Eight-fold increased COVID-19 mortality in autosomal dominant tubulointerstitial kidney disease due to *MUC1* mutations: an observational study

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Abstract

Background *MUC1* and *UMOD* pathogenic variants cause autosomal dominant tubulointerstitial kidney disease (ADTKD). *MUC1* is expressed in kidney, nasal mucosa and respiratory tract, while *UMOD* is expressed only in kidney. Due to haplo-insufficiency ADTKD-*MUC1* patients produce approximately 50% of normal mucin-1.

Methods To determine whether decreased mucin-1 production was associated with an increased COVID-19 risk, we sent a survey to members of an ADTKD registry in September 2021, after the initial, severe wave of COVID-19. We linked results to previously obtained ADTKD genotype and plasma CA15-3 (mucin-1) levels and created a longitudinal registry of COVID-19 related deaths.

Results Surveys were emailed to 637 individuals, with responses from 89 ADTKD-*MUC1* and 132 ADTKD-*UMOD* individuals. 19/83 (23%) ADTKD-*MUC1* survey respondents reported a prior COVID-19 infection vs. 14/125 (11%) ADTKD-*UMOD* respondents (odds ratio (OR) 2.35 (95%CI 1.60–3.11, *P*=0.0260). Including additional familial cases reported from survey respondents, 10/41 (24%) ADTKD-*MUC1* individuals died of COVID-19 vs. 1/30 (3%) with ADTKD-*UMOD*, with OR 9.21 (95%CI 1.22–69.32), *P*=0.03. The mean plasma mucin-1 level prior to infection in 14 infected and 27 uninfected ADTKD-*MUC1* individuals was 7.06±4.12 vs. 10.21±4.02 U/mL (*P*=0.035). Over three years duration, our longitudinal registry identified 19 COVID-19 deaths in 360 ADTKD-*MUC1* individuals (5%) vs. 3 deaths in 478 ADTKD-*UMOD* individuals (0.6%) (*P*=0.0007). Multivariate logistic regression revealed the following odds ratios (95% confidence interval) for COVID-19 deaths: ADTKD-*MUC1* 8.4 (2.9–29.5), kidney transplant 5.5 (1.6–9.1), body mass index (kg/m^2) 1.1 (1.0-1.2), age (y) 1.04 (1.0-1.1).

Conclusions Individuals with ADTKD-*MUC1* are at an eight-fold increased risk of COVID-19 mortality vs. ADTKD-*UMOD* individuals. Haplo-insufficient production of mucin-1 may be responsible.

Keywords Autosomal Dominant Tubulointerstitial kidney disease, MUC1, UMOD, COVID-19, Mucin-1, CA15-3

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Kidd *et al. BMC Nephrology*   (2024) 25:449

Page 2 of 10

Background

Mucin-1 is a membrane-anchored glycoprotein that provides physical protection to the epithelial surface of many tissues [1] as well as performing other functions, including preventing infection [2], mediating inflammation [3], and modulating apoptosis [4]. In autosomal dominant tubulointerstitial kidney disease (ADTKD) due to heterozygous frameshift variants in the *MUC1* gene (ADTKD-*MUC1*) (OMIM 174000) [5], the wild-type allele synthesizes normal mucin-1, and the allele with the pathogenic *MUC1* variant produces a frameshift mucin-1 protein that deposits in the endoplasmic reticulum Golgi intermediate compartment (ERGIC) [6]. While abnormal protein deposition occurs within all epithelial cells expressing mucin-1[7], clinical sequelae of the disease were thought to be limited to the kidney, with no respiratory, gastrointestinal, or skin manifestations previously identified [8, 9]. Affected individuals develop slowly progressive chronic kidney disease (CKD) that leads to kidney failure at a mean age of 45 years [8]. ADTKD-*UMOD* (OMIM 162000, 603860) is phenotypically similar and often clinically indistinguishable from ADTKD-*MUC1* (OMIM 17400) [10]. Unlike mucin-1, uromodulin is expressed exclusively in the thick ascending limb of Henle [11]. The median age of kidney failure in ADTKD-*UMOD* is 49 years [12]. Both groups of individuals have excellent outcomes with kidney transplantation [13], as the diseases do not recur in the transplanted kidneys and individuals usually have few other comorbid conditions.

Mucin-1 has been implicated as a protective factor in COVID-19, though this relationship has not been firmly established in human studies. Mucin-1 is produced in both the nares and the lungs, primary sites of COVID-19 infection [14, 15]. Mucin-1 in breast milk has been shown to inhibit SARS-CoV-2 infection [16]. In in vitro studies, mucin-1 was highly expressed on the surface of ACE2-positive respiratory epithelial cells, and the glycosylated extracellular domain of mucin-1 restricted SARS-CoV-2 binding and entry [17].

Patients with ADTKD-*MUC1* may be at increased risk of COVID-19 due to haploinsufficiency of mucin-1. In ADTKD-*MUC1*, there is one wild-type allele that produces mucin-1 and one mutated allele that produces a truncated version of mucin-1 that deposits intracellularly and does not function as a normal mucin-1 protein. In a recent investigation, the mean plasma CA15-3 level, which measures mucin-1 levels with an immunoassay using the DF3 antibody [18], was 8.6 ± 4.3 U/mL in individuals with ADTKD-*MUC1* vs. 14.6 ± 5.6 U/mL in controls ($P < 0.001$).[19] The mucin-1 content of plasma is derived primarily from the lungs [20]. Thus, ADTKD-*MUC1* patients produce less mucin-1, which may protect against COVID-19.

