JASN Journal of the American Society of Nephrology

Kidney Outcomes in Long COVID

Journal:	*Journal of the American Society of Nephrology*
Manuscript ID	JASN-2021-06-0734.R1
Manuscript Type:	Original Article - Clinical Epidemiology
Date Submitted by the Author:	25-Jul-2021
Complete List of Authors:	Bowe, Benjamin; VA Saint Louis Health Care System Clinical Epidemiology Center, Research and Development Service; Saint Louis University College for Public Health and Social Justice, Department of Epidemiology and Biostatistics; Veterans Research and Education Foundation of Saint Louis Xie, Yan; VA Saint Louis Health Care System Clinical Epidemiology Center, Research and Development Service; Saint Louis University College for Public Health and Social Justice, Department of Epidemiology and Biostatistics; Veterans Research and Education Foundation of Saint Louis Xu, Evan; VA Saint Louis Health Care System Clinical Epidemiology Center, Research and Development Service; Saint Louis University School of Medicine Al-Aly, Ziyad; VA Saint Louis Health Care System Clinical Epidemiology Center, Research and Development Service; Veterans Research and Education Foundation of Saint Louis; Washington University School of Medicine in Saint Louis, Department of Medicine; Medicine Service, VA Saint Louis Health Care System, Department of Medicine
Keywords:	ESRD, ESKD, Acute Kidney Injury, Post-acute Sequelae of SARS-CoV-2 Infection, PASC, Post-acute COVID, Long COVID, eGFR decline, Kidney function, COVID-19

Authors: Bowe, Benjamin; Xie, Yan; Xu, Evan; Al-Aly, Ziyad

Title: Kidney Outcomes in Long COVID

Running title: Post-acute COVID-19 and the kidney

Manuscript Type: Original Article - Clinical Epidemiology

Funders: American Society of Nephrology, (Grant / Award Number:)
U.S. Department of Veterans Affairs, (Grant / Award Number:)

Financial Disclosure: CUST_FINANCIAL_DISCLOSURE :No data available. Z. Al-Aly reports Research Funding from US Department of Veteran Affairs, Institute for Public Health, and Washington University in Saint Louis. All remaining authors have nothing to disclose.

Study Group/Organization Name: CUST_STUDY_GROUP/ORGANIZATION_NAME :No data available.

Study Group Members' Names: CUST_STUDY_GROUP_MEMBERS :No data available.

Total number of words: 2965

Abstract: Background: COVID-19 is associated with increased risk of post-acute sequelae involving pulmonary and extrapulmonary organ systems â€" referred to as long COVID. However, a detailed assessment of kidney outcomes in long COVID is not yet available.
Methods: We built a cohort of 1,726,683 US Veterans identified from March 01, 2020 to March 15, 2021 including 89,216 30-day COVID-19 survivors and 1,637,467 non-infected controls. We examined risks of AKI, eGFR decline, ESKD, and major adverse kidney events (MAKE) defined as eGFR decline â‰¥50%, ESKD, or all-cause mortality using inverse probability weighted survival regressions, adjusting for predefined demographic and health characteristics, and algorithmically selected high-dimensional covariates including diagnoses, medications, and laboratory tests. Linear mixed models characterized intra-individual eGFR trajectory.
Results: Beyond the acute illness, 30-day survivors of COVID-19 exhibited a higher risk of AKI (aHR=1.94 (95%CI: 1.86,2.04)), eGFR decline â‰¥30% (1.25 (1.14,1.37)), eGFR decline â‰¥40% (1.44 (1.37,1.51)), eGFR decline â‰¥50% (1.62 (1.51,1.74)), ESKD (2.96 (2.49-3.51)), and MAKE (1.66 (1.58,1.74)). There was a graded increase in risks of post-acute kidney outcomes according to the severity of the acute infection (whether patients were non-hospitalized, hospitalized, or admitted to intensive care). Compared to non-infected controls, 30-day COVID-19 survivors exhibited excess eGFR decline of -3.26 (-3.58, -2.94), -5.20 (-6.24, -4.16), and -7.69 (-8.27, -7.12) mL/min/1.73m²/year in non-hospitalized, hospitalized, and those admitted to intensive care during the acute phase of COVID-19 infection.
Conclusions: COVID-19 survivors exhibited increased risk of kidney outcomes in the post-acute phase of the disease. Post-acute COVID-19 care should involve attention to kidney disease.

