-19 status, demographics, preexisting conditions (including COVID-19 risk factors), pretesting and post-testing symptoms, conditions, and procedures on August 18, 2020 from the COVID-19 shared resources provided by the VA Informatics and Computing Infrastructure (VINCI; https://www.hsrd.research.va.gov/covid19.cfm). We identified the patients in the VA cystic kidney and liver cohort from the COVID-19 shared resources. Variables that are not in the COVID-19 shared resources were extracted from the VA Observational Medical Outcomes Partnership datasets (9) and the VA electronic medical records (restricted to 2 years before COVID-19 testing). COVID-19 outcomes were ascertained within 60 days after each patient’s COVID-19 test. The CKD stage used in our analyses was the highest-documented CKD stage within 2 years before the COVID-19 testing date. The CKD stages were extracted using ICD codes (stage 1, N18.1 and S85.1; stage 2, N18.2 and S85.2; stage 3, N18.3 and S85.3; stage 4, N18.4 and S85.4; stage 5, N18.5 and S85.5; ESKD, N18.6 and S85.6).

Summary statistics were generated using the R package TableOne. P values were from the Fisher exact test or chi-squared test for categoric variables (depending on sample size), and the Wilcoxon rank sum test for continuous variables. The multivariable logistic regression was conducted using only patients with nonmissing outcomes. Race was the only variable for which all patients had a value. The R packages finalfit, ggplot2, and jtools were used for the summary and visualization of results.

This study was approved by the Emory University Institutional Review Board (IRB00115069) and Atlanta VA Medical Center R&D Committee (2019-111232).

Results

The distribution of demographic characteristics of patients positive for COVID-19 in the studied VA cystic kidney and liver cohort (Figure 1A) closely resembles the predominantly male (approximately 90%) VA patient population (Table 1). The ADPKD-enriched group had a lower median age (66 years) versus the other cystic kidney and cystic liver–only groups (72 and 71 years, respectively), but a higher rate of kidney-related preexisting conditions (e.g., acute kidney failure, CKD stage, and dialysis requirement).

The incidence rates for major COVID-19 outcomes were compared between patients who tested positive and negative for COVID-19 and disease groups (Figure 1B). The hospitalization rate was similar between patients positive and negative for COVID-19 in the ADPKD-enriched and other cystic kidney disease groups (34% and 40%, respectively), and lower in the cystic liver–only group (approximately 25%). The lack of an increase in hospitalization rate among the patients positive for COVID-19 across all three groups was likely related to the priority testing of hospitalized patients during the study period. The ICU admission rate was higher among the patients positive (versus negative) for COVID-19 across all three disease groups (16% of patients positive for COVID-19 in the ADPKD-enriched and the other cystic kidney disease groups, and 10% in the cystic liver–only group). The respective rates in patients positive versus negative for COVID-19 were not significantly different among patients in the ADPKD-enriched or cystic liver–only groups, likely due to the relatively small sample size. The rates of ventilator requirement across groups among patients positive for COVID-19 (8%–9%) was double that among patients negative for COVID-19 (3%–4%); significance was only reached in the other cystic kidney disease group (not the ADPKD-enriched and cystic liver–only groups due to smaller sample sizes). The incidence rates were similar among the three groups. The death rates of patients positive for COVID-19 across groups were significantly higher than those in patients negative for COVID-19 (death rate of 10% versus 2%–3%, respectively). Similar results for the four major outcomes were obtained when the above analyses were conducted on hospitalized patients alone (to make our data more comparable with earlier studies that analyzed only hospitalized patients).

To evaluate the effect of ADPKD as an independent risk factor for the four major COVID-19 outcomes in patients positive for COVID-19, we conducted multivariable logistic regression analysis (indicated as black symbols on Figure 2A). Disease status (ADPKD versus other cystic kidney versus cystic liver only) was the main exposure. We controlled for age, body mass index, prior CKD, T2DM, dialysis, cancer, and liver problems. ADPKD did not achieve statistical significance as an independent risk factor for any of the four COVID-19 outcomes (hospitalization, ICU admission, ventilator requirement, and mortality). However, an odds ratio (OR) of greater than one was estimated for hospitalization (1.52 [95% CI, 0.71 to 3.26]), ICU admission (1.93 [95% CI, 0.79 to 4.70]), and ventilator requirement (1.71 [95% CI, 0.52 to 5.70]), and this might reach statistical significance when more data are available. As a background comparison, we also modeled the patients negative for COVID-19 (gray in Figure 2).