To determine if individuals with ADTKD-*MUC1* were at increased risk of COVID-19, we decided to compare the rates of COVID-19 infections between patients with ADTKD-*MUC1* and patients with ADTKD-*UMOD* in the Wake Forest Rare Inherited Kidney Disease registry. The registry attempts to recruit all individuals with ADTKD-*UMOD* and ADTKD-*MUC1* and includes 360 adults from 119 families affected with ADTKD-*MUC1* and 478 individuals from 171 families affected with ADTKD-*UMOD*. The registry has grown over the last two decades, with approximately 25% of individuals making contact with the Wake Forest Rare Inherited Kidney Disease Team independently without physician referral [21]. The registry keeps in contact with family members through webinars, in-person meetings, email, and a private Facebook© support page. Thus, there is a large registry containing individuals with ADTKD-*MUC1* and ADTKD-*UMOD*, without any perceived bias in interactions based on ADTKD type. The two diseases have a bland urinary sediment, slowly progressive chronic kidney disease leading to kidney failure at a mean age of approximately 45 years, and the absence of non-renal clinical manifestations.

To determine if individuals with ADTKD-*MUC1* were at increased risk of COVID-19, we first conducted a systematic survey of individuals with these two conditions in September 2021 (see Fig. 1), with a specific goal of avoiding any ascertainment bias between the ADTKD-*UMOD* and ADTKD-*MUC1* groups. At that time, most individuals had had the opportunity to obtain COVID-19 vaccination, and the worst wave of COVID-19 deaths in the US had occurred. We informed patients in our registry of our interest in COVID-19 deaths in ADTKD-*UMOD* and ADKTD-*MUC1* patients and began tracking these occurrences.

Materials and methods

This study was approved by the Wake Forest University Health Sciences Institutional Review Board (IRB00000352, Sub-study: COVID-19 Effects in Inherited Kidney Disease, approved September 8, 2021). We developed a survey and distributed it electronically to all individuals with ADTKD within our registry (see Fig. 1 and Supplementary Material). Survey data were collected between September 24, 2021 and November 1, 2021 and managed using REDCap electronic data capture tools hosted at Wake Forest School of Medicine. REDCap is a secure, web-based, National Institutes of Health (NIH)–sponsored application [22] that supports confidential data capture for research studies. Information collected included: COVID-19 vaccination type and number of vaccines administered; COVID-19 infection characteristics including the date of first clinical

Kidd *et al. BMC Nephrology*   (2024) 25:449

Page 3 of 10
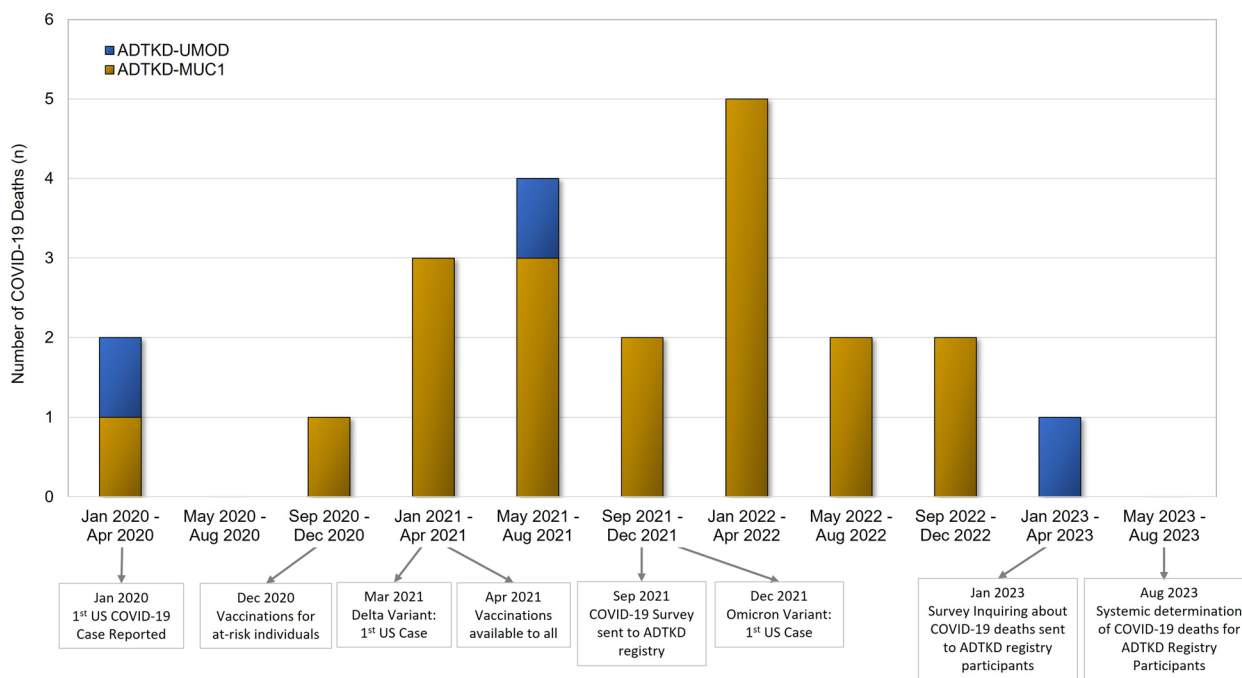
Fig. 1 Study timeline and COVID-19 related deaths in ADTKD patients