Significance Statement

COVID-19 survivors are at higher risk of post-acute sequelae involving pulmonary and several extrapulmonary organ systems — generally referred to as long COVID. However, a detailed assessment of kidney outcomes in long COVID is not yet available. Here we show that beyond the acute phase of illness, 30-day survivors of COVID-19 exhibited higher risks of AKI, eGFR decline, ESKD, major adverse kidney events (MAKE), as well as steeper longitudinal decline in eGFR. The risks of kidney outcomes increased according to the severity of the acute infection (categorized by care setting into non-hospitalized, hospitalized, and admitted to intensive care). The findings provide insight into the long-term consequences of COVID-19 on kidney outcomes and suggest that post-acute COVID-19 care should include attention to kidney function and disease.

Kidney Outcomes in Long COVID

Benjamin Bowe[1,2,3], Yan Xie[1,2,3], Evan Xu[1,4], and Ziyad Al-Aly[1,3,5,6,7]

[1]Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[2]Department of Epidemiology and Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri

[3]Veterans Research and Education Foundation of Saint Louis, Saint Louis, Missouri

[4]Saint Louis University School of Medicine, Saint Louis, Missouri

[5]Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri

[6]Nephrology Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[7]Institute for Public Health, Washington University in Saint Louis, Saint Louis, Missouri

Short running title: Post-acute COVID-19 and the kidney

Word count for abstract: 250
Word count for text: 2965

Corresponding Author:
Ziyad Al-Aly, M.D.
VA Saint Louis Health Care System
915 North Grand Boulevard, 151-JC
Saint Louis, MO 63106
Telephone: (314) 289-6333
E-mail: zalaly@gmail.com

Abstract:

Background: COVID-19 is associated with increased risk of post-acute sequelae involving pulmonary and extrapulmonary organ systems — referred to as long COVID. However, a detailed assessment of kidney outcomes in long COVID is not yet available.

Methods: We built a cohort of 1,726,683 US veterans identified from March 01, 2020 to March 15, 2021, including 89,216 30-day COVID-19 survivors and 1,637,467 non-infected controls. We examined risks of AKI, eGFR decline, ESKD, and major adverse kidney events (MAKE). MAKE is defined as eGFR decline ≥50%, ESKD, or all-cause mortality using inverse probability weighted survival regression, adjusting for predefined demographic and health characteristics and algorithmically selected high-dimensional covariates including diagnoses, medications, and laboratory tests. Linear mixed models characterized intra-individual eGFR trajectory.

Results: Beyond the acute illness, 30-day survivors of COVID-19 exhibited a higher risk of AKI (aHR=1.94 (95%CI: 1.86,2.04)), eGFR decline ≥30% (1.25 (1.14,1.37)), eGFR decline ≥40% (1.44 (1.37,1.51)), eGFR decline ≥50% (1.62 (1.51,1.74)), ESKD (2.96 (2.49-3.51)), and MAKE (1.66 (1.58,1.74)). Increase in risks of post-acute kidney outcomes was graded according to the severity of the acute infection (whether patients were non-hospitalized, hospitalized, or admitted to intensive care). Compared to non-infected controls, 30-day COVID-19 survivors exhibited excess eGFR decline of -3.26 (-3.58, -2.94), -5.20 (-6.24, -4.16), and -7.69 (-8.27, -7.12) mL/min/1.73m^2/year in non-hospitalized, hospitalized, and those admitted to intensive care during the acute phase of COVID-19 infection.

Conclusions: COVID-19 survivors exhibited increased risk of kidney outcomes in the post-acute phase of the disease. Post-acute COVID-19 care should include attention to kidney disease.

Introduction:

COVID-19 is associated with substantial short-term (acute) morbidity and mortality(1). Evidence suggests that beyond the acute illness, COVID-19 survivors may experience post-acute sequelae — also referred to in the lay vernacular as long COVID — which can involve pulmonary and broad extrapulmonary organ system manifestations including the kidneys(2). However, a detailed in-depth assessment of kidney outcomes in the post-acute phase of COVID-19 infection is not yet available. A better understanding of post-acute COVID-19 kidney outcomes would inform development of care strategies to improve the health and wellbeing of people with long COVID.