We confirmed the effect of established COVID-19 risk factors on the major COVID-19 outcomes in the studied cohort. T2DM was the most prominent independent risk factor for hospitalization (OR, 2.39; 95% CI, 1.67 to 3.40), for ICU admission (OR, 2.33; 95% CI, 1.53 to 3.54), and ventilator requirement (OR, 2.32; 95% CI, 1.33 to 4.03). Other significant risk factors included Black race for ventilator requirement (OR, 2.08; 95% CI, 1.22 to 3.55) and age for death (OR, 1.10; 95% CI, 1.07 to 1.13), where the unit for age was 1 year.

Finally, we analyzed the effect of COVID-19 on new start of dialysis. In patients negative versus positive for COVID-19, dialysis was started after their COVID-19 test in 7%
versus 8% of patients, respectively, in the ADPKD-enriched group; 2% versus 4% of patients in the other cystic kidney group; and 1% of patients in the cystic liver–only disease group. The risk of starting dialysis among patients who were not on dialysis at the time of their COVID-19 test was evaluated using multivariable logistic regression (Figure 2B and Table 2). Due to the small number of patients newly starting dialysis, we combined the other cystic kidney and cystic liver–only groups as the reference group for the ADPKD-enriched group. We also analyzed CKD status (yes versus no) without further separation into CKD stages. The most significant risk factor for new dialysis among patients positive for COVID-19 was preexisting CKD (OR, 6.37; 95% CI, 2.43 to 16.7). The relationship was even more prominent in patients negative for COVID-19 (OR, 3.48; 95% CI, 0.97 to 12.4).

Discussion

Among the 61 Veterans Health Administration–enrolled patients with ADPKD who were positive for COVID-19, the rates of hospitalization, ICU admission, ventilator requirement, and death were comparable with those from patients with other cystic kidney disease and cystic liver–only disease (the proportion of the hospitalized patients with COVID-19 in these studied groups was 35%, 35%, and 20%, respectively, in the ADPKD, other cystic kidney disease, and cystic liver–only groups, allowing meaningful comparison of these major outcomes, especially in the ADPKD versus the other cystic kidney disease groups). As expected, these rates were consistently higher than those in patients negative for COVID-19. The ICU admission rate among hospitalized patients with ADPKD who were positive for COVID-19 was similar to the reported 49% among male patients positive for COVID-19 who were admitted to
Kaiser Permanente hospitals (10). The death rate among hospitalized patients positive for COVID-19 was also comparable (around 20% in both studies). The ADPKD diagnosis did not appear to be an independent risk factor for contracting COVID-19, and it did not increase the major complications associated with this illness (including death).

The validity of our study is supported by identifying established risk factors for severe COVID-19 illness as statistically significant in the studied cohort (e.g., T2DM as an independent risk factor for hospitalization, ICU admission, and ventilator use; and Black race and age as risk factors for ventilator requirement and death). In addition, consistent with the recognition of CKD as the central risk factor for AKI (11), we identified CKD as the leading risk factor for new dialysis among patients positive for COVID-19 in this cohort.

Whereas the design of this study only allowed us to analyze major COVID-19 outcomes, and to evaluate effects of ADPKD as an independent contributor to these outcomes after controlling for CKD stages, we cannot prove that the level of CKD in the ADPKD population is an independent contributing factor to the severity of the COVID-19 outcomes without knowing the comparable effects of CKD stage using a matched ADPKD cohort without COVID-19 infection.

Although our study had an adequate sample size to reveal the robust effects of known risk factors for severe COVID-19 illness, it was underpowered to detect smaller effects that might be exerted by ADPKD. Similarly, it did not allow stratification into individual CKD stages and the subsequent mediation analyses to delineate the direct and indirect risk contributions. This study should also be interpreted in the context of the predominantly male VA cohort that lacks “healthy” individuals, and likely biased preferential COVID-19 testing of patients admitted to hospital during the studied time interval. Finally, although ICD codes are commonly used for disease phenotyping on the basis of electronic medical records, their accuracy is often inferior to machine learning–based, complex methods (12).