symptoms, need for hospitalization, need for intensive care unit admission, and death or recovery from infection. Survey respondents provided information about their personal COVID-19 infections as well as those of family members, as family members may have died or become too sick to respond to our survey. For reported COVID-19 deaths, we spoke personally with first-degree family members to ascertain that the death was related to COVID-19. We only included individuals from our registry who had died of COVID-19 and did not include other family members who may have died of COVID-19 but were not part of our registry. Data from the survey respondents were linked to other data in our registry that had been obtained prior to COVID-19 infections. This data included the ADTKD mutation (*UMOD* vs. *MUC1*) and plasma CA15-3 (mucin-1) levels. CA15-3 levels were measured as previously reported [19]. We collected available information from our prior surveys about the presence of cancer and smoking. As we had not asked on prior surveys about chronic obstructive pulmonary disease, diabetes, or hyperlipidemia, we reviewed the medication lists to see if study participants were taking medications indicated for these conditions.

We continued to ascertain COVID-19 deaths in our survey. In January 2023, an additional survey was sent to individuals with ADTKD that requested information about COVID-19 deaths. In August 2023, we reviewed all family trees of ADTKD-*UMOD* and ADTKD-*MUC1*

families to identify new deaths by searching each name on-line for potential obituaries and then contacting family members about causes of death. We then performed a case-control study with cases including adults affected with ADTKD-*UMOD* and ADTKD-*MUC1* who died of COVID-19 and controls including adults affected with ADTKD-*UMOD* and ADTKD-*MUC1* who did not die from COVID-19.

Statistical analysis

Survey questions were summarized with the addition of descriptive statistics and additional descriptive data were added from registry data when available. Associations were assessed using a generalized estimating equation to account for the family structure. We assumed exchangeable correlation within family and computed a robust sandwich estimator of variance [23]. A compound-symmetry covariance structure was used to account for the correlation between family members for continuous outcomes.

Genotyping

Individuals were genotyped for *UMOD* pathogenic variants using standard genetic techniques [12]. For *MUC1* sequencing, a CLIA-approved mass spectrometry-based assay was performed the Broad Institute of MIT and Harvard, Cambridge, MA [24] or Illumina and/or PacBio® sequencing of *MUC1* PCR amplicon was performed by

Kidd *et al. BMC Nephrology*   (2024) 25:449

Page 4 of 10

the Kmoch laboratory, First Faculty of Medicine, Prague, Czech Republic [7].

Results

The initial survey was emailed to 637 individuals (see Fig. 2a), including 256 patients with ADTKD-*MUC1* and 381 patients with ADTKD-*UMOD*. There were 221 respondents (35% response rate). The response rate for individuals with ADTKD-*MUC1* was 89/256(35%), and the response rate for individuals with ADTKD-*UMOD* was 132/381(35%). Compared to non-respondents, respondents were more likely to be White (97% vs. 90%, $P=0.02$) and older (50.2 ± 15.2 years vs. 47.0 ± 16.0 years, $P=0.02$) (see Supplementary Table S1). Of the respondents, six individuals with ADTKD-*MUC1* and seven with ADTKD-*UMOD* did not complete the survey about personal COVID-19 infection and were removed. Clinical characteristics were similar between the remaining 83 respondents with ADTKD-*MUC1* and 125 individuals with ADTKD-*UMOD* (see Supplementary Table S2). The respondents provided information on an additional 16 family members with ADTKD-*MUC1*, resulting in 105 individuals with ADTKD-*MUC1* and an additional nine family members with ADTKD-*UMOD*, resulting in 141 individuals (see Fig. 2a).