Here, we leverage the breadth and depth of the US Department of Veterans Affairs national health care databases to build a cohort of 89,216 US Veterans who survived the first 30 days of COVID-19 infection and 1,726,683 non-infected controls and followed them longitudinally to provide an in-depth detailed characterization of the risks (and associated burdens) of post-acute kidney outcomes in the overall cohort, and according to severity of the acute infection (that is whether patients were non-hospitalized, hospitalized, and admitted to intensive care).

Methods:

Cohort:

Among users of the Department of Veterans Health Care System (VHA), we identified 203,476 US Veterans who had a record of a laboratory confirmed COVID-19 test between March 01, 2020 and March 15, 2021 (Supplemental Figure 1); of these, 191,958 had a recorded encounter with the VHA in 2019. We selected from these 181,384 who were alive 30 days after testing positive (did not succumb to death during the acute phase of the infection). The date of testing positive was set as T_0. For a comparison group we identified 5,808,018 users of the VHA who had a record of an encounter with the VHA in 2019; 5,606,309 of whom were alive as of March 01, 2020, and 5,414,351 of whom did not have a positive COVID-19 test between March 01, 2020 and

March 15, 2021. We randomly assigned a T_0 to the control group participants by matching them with a COVID-19 participant at a 25 to 1 rate, resulting in 4,534,600 control group participants, of which 4,397,509 were alive 30 days after their T_0. Those with a record of end stage kidney disease (ESKD) before or in the 30 days after T_0 were excluded from both groups, and then we finally selected those with a recorded serum creatinine measurement after 30 days from time zero (1,637,467 control and 89,216 COVID-19), resulting in a final analytic cohort of 1,726,683. Those with a recorded COVID-19 positive test were further defined as being non-hospitalized, hospitalized, and being admitted to the intensive care unit (ICU) by record of inpatient care or admittance to the ICU during the 30 days following T_0 (the acute phase of the illness).

Data sources:

This study utilized data collected during the routine delivery of care from the United States Department of Veterans Affairs (VA) Veterans Health Administration (VHA). Demographic and clinical data were obtained from the Corporate Data Warehouse (CDW)(3-10). The VA COVID-19 Shared Data Resource (CSDR)(11) provided information on COVID-19 positive Veterans. The CSDR providers information collated by the VA's National Surveillance Tool, which collects near real time data on COVID-19 cases from laboratory results and clinical notes (which are examined via natural language processing and subsequent human review). The Area Deprivation Index (ADI) — a composite contextual measure of poverty, housing quality, employment, and education(12, 13) — supplied a measure of the level of socio-economic disadvantage at participants' residential locations.

Outcomes:

Outcomes were examined in the period of follow-up from 30 days after T_0 up to April 30th, 2021, censoring at death or ESKD where applicable. Acute kidney injury (AKI) was defined as having an inpatient serum creatinine measurement 30-days after T_0 that was 0.3 mg/dL or 50% greater than baseline, where baseline was assessed as the average of all values in the two years prior to T_0. We also assessed outcomes of

estimated glomerular filtration rate (eGFR) decline of greater than or equal 30%, 40%, and 50% from baseline. Baseline eGFR was defined by the eGFR measurement most proximal but prior to T_0, including measures up to two years prior to T_0. If outpatient values were available, these were utilized first, otherwise inpatient values were used (less than 1%). In the case of missing baseline kidney function values (1.8% and 3.2% in COVID-19 and VHA user groups, respectively), values were imputed based on demographics and baseline health characteristics. An ESKD outcome was defined at date of first record of receipt of chronic outpatient dialysis or kidney transplant. Major adverse kidney events (MAKE) was defined as a composite of eGFR decline greater than or equal to 50%, ESKD, or all-cause mortality. Finally, we examined the rate of change in eGFR during the follow-up period using all outpatient and inpatient values 30 days after T_0. All eGFR were calculated using the CKD-EPI equation(14).

Covariates:

Covariates included a set of 29 predefined potential confounders of the association between COVID-19 and adverse kidney outcomes(1, 2, 15). Demographics, behavioral, and contextual characteristics included age, ADI, race, sex, and smoking status. Health characteristics included a participant's baseline eGFR, systolic and diastolic blood pressure, body mass index (BMI), and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, and peripheral artery disease. Systolic and diastolic blood pressure were defined as the average of all corresponding measures in the year prior to T_0. Medication history included angiotensin converting enzyme inhibitors (ACE)/angiotensin II receptor blockers (ARB), antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors(16-19). Clinical comorbidities and medication usage were assessed in the year prior to T_0. We additionally adjusted for record of residence at a long-term care facility, and the number of eGFR measurements in the year prior to T_0 as a measure of intensity of interaction with the health care system. All continuous covariates

were adjusted for as restricted cubic splines with knots at the 5th, 33rd, 66th, and 95th percentiles. Missing baseline BMI (0.4%) and blood pressure (1%) were imputed.