In summary, we studied hospitalization, ICU admission, ventilator requirement, and death rates among veterans positive and negative for COVID-19 assigned to ADPKD–enriched, other cystic kidney disease, or cystic liver–only disease groups. ADPKD, a CKD type that mostly affects the kidneys, was not identified as a significant independent risk factor for any of the four studied outcomes in multiple logistic regression analyses, and it did not significantly increase the risk for newly starting dialysis (after controlling for CKD). In contrast, established risk factors for severe COVID-19 illness had significant effects in this cohort (e.g., T2DM and Black race). The leading risk factor for new dialysis treatment initiation was CKD and Black race. Together, this study suggests that ADPKD is not a robust risk factor for the major COVID-19 outcomes among veterans, when compared with other cystic kidney or liver diseases. However, this initial study will require validation when larger

| Variables                        | Other Cystic Kidney (n=803) | Cystic Liver Only (n=52) | ADPKD (n=61) | P Value |
|----------------------------------|-----------------------------|--------------------------|-------------|---------|
| Male sex, n (%)                  | 768 (96)                    | 46 (89)                  | 58 (95)     | 0.06    |
| Race, n (%)                      |                             |                          |             | 0.80    |
| American Indian or Alaska Native| 3 (0.4)                     | 0 (0)                    | 1 (2)       |         |
| Asian                            | 3 (0.4)                     | 0 (0)                    | 0 (0)       |         |
| Black                            | 305 (38)                    | 23 (44)                  | 24 (39)     |         |
| Native Hawaiian or Other Pacific Islander | 6 (0.7)                     | 0 (0)                    | 0 (0)       |         |
| Unknown                          | 38 (5)                      | 1 (2)                    | 1 (2)       |         |
| White                            | 448 (56)                    | 28 (54)                  | 35 (57)     |         |
| Age (yr), median (IQR)           | 72.0 (65.0–78.0)            | 71.0 (61.8–76.0)         | 65.0 (54.0–74.0) | <0.001 |
| BMI (kg/m²), median (IQR)        | 28.7 (25.4–33.0)            | 30.3 (25.4–33.5)         | 28.1 (25.3–32.2) | 0.71    |
| Chronic lung disease, n (%)      | 322 (40)                    | 24 (46)                  | 22 (36)     | 0.55    |
| Cancer, n (%)                    | 288 (36)                    | 17 (33)                  | 18 (30)     | 0.56    |
| Any diabetes, n (%)              | 386 (48)                    | 15 (29)                  | 24 (39)     | 0.01    |
| Liver disease, n (%)             | 86 (11)                     | 18 (35)                  | 5 (8)       | <0.001  |
| Active liver injury, n (%)       | 3 (0.4)                     | 0 (0)                    | 0 (0)       | 0.81    |
| AKF, n (%)                       | 137 (17)                    | 2 (4)                    | 16 (26)     | 0.006   |
| CKF, n (%)                       | 63 (8)                      | 1 (2)                    | 19 (31)     | <0.001  |
| CKD, n (%)                       | 301 (38)                    | 12 (23)                  | 45 (74)     | <0.001  |
| CKD stage, n (%)                 |                             |                          |             |         |
| 1                                | 2 (0.2)                     | 0 (0)                    | 1 (2)       |         |
| 2                                | 15 (2)                      | 0 (0)                    | 2 (3)       |         |
| 3                                | 119 (15)                    | 5 (10)                   | 10 (16)     |         |
| 4                                | 27 (3)                      | 0 (0)                    | 4 (7)       |         |
| 5                                | 7 (0.9)                     | 0 (0)                    | 1 (2)       |         |
| ESKD                             | 55 (7)                      | 1 (2)                    | 19 (31)     |         |
| Stage absent                     | 578 (72)                    | 46 (89)                  | 24 (39)     |         |
| Dialysis, n (%)                  | 61 (8)                      | 1 (2)                    | 19 (31)     | <0.001  |
| Dialysis at testing, n (%)       | 22 (3)                      | 1 (2)                    | 8 (13)      | <0.001  |

There were no missing data for any of these variables. COVID-19, coronavirus disease 2019; ADPKD, autosomal dominant polycystic kidney disease; IQR, interquartile range; BMI, body mass index; AKF, acute kidney failure; CKF, chronic kidney failure.
numbers of patients positive for COVID-19 become available.

Disclosures
M. Mrug reports having consultancy agreements with Chinook, Goldilocks Therapeutics, Natera, Otsuka Corporation, and Sanofi; receiving research funding from Chinook, Goldilocks Therapeutics, Otsuka Corporation, and Sanofi; receiving honoraria from Chinook, Natera, Otsuka Corporation, and Sanofi; and serving as a scientific advisor for—or member of—the PKD Foundation, on an advisory board for Santa Barbara Nutrients, and on the STAGED-PKD steering committee for Sanofi. All remaining authors have nothing to disclose.

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Author Contributions

X. Cui, J. W. Gallini, and C.L. Jansen were responsible for data curation; X. Cui, J. W. Gallini, and M. Mrug were responsible for visualization; X. Cui and M. Mrug conceptualized the study, provided supervision, were responsible for funding acquisition, and wrote the original draft; and all authors reviewed and edited the manuscript, and were responsible for formal analysis, investigation, methodology, resources, and validation.

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