COVID-19 outcomes during the early phase of the pandemic

We compared COVID-19 outcomes in survey respondents with ADTKD-*MUC1* vs. ADTKD-*UMOD* in Sep 2021, after the Delta variant had peaked in the US (see Fig. 2a). Of 83 ADTKD-*MUC1* individuals, 19 (22%) developed COVID-19 infection vs. 14/125 (11%) of ADTKD-*UMOD* individuals (odds ratio (OR) 2.35 (95%CI 1.60–3.11, $P=0.026$). Table 1 shows a comparison of the individuals who developed COVID-19 by disease type. There was no statistical difference between individuals with regards to age, gender, or body mass index, though numbers were small in each group. At the time of COVID-19 infection, 16% of ADTKD-*MUC1* and 21% of ADTKD-*UMOD* individuals were unvaccinated. ADTKD-*MUC1* individuals who did not develop COVID-19 were more likely to be vaccinated, but this is likely related to bias, as ADTKD-*MUC1* individuals who developed COVID-19 may have developed it several months prior to the survey and often did so before the vaccine was available, while individuals who did not develop COVID-19 could have received the vaccine up until the time of the survey. As stated above, in a univariate model the odds ratio for developing COVID-19 infection was 2.35 for ADTKD-*MUC1* vs. ADTKD-*UMOD*.
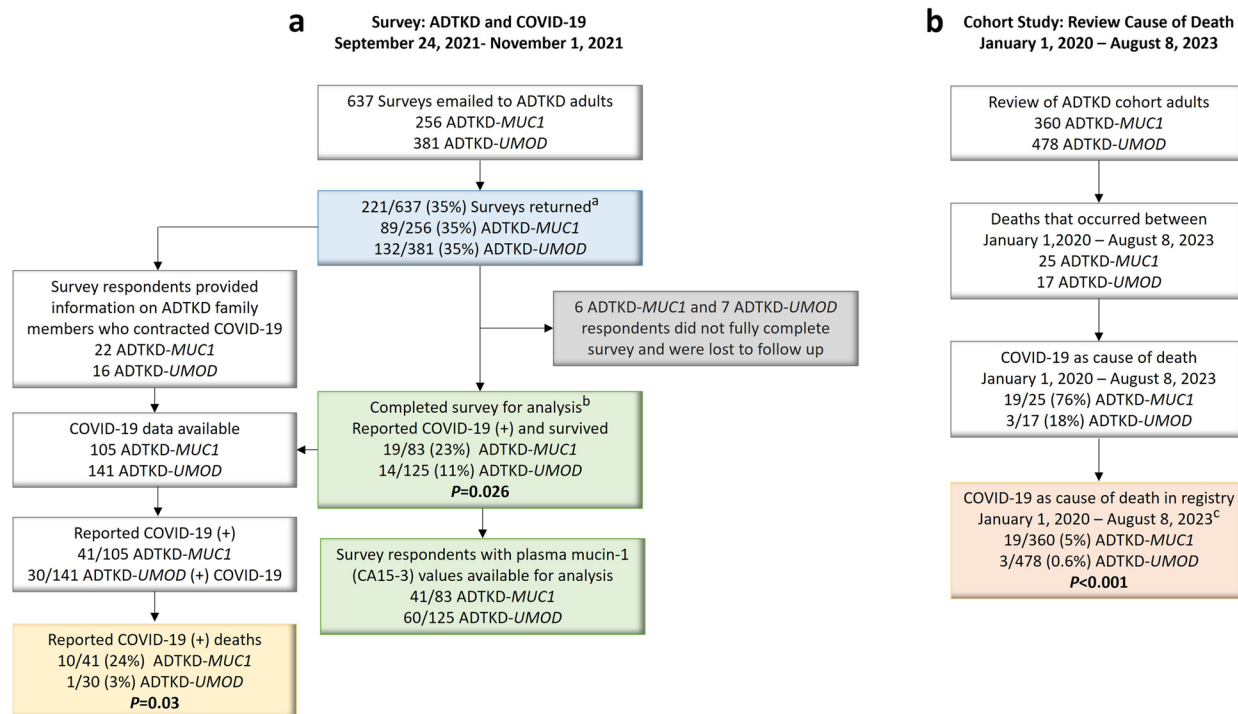
Fig. 2 Flow diagram for the study. **A** Initial ADTKD Registry COVID-19 Survey. [a]Survey respondents and non-respondents described in Supplementary Table S1.[b]Survey respondent results are described in Table 1 and Supplemetary Table S2. **B** Cohort study reviewing the ADTKD registry for COVID-19 related deaths. [c]This includes the 11 COVID-19 deaths reported in the 2021 survey and used for analysis described in Table 2, Table 3, and Supplementary Table S3