In addition to these predefined covariates, and to further enhance adjustment of models, we also included a set of 100 variables selected by a high-dimensional variable selection algorithm from several data domains including diagnoses, pharmacy records, and laboratory tests(20-23). In brief, from data domains of diagnoses, medication prescriptions, and laboratory tests, all available variables that occurred at least 10 times in each group (a total of 834) were examined for differences between the COVID-19 and VHA users group by assessment of unadjusted relative risk. We selected among these the top 100 variables with the strongest association with group membership for inclusion in adjustment with the predefined covariates. All covariates were assessed in the year prior to T_0.

Statistical analyses:

Cohort participant's characteristics overall and by COVID-19 status are reported as means (standard deviations), medians (interquartile ranges), or frequencies (percentages), where appropriate.

Unadjusted outcome rates are presented. Differences in the risk of outcomes were assessed by application of inverse probability weighting to cause specific Cox proportional hazard models. Propensity scores were estimated using logistic regression, which were then used to construct weights stabilized by unadjusted group membership probability. Truncation was not applied after examination of mean and standard deviation of weights. Balance was examined by standardized mean differences in the predefined covariates and 100 selected high dimensional covariates before and after weighting. In addition to this, we examined balance in the 734 high dimensional covariates not selected as a means of testing for residual differences in these covariates that were not included in the propensity score model, where lack of balance may have suggested that our analytic algorithm did not address potential measured confounders. A standardized mean difference less than 0.15 was taken as evidence of balance between the COVID-19 and VHA users group(24, 25). We

estimated the excess burden per 1000 persons of the outcomes associated with COVID-19 at 6 months after T_0, where excess burden was estimated by computing the difference between the average estimated survival probability from the weighted Cox model in those with COVID-19 and the VHA user group. Baseline survival probability was estimated using the Breslow method(26). To examine the impact of underlying severity of the acute phase of the illness (non-hospitalized, hospitalized, and admitted to the ICU), analyses were repeated in the comparisons to VHA-users employing a similar analytic design(27).

We additionally conducted an analysis examining the risks and burdens of AKI, ESKD, and MAKE by the occurrence of AKI during the acute phase of COVID-19 (first 30 days after a positive test). COVID-19 groups examined included those during the acute phase that were non-hospitalized, hospitalized with no evidence of AKI, and hospitalized with evidence of an AKI. Evidence of an AKI was assessed as an inpatient serum creatinine 0.3 mg/dL or 50% higher than the baseline serum creatinine. Propensity scores and outcome definitions were revised to incorporate changes in baseline eGFR and serum creatinine through the acute phase of the illness, using the most recently available measure through the 30-day period after a positive test.

We finally examined differences in the intra-individual trajectory of eGFR starting from 30-days after T_0 by severity of the acute infection using linear mixed models. Analyses were conducted in those who had at least two measurements of eGFR during this follow-up period to enhance characterization of intra-individual eGFR change. Trajectories were compared to that of the VHA user group (control). Models were weighted by the stabilized inverse probably of group membership, as previously described. Individual level random intercepts were included. Differences in the trajectory of eGFR were examined by an interaction between the COVID-19 group and time; differences in the linear slope of eGFR are presented. We additionally examined potential non-linear changes, including a quadratic time term (identified by improvement by Akaike Information Criterion). Differences in the trajectory of eGFR as compared to the control group starting from day 30 over the course of a year are plotted with 95% CI obtained through bootstrap. Differences in trajectories by AKI status during the acute phase of the illness were also assessed. Estimates of all risks, excess burdens, and eGFR trajectories

were additionally generated in weighted models that only incorporated the pre-defined covariates in the modeling of the propensity score.

In order to examine the robustness of results to study design specifications we examined a set of positive and negative outcome controls(28). We examined the association of COVID-19 with positive outcome controls of all-cause mortality and hospitalization, where based on prior evidence we would expect to see an association(21, 29). Positive outcome controls may be employed to detect the presence of latent biases that may result in the absence of associations where one would be expected. We also examined the association of COVID-19 status with negative outcome controls including being fitted or having an adjustment of casts or bandages, and atopic dermatitis. Negative outcome control may be employed to detect the presence of latent biases that result in spurious associations where none would be expected.