Kidd *et al. BMC Nephrology*   (2024) 25:449

Page 5 of 10

Table 1 Characteristics of individuals developing COVID-19 by disease type

	ADTKD-MUC1			ADTKD-UMOD		
COVID-19 infection	Yes	No	*P*-value	Yes	No	*P*-value
Individuals (n(%))[a]	19 (22%)	64 (88%)	--	14 (11%)	111 (89%)	--
Gender (n male (%))	11(58%)	24 (38%)	0.079	2 (14%)	44 (40%)	0.063
Age, years (mean ± sd (median))	49.6 ± 19.9 (50.6)	51.6 ± 16.8 (55.6)	0.63	47.0 ± 13.3 (49.5)	51.6 ± 14.0 (52.8)	0.14
Age > 60 (n (%))	6 (32%)	22 (34%)	0.99	1 (7%)	37 (33%)	0.029
Body mass index, kg/m^2 (mean ± sd (median))	25.5 ± 5.6 (24)	25.1 ± 5.0 (24.5)	0.76	24.9 ± 4.5 (24.5)	25.9 ± 5.1 (25)	0.47
Active Cancer Diagnosis [b]	0	0	--	0	1 (1%)[b]	0.72 [d]
Diabetes[c]	0	0	--	0	1 (1%)[c]	0.72 [d]
Chronic obstructive pulmonary disease/asthma	0	1 (2%)	0.58 [d]	0	1 (1%)	0.72 [d]
Hyperlipdemia at risk for cardiovascular disease	0	4 (6%)	0.26 [d]	2 (14%)	11 (10%)	0.61
Current Smoker	0	1 (2%)	0.26 [d]	0	8 (7%)	0.30 [d]
eGFR[e] (mean ± sd (median)) for pre-kidney failure, non-kidney transplanted	49.7 ± 32.5 (42.6)	49.4 ± 37.5 (37.6)	0.98	43.9 ± 22.4 (37.5)	46.2 ± 29.8 (41.7)	0.77
eGFR > 60 ml/min/1.73m^2 (n, column percent)	2 (11%)	8 (13%)	0.52	3 (21%)	15 (14%)	0.33
eGFR 30 to ≤ 60 ml/min/1.73m^2 (n, column percent)	5 (28%)	8 (13%)		4 (29%)	29 (26%)	
eGFR < 30 ml/min/1.73m^2 (n, column percent) and not kidney failure	2 (11%)	11 (17%)		3 (21%)	21 (19%)	
Transplanted	9 (50%)	36 (56%)		4 (29%)	44 (40%)	
Receiving dialysis	0	1 (2%)		0	1(1%)	
Duration kidney failure to COVID or time of survey	14.2 ± 14.5 (11.5)	17.1 ± 13.0 (17)	0.57	4.4 ± 4.9 (2.6)	10.8 ± 8.3 (10)	0.014
Pre-kidney failure	10 (53%)	27 (42%)	0.30	10 (71%)	66 (60%)	0.44
Duration kidney failure < 10 years	4 (21%)	14 (22%)		3 (21%)	21 (19%)	
Duration kidney failure 10 to < 15 years	2 (11%)	2 (3%)		1 (7%)	11 (10%)	
Duration kidney failure 15 to < 20 years	0	5 (8%)		0	6 (5%)	
Duration kidney failure > 20 years	3 (16%)	16 (25%)		0	7 (11%)	
No vaccination (n (percent of those reporting vaccination status))	3 (16%)	1 (2%)	0.040[d]	3 (21%)	12 (11%)	0.24[e]
Partial vaccination (n (percent of those reporting vaccination status))	1 (5%)	2 (3%)		1 (7%)	0	
Full vaccination (n (percent of those reporting vaccination status))	15 (79%)	59 (95%)		10 (71%)	95 (89%)	
Full vaccination and 3rd dose (n (percent of those with full vaccination))	5 (33%)	26 (44%)	0.49	2 (20%)	40 (42%)	0.18

[a] Percentages in the first row represent row percent. For other rows in the table, column percentages are given

[b] Non-Hodgkins Lymphoma

[c] Type 1 Diabetes Mellitus

[d] *P*-values calculated using permutation test

[e] Estimated glomerular filtration rate

Kidney transplantation status, body mass index, age, and gender were not significant in univariate models or when added to ADTKD type in a multivariate model.

At this stage of the analysis, we started to include data that respondents had provided regarding affected family members with COVID-19 (see Fig. 2a), including 16 individuals with ADTKD-*MUC1* and nine individuals with ADTKD-*UMOD*, all of whom were previously in our registry. Of the total number of cases of COVID-19 identified, 10/41 (24%) of

ADTKD-*MUC1* COVID-19 individuals died vs. 1/30 (3%) ADTKD *UMOD* COVID-19 individuals. Using a generalized estimating equation to account for the family structure, we found an odds ratio of mortality in ADTKD-*MUC1* vs. ADTKD-*UMOD* of 9.21, 95% CI 1.22–69.32, *P* = 0.03.

Thus, in the early and more virulent phase of the COVID-19 epidemic, patients with ADTKD-*MUC1* were more likely to develop COVID-19 and were much more likely to die from COVID-19 compared to patients with ADTKD-*UMOD*.

Kidd *et al. BMC Nephrology* (2024) 25:449

Page 6 of 10

International assessment of mortality in COVID-19 according to ADTKD type

We then queried collaborators (CS, JAS, PJC, LR) from three other academic centers in November 2021 and found 3/24 (13%) deaths in individuals with ADTKD-*MUC1* who developed COVID-19 vs. 0 deaths in 11 individuals with ADTKD-*UMOD* who developed COVID-19. Six of the 24 individuals with ADTKD-*MUC1* were kidney transplanted vs. 4/11 in the ADTKD-*UMOD* group. The mean age of the ADTKD-*MUC1* group was 50.8 ± 14.4 years vs. 53.7 ± 12.3 years in the ADTKD-*UMOD* group.

Plasma mucin-1 levels in ADTKD- MUC1 in infected vs. uninfected ADTKD- MUC1 patients

To evaluate stability of plasma CA $15-3$ levels over time, we used a paired t-test to compare baseline plasma CA15-3 levels with levels measured at least a year later in 11 patients. Initial levels were similar to follow-up levels (13.24 ± 5.63 U/ml vs. 11.01 ± 7.44 U/ml ($p = 0.18$)).

To determine whether the increased infection rate was associated with decreased mucin-1 production, we compared plasma CA15-3 (mucin-1) levels obtained as part of a prior study [19] on many of the survey individuals. Plasma CA $15-3$ concentrations were measured on average 18.6 ± 17.7 months (range 8 to 52 months) prior to COVID-19. The mean CA15-3 level for 14 COVD-19 infected ADTKD-*MUC1* individuals was 7.06 ± 4.12 U/ mL vs. 10.21 ± 4.02 U/mL for 27 uninfected ADTKD-*MUC1* individuals ($P = 0.035$). For 11 COVID-19 infected ADTKD-*UMOD* individuals, the mean CA15-3 level was 14.18 ± 2.35 U/mL vs. 13.28 ± 5.53 U/mL for 49 uninfected individuals ($P = 0.60$).

Observational cohort study of COVID-19 deaths in ADTKD-MUC1

We then continued an observational cohort study of COVID-19 deaths (see Figs. 1 and 2b). Table 4 shows the characteristics of adults in our registry according to ADTKD type. 19/360 (5%) individuals with ADTKD-*MUC1* died from COVID-19 vs. 3/478 (0.6%) individuals with ADTKD-*UMOD* ($P = 0.0007$). The 19 deaths in ADTKD-*MUC1* individuals occurred in 16 families. The three deaths in ADTKD-*UMOD* individuals occurred in three families. Table 2 shows the characteristics of patients who died of COVID-19 according to ADTKD type. Univariate and multivariate logistic models were then created with death from COVID-19 as the binary outcome (see Table 3). Patients with ADTKD-*MUC1* had an eight-fold increased risk of death (8.4 (29–29.5%, $P = 0.009$)) vs. ADTKD-*UMOD* after adjustment for body mass index, kidney transplant status, and age. Of the patients with ADTKD-*MUC1* who died (see Supplemental Table S3), 84% had undergone kidney transplant vs. 53% in ADTKD-*MUC1* patients who had not died ($P = 0.008$). 43% of the ADTKD-*MUC1* patients who died

Table 2 Characteristics of individuals who died of COVID-19 related infection

Characteristic	ADTKD-MUC1	ADTKD-UMOD	*P*-value
Individuals (n)	19	3	
Gender (n male (%))	11 (58%)	2 (67%)	0.89
Age, years (mean ± sd (median))	56.49 ± 8.45 (57.62)	71.44 ± 7.25 (74.80)	0.0002
Age > 60 years (n (%))	7 (37%)	3 (100%)	< 0.0001[b]
Body mass index, kg/m² (mean ± sd (median))	30.78 ± 6.46 (30.74)	25.56 ± 2.02 (25.11)	0.02
Kidney transplanted (n (%))	16 (84%)	3 (100%)	0.46[b]
Pre-kidney failure (n (%))	2 (11%)	0	0.01[b]
No vaccination (n (percent of those reporting vaccination status)	11/16 (69%)	1 (33%)	0.23
Heart failure	0/18	0/3	---
Chronic obstructive pulmonary disease or asthma	1/18	0/3	0.14[b]
Diabetes mellitus	4/18	0/3	0.14[b]
Active malignancy	0/18	0/3	---
Past malignancy[c]	3/18	1/3	0.15[b]
Average length of hospital stay (mean ± sd (median))	18.67 ± 10.80 (21)	12 ± 5 (12)	0.15
Required mechanical ventilation	18/18 (100%)	2 (67%)	0.01[b]
Years of kidney failure[a] (mean ± sd (median))	12.86 ± 10.84 (9)	21.93 ± 14.96 (13.76)	0.45
> 10 years kidney failure[a]	9/17 (53%)	3 (100%)	0.003[b]

[a] Years of kidney failure are years from start of kidney failure until contracting COVID-19

[b] *P*-values calculated using permutation test

[c] Past malignancies included Burkitts lymphoma, renal low grade papillary carcinoma, and cervical cancer in ADTKD-*MUC1* and breast cancer in ADTKD-*UMOD*

Kidd *et al. BMC Nephrology*   (2024) 25:449

Page 7 of 10

Table 3 Univariate and multivariate logistic regression models with death from COVID-19 as the outcome variable for 291 MUC1 patients (18 deaths) and 379 UMOD patients (3 deaths)

			Univariate		Multivariate	
Parameter	Reference	Risk group	Odds Ratio	*P*-value	Odds Ratio	*P*-value
ADTKD	*UMOD*	*MUC1*	8.26 (2.42–28.14)	0.0007	8.68 (2.46–30.58)	0.0008
Body mass index (kg/m^2)		Increase by 1 kg/m^2	1.09 (1.03–1.15)	0.003	1.11 (1.04–1.18)	0.002
Kidney Transplant Status	No	Yes	9.72 (2.79–33.86)	0.0004	5.49 (1.58–19.05)	0.009
Age (years)		Increase by 1 year	1.06 (1.03–1.09)	0.0002	1.04 (1.01–1.07)	0.002