Statistical tests were two sided, where a 95% confidence interval that did not contain unity or a p-value less that 0.05 was considered evidence of an association. Imputation was done using fully conditional specification. Analyses were conducted using SAS Enterprise Guide version 8.2 (SAS Institute, Cary, NC), and results were visualized using R version 4.0.4(30). This study was approved by the Institutional Review Board of the Department of Veterans Affairs St Louis Health Care System, Saint Louis, MO.

Results

There were 1,726,683 US Veterans in the cohort overall; 89,216 (5.2%) and 1,637,467 (94.8%) were in the COVID-19 and VHA users (control) group, respectively (Table 1). Median follow-up time was 164 days (interquartile range: 127-268) in those with COVID-19, and 172 days (133-282) in the VHA user group (Table 1). Compared to VHA users (control group), those with COVID-19 were more likely to be younger, of Black race, living in long term care, and had a higher comorbidity burden including higher rates of chronic lung disease, diabetes, and cardiovascular disease, and higher rates of being prescribed medications including proton pump inhibitors and nonsteroidal anti-inflammatory drugs (Table 1). Median time to outcomes of AKI,

eGFR decline ≥30%, eGFR decline ≥40%, eGFR decline ≥50%, ESKD, and MAKE by COVID-19 status and intensity of care are provided in Supplemental Table 1.

Risks and burdens of post-acute COVID-19 kidney outcomes

Assessment of covariate balance after application of inverse probability weighting suggested that in overall cohort predefined covariates, high dimensional covariates selected by our algorithm, and those not selected were balanced (Supplemental Figure 2 and Supplemental Table 2).

After adjustment for baseline characteristics, beyond the acute illness and compared to VHA users, 30-day survivors of COVID-19 exhibited a higher risk of AKI (aHR=1.94 (95%CI: 1.86-2.04)), eGFR decline ≥30% (1.25 (1.14-1.37)), eGFR decline ≥40% (1.44 (1.37-1.51)), eGFR decline ≥50% (1.62 (1.51-1.74)), ESKD (2.96 (2.49-3.51)), and MAKE (1.66 (1.58-1.74)) (Figure 1).

Among 30-day survivors of COVID-19, and beyond the first 30 days of illness, excess burden of several kidney outcomes was evident in the post-acute phase of COVID-19 including AKI (11.50 (95%CI: 10.91, 12.07)) per 1000 persons at 6 months, eGFR decline ≥30% 10.37 (9.11, 11.59), eGFR decline ≥40% 6.95 (6.14, 7.72), eGFR decline ≥50% (4.74 (4.20, 5.24)), ESKD (1.46 (1.32, 1.57)), and MAKE (9.71(8.99, 10.40) (Figure 1). Results were consistent in models only adjusting for the predefined covariates (Supplemental Table 3).

Post-acute COVID-19 kidney outcomes by severity of the acute infection

We then further examined the risks and burdens of post-acute kidney outcomes by the severity of disease during the acute phase of the infection (non-hospitalized, hospitalized, and admitted to intensive care). Assessment of covariate balance after application of weights suggested covariates were well balanced (Supplemental Figure 3 and Supplemental Table4-9). Compared to VHA users (control group), the risks and burdens of post-acute COVID-19 kidney outcomes increased according to the severity of the acute infection among those with COVID-19 (Figure 2). Pairwise comparisons between all four mutually exclusive groups are

provided in Supplemental Table 10. Results were consistent in models only adjusting for the predefined covariates (Supplemental Tables 11a-b).

Post-acute COVID-19 kidney outcomes by occurrence of AKI during the acute phase

In consideration of changes in kidney function that may have occurred during the acute phase of the illness, we assessed the risks and burden of post-acute kidney outcomes (AKI, ESKD, and MAKE) in those who had COVID-19 and were not hospitalized, those who were hospitalized but did not have an AKI, and those who were hospitalized and had an AKI during the acute phase of the infection. Assessment of covariate balance after application of weighting suggested that covariates were well balanced (Supplemental Tables 12-17, Supplemental Figure 4). Compared to VHA users (control group), a gradient was evident in that risks (and associated burdens) increased across the three examined COVID-19 groups from non-hospitalized individuals to those who were hospitalized with no evidence of an AKI, and risk was highest in people who were hospitalized and had an AKI during the acute phase of the COVID-19 infection (Figure 3, Supplemental Table 18). Compared to those who were hospitalized and did not have an AKI during the acute phase, the risk of post-acute kidney outcomes (AKI, ESKD, and MAKE) was higher in those who were hospitalized and had an AKI during the acute phase of the infection (Supplemental Table 18). Results were consistent in models only adjusting for the predefined covariates (Supplemental Tables 19a-b).

Post-acute COVID-19 eGFR trajectories

We built linear mixed models to characterize post-acute COVID-19 eGFR trajectories of 30-day survivors of COVID-19 who had at least two measurements of serum creatinine during follow-up (n=373,151). Adjusted analyses of intra-individual change in eGFR suggested that compared to VHA users (control group with eGFR slope of -0.49 (-0.57, -0.42) ml/min/1.73m^2 per year, COVID-19 was associated with an excess eGFR decline of -3.26 (95% CI: -3.58, -2.94) ml/min/1.73m^2 per year in those who were not hospitalized, -5.20 (-6.24, -4.16) ml/min/1.73m^2 per year in those who were hospitalized, and -7.69 (-8.27, -7.12) ml/min/1.73m^2 per year in those who were admitted to intensive care during the acute phase of COVID-19 infection. Non-linear

trajectories suggested that as follow-up progressed, the rate of excess decline in eGFR attenuated (Figure 4). Additional examination of eGFR trajectories by AKI status during the acute phase suggested a steeper decline in eGFR in those who had an AKI during the acute phase of the illness (Figure 5). Adjusted analyses of intra-individual change in eGFR by AKI status suggested that compared to the VHA users, COVID-19 was associated with an excess eGFR decline of -3.30 (-3.62, -2.99) ml/min/1.73m^2 per year in those not hospitalized, -5.27 (-5.86, -4.68) ml/min/1.73m^2 per year in those hospitalized without an AKI, and -8.41 (-9.72, -7.10) ml/min/1.73m^2 per year in those hospitalized with an AKI. Results were consistent in models only adjusting for the predefined covariates (Supplemental Figures 5-6).

Positive and Negative Outcome Controls

In order to test for potential presence of latent biases, we conducted analyses of positive and negative outcome controls, where based on prior evidence, one would expect to observe an association (positive controls) or the absence of an association (negative controls). Analyses suggested an association of COVID-19 with an increased risk and excess burden of positive outcome controls including all-cause mortality (HR=1.76; 95%CI=1.66-1.87) and hospitalization (1.77; 1.72-1.81) after 30 days following testing positive for COVID-19 (Supplemental Table 20). No evidence of an association was observed with negative outcome controls including fitting or adjustment of casts and bandages (HR=0.97; 95%CI= 0.89-1.06), and atopic dermatitis (0.99; 0.83-1.18).

Discussion:

In this work, we characterize post-acute kidney outcomes in a cohort of 89,216 30-day survivors of COVID-19. The results show that beyond the first 30 days of infection, COVID-19 survivors exhibited increased risk (and burden) of AKI, eGFR decline, ESKD, and MAKE. The risks (and burdens) of kidney outcomes increased according to the severity of the acute infection. While AKI during the acute phase contributed to the increased risk of post-acute kidney outcomes, our analyses also suggest that increased risk of post-acute kidney

outcomes was evident even among those who did not experience AKI in the acute phase. Examination of intra-individual longitudinal change in eGFR suggested that COVID-19 survivors experienced greater loss of eGFR than non-infected controls and that eGFR loss was more profound as the severity of the acute COVID-19 infection increased. Taken together, these results suggest that beyond the acute phase of COVID-19 infection, people with COVID-19 experience higher risk adverse kidney outcomes. Post-acute care of people with COVID-19 should involve attention and care for acute and chronic kidney disease.

The implications of our findings are clear. Given the large number of people infected with COVID-19 (>34 million people in the US, and > 193 million globally), and given that estimates by the World Health Organization suggest that 10% of people infected with COVID-19 may experience post-acute sequelae, the numbers of people with long COVID in need of post COVID care will likely be staggering and will present substantial strain on already overwhelmed health systems. Governments and health systems around the world are establishing post-acute COVID clinics to attend to the needs of people with post-acute COVID sequelae. The optimal composition of those clinics is not yet clear. The higher risks of adverse kidney outcomes reported in this study highlights the need for integration of kidney care as a component of the multidisciplinary post-acute COVID care. Our estimates of burden of kidney sequelae may also be useful to inform capacity planning.

While our analyses suggest that AKI during the acute phase contributes to the increased risk of post-acute kidney outcomes (in that the risk of post-acute kidney outcomes was higher in those hospitalized with an AKI than those hospitalized without an AKI during the acute phase of the infection), it is also evident that the risk was increased in those who did not experience an AKI during the acute phase. Furthermore, our analyses of risks and burdens of post-acute kidney outcomes by care setting of the acute infection highlight two key messages: (1) that the risk and associated burden of post-acute kidney outcomes was evident even among individuals whose acute disease was not severe enough to necessitate hospitalization (this will likely have broad implications because this group represents the majority of people with COVID-19) and (2) that the risk

and associated burden increased across the severity spectrum of the acute COVID-19 infection (from non-hospitalized to hospitalized individuals, to those admitted to intensive care).

The mechanism or mechanisms of increased risk of acute kidney injury, eGFR decline, ESKD, and MAKE in the post-acute phase of COVID-19 infection are not clear. While initial observations suggested that SARS-CoV-2 may have kidney tropism, more recent evidence does not endorse the earlier assessment(31). Other potential explanations include dysregulated immune response or autoimmunity, persistent inflammation, disturbances in endothelial function and the coagulation system, and disturbances in the autonomic nervous system. Mechanisms related to changes in the broader economic and social conditions in the context of the global pandemic that may have differentially impacted people with COVID-19 may be also at play(32-38). A deeper understanding of the mechanistic and epidemiologic drivers of the post-acute kidney sequelae of SARS-CoV-2 infection (and more broadly the entire spectrum of post-acute sequelae of SARS-CoV-2) is urgently needed to help inform care strategies.

This study has several strengths. To build our cohort, we capitalized on the breadth and depth of the electronic health databases of the US Department of Veterans Affairs which operates the largest nationally integrated healthcare delivery system in the US. We broadened our covariate specification approach to include a set of 29 predefined variables selected based on prior evidence as well as 100 algorithmically selected variables from several VA high dimensional data domains including diagnostic codes, prescription records, and laboratory test results. We evaluated several kidney outcomes including AKI, eGFR decline, the terminal endpoint of ESKD, as well assessing intra-individual longitudinal changes in eGFR. Our outcomes (for AKI, eGFR decline, and longitudinal eGFR changes) were defined based on laboratory values rather than relying on ICD codes. We tested for potential presence of spurious biases by applying positive and negative outcome controls. We not only provided estimates of risks on the ratio scale (hazard ratios), but also reported estimates of excess burden per 1000 persons due to COVID-19 on the absolute scale; this measure additionally reflects

the contribution of baseline risk and provides a useful estimate of potential harm and would be more easily understood by a broader public than relative risk (e.g. hazard ratio).

This study has several limitations. The demographic and health characteristics of our VA cohort (older white males) may limit generalizability of the findings. Although we adjusted (through weighting) for both predefined and algorithmically selected high dimensional covariates, and although covariate balance assessment suggested small standardized mean differences even in the covariates that were not directly included in the propensity score model, residual confounding may not be completely ruled out. Our datasets did not include individual data on urine measures for incorporation in AKI definitions. Although we provide estimates of risk and excess burden by intensity of care during the acute phase of the disease (non-hospitalized, hospitalized, and admitted to intensive care), our analyses did not adjust for other markers of severity within these categories. Finally, as the pandemic continues to evolve, as the impact of vaccinations and new variants (e.g. delta variant) is realized, as long-term follow-up of COVID-19 survivors extends, and as treatment strategies of the acute disease improves, it is possible that the epidemiology of post-acute COVID-19 kidney outcomes will change as time progresses.

In sum, we show that 30-survivors of COVID-19 exhibited higher risk of AKI, eGFR decline, ESKD, and MAKE than those not infected by COVID-19. Greater longitudinal eGFR loss was observed in COVID-19 survivors (compared to non-infected controls). The risk of adverse kidney outcomes increased according to the severity of the acute infection as proxied by the care setting (non-hospitalized, hospitalized, and admitted to intensive care). The totality of the evidence suggests that substantial risk of kidney outcomes in people with COVID-19 and highlights the need to integrate a kidney care component in post-acute COVID care pathways.

Acknowledgements: This study used data from the VA COVID-19 Shared Data Resource