Table 4 Characteristics ADTKD-*MUC1* and ADTKD-*UMOD* adults in registry

Characteristic	ADTKD-MUC1	ADTKD-UMOD	*P*-value Odd Ratio (OR) given with 95% Confidence Interval (CI) where applicable	*P*-value grouping for Kidney Failure Modality (No Kidney Failure, Dialysis, Kidney Transplant) To consider a change to the table
n	360	478		
Gender (% male)	41%	45%	0.19	
Age, y (mean ± s.d. (median))	47.40 ± 15.8 (47.74)	47.38 ± 14.89 (48.07)	0.97	
Age > 60 (n,%)	86 (24%)	118 (25%)	0.68	
Race (% White)	86%	95%		
Body mass index, kg/m^2 (mean ± sd (median))	26.22 ± 5.58 (25.5)	26.86 ± 5.75 (25.8)	0.47	
Body mass index, greater than 25 kg/m^2 (n,%)	161 (55%)	211 (56%)	0.89	
On dialysis	34 (9%)	26 (5%)	0.0027	0.0011
Living with kidney transplant	166 (46%)	164 (34%)	0.0037	
Not on dialysis or kidney transplanted (n, column percent)	159 (44%)	287 (60%)	< 0.0001	
Duration kidney failure[a] < 10 years	104 (29%)	110 (38%)		
Duration kidney failure 10 to ≤ 15 years	25 (7%)	33 (11%)		
Duration kidney failure 15 to ≤ 20 years	31 (9%)	18 (6%)		
Duration kidney failure > 20 years	41 (11%)	25 (9%)		

[a] Duration of kidney failure until the start of 2020

had reached kidney failure > 10 years prior to death vs. 26% of ADTKD-*MUC1* patients in our registry who did not die of ADTKD-*MUC1* (*P* = 0.001). Table S3 shows a comparison of characteristics for patients with ADTKD-*MUC1* who died vs. those who did not.

Discussion

This investigation found that patients with ADTKD-*MUC1* are at a markedly increased risk of death from COVID-19, with 5% of adult ADTKD-*MUC1* patients dying of COVID-19 during the three years of the pandemic vs. 0.6% of ADTKD-*UMOD* adults (*P* = 0.0007). Most, but not all, of the deaths occurred in patients who had undergone kidney transplantation, though the death rate was not similarly high in transplanted patients with ADTKD-*UMOD*. Patients died of respiratory complications, and many had prolonged hospitalizations. While most of the deaths occurred early in the pandemic, deaths have continued to occur. Patients with ADTKD-*MUC1* who died of COVID-19 had a low prevalence of comorbidities (Table 2) except for kidney transplantation (84%).

While patient numbers were small due to the rarity of ADTKD, we showed consistent results with several different analyses: (1) We identified a 2.35 (95% confidence interval 1.60–3.11) increased odds of COVID-19 infection in ADTKD-*MUC1* individuals early in the pandemic, with 23% of ADTKD-*MUC1* individuals

Kidd *et al. BMC Nephrology*   (2024) 25:449

Page 8 of 10

developing COVID-19 vs. 11% of ADTKD-*UMOD* individuals ($P = 0.026$). (2) There was an early increased risk of death, with 24% of individuals with ADTKD-*MUC1* who developed a clinical COVID-19 infection dying from COVID-19 vs. 3% in individuals with ADTKD-*UMOD* ($P = 0.03$). (3) We found that the mean steady state CA15-3 level at least 30 days prior to COVID-19 infection [19] for 14 COVD-19 infected ADTKD-*MUC1* individuals was 7.06 ± 4.12 U/mL vs. 10.21 ± 4.02 U/mL for 27 uninfected individuals ($P = 0.035$). (4) Our longitudinal study then revealed an 8-fold risk of death from COVID-19 in patients with ADTKD-*MUC1* vs. ADTKD-*UMOD* ($P = 0.0009$). Thus, compared to ADTKD-*UMOD* individuals, ADTKD-*MUC1* individuals had a higher COVID-19 infection rate and were more likely to die from COVID-19. ADTKD-*MUC1* individuals were more likely to contract COVID-19 if their plasma CA15-3 levels were low.

In the early stages of COVID-19, eight (36%) of twenty-two ADTKD-*MUC1* kidney transplanted patients with COVID-19 infection died, compared to one (25%) of four ADTKD-*UMOD* kidney transplanted patients. In a meta-analysis of COVID-19 outcomes in patients with kidney transplants during the Delta strain of SARS-CoV-2[25], the mortality rate was approximately 21%. While it is difficult to compare patient characteristics between studies, ADTKD-*MUC1* patients are in general quite healthy with few comorbidities except kidney disease (see Table 2). In the meta-analysis of COVID-19 in transplant patients [25], there was an approximate 10% prevalence of diabetes and 8% prevalence of cardiovascular disease.

There were several weaknesses in our study. Most importantly, the sample size was small. Fortunately, we have the largest registry of ADTKD, with over 280 families and 800 individuals, and the response rate to our survey was good. However, by definition, any study of rare diseases will be associated with a small patient population. Another potential weakness was ascertainment and selection bias. We attempted to eliminate as many sources of bias as possible. Our registry has been historically designed to study all individuals with ADTKD-*UMOD* and ADTKD-*MUC1* in a similar manner. The surveys were sent out in an un-biased fashion, and the characteristics of respondents was similar for ADTKD-*UMOD* and ADKTD-*MUC1*. However, there could be unanticipated forms of bias that we did not identify. For ADTKD-*MUC1* patients who developed COVID-19 early in the pandemic, we calculated a 24% mortality rate. This death rate from COVID-19 may have been lower due to mild cases of COVID-19 that were undetected. While we could adjust for transplant status, we could not adjust for eGFR because we did not collect these values in the transplant patients in our registry. We also did not have more specific information about the COVID-19 hospitalizations leading to death. Another weakness of our study is that we did not examine the prevalence of other respiratory infections according to disease type. We plan to do this in the future.

The results of our investigation provide unique clinical information regarding the role of mucin-1 in COVID-19 infection. Our investigation shows that ADTKD-*MUC1* individuals are at increased risk from COVID-19, based on lower mucin-1 levels prior to infection. There is emerging information that mucin-1 in the nares and lungs serves as an initial protective barrier against infection. Lai et al. showed that mucin-1 inhibited SARS-CoV-2 viral attachment, entry, and post-entry replication [16]. Biering et al. performed genome-wide bidirectional CRISPR screens to define host-pathogen interactions required for facilitating or restricting SARS-CoV-2 in a human lung cell line and identified mucin-1 as an important host defense factor [14]. The investigators then showed an antiviral role for membrane-anchored mucins (including mucin-1) in vitro and in mouse models of SARS-CoV-2 infection. Membrane-bound mucins specifically inhibited spike-mediated viral entry into lung cells. Chatterjee et al. showed that mucin-1 is highly expressed on the ACE2-positive respiratory epithelial cells, and that removal of the mucin domains enhances spike binding [17]. Our investigation provides complementary evidence in humans. Patients with ADTKD-*MUC1* have mutations that prevent expression of the mucin domain, and these patients are at markedly increased risk of infection and death from COVID-19.

While there is evidence that decreased production of mucin-1 is associated with an increased risk from COVID-19, there is also evidence that increased production of mucin-1 may be harmful. Mucin-1 participates in the cytokine storm that occurs with COVID-19 and leads to an inflammatory response that is highly damaging. In studies of individuals who do not have ADTKD-*MUC1*, elevated mucin-1 content of bronchoalveolar fluid [26], airway mucus [27], and blood [28–31] at the time of infection is associated with worse and more severe COVID-19 outcomes. A recent genome-wide association study [32] identified the rs41264915 intronic variant *THBS3* (associated with increased mucin-1 expression) as being associated with critical COVID-19. Another GWAS study suggested that increased mucin-1 expression is associated with more severe COVID-19, while other GWAS studies have not found this association [33]. Thus, lowering mucin-1 production during infection has been postulated as a potential therapy for COVID-19[34].

Compounds increasing mucin-1 production could be prophylactic for individuals with low mucin-1 levels, whereas compounds reducing mucin-1 production could be therapeutic during acute infection. The finding that

Kidd *et al. BMC Nephrology*   (2024) 25:449

Page 9 of 10

both pathologically low and elevated clinical characteristics are associated with increased mortality is well known and has also been noted with body mass index [35], sleep time [36], and many laboratory parameters [37].

Given the increased risk associated with ADTKD-*MUC1* individuals from COVID-19, it would be prudent for families with an unknown cause of ADTKD (chronic kidney disease, autosomal dominant transmission, bland urinary sediment) to be tested for a *MUC1* mutation. As these mutations are not identified by standard Sanger sequencing [38], commercial laboratories in the US do not currently provide genetic testing for *MUC1* mutations. However, clinical testing is currently available at no cost through the Broad Institute of Harvard and MIT (contact ableyer@wakehealth.edu for information). Mucin-1 plays an important role in other respiratory tract infections [14], and we need to extend our studies in patients with ADTKD-*MUC1* to other pulmonary infections.

Conclusions
This investigation shows that individuals with ADTKD-*MUC1* are at increased risk of COVID-19 infection and mortality, especially for immunosuppressed and kidney transplanted patients exposed to more virulent COVID-19 variants. ADTKD-*MUC1* patients with low plasma mucin-1 levels may be especially at increased risk. We believe that clinicians should consider more aggressive preventive care and treatment for COVID-19 in patients with ADTKD-*MUC1*.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03896-1.

Supplementary Material 1.

Data availability
The datasets generated and analysed during the current study are not publicly available to protect patient confidentiality. We are very happy to work with any groups interested in studying this condition and providing genetic information that can satisfy their research requests. An anonymized dataset analyzed in the study will be available from the European Genome-Phenome Archive (EGA-archive.org), with request of data access.

Declarations

Ethics approval and consent to participate
This study was approved by the Wake Forest University Health Sciences Institutional Review Board, Winston-Salem, NC, United States, in accordance with the Declaration of Helsinki. All individuals presented in the study provided voluntary, autonomous consent to participate.

Consent for publication
Not applicable.

Competing interests
AJB has also received funding from the Black Brogan Foundation, The Slim Health Foundation, Soli Deo Gloria. He has received compensation as follows: advisory board, Horizon Pharma; speaker, Natera; author, UpToDate; advisor, First Faculty of Medicine, Charles University; royalty; patent for UMOD genetic diagnosis. PJC has received funding from Astra Zeneca, Bohringher, Hansa, and medical advisory board fees. KOK, AHW, AT, AK, LM, VR, APR-C, JAS, EO, HRM, GP, CD, CS, REH, EE, DS, CI, AV, LP, TZ, MP, MR, PV, KH, MZ, and SK have nothing to disclose.

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Kidd *et al. BMC Nephrology*   (2024) 25:449

Page 10 of 10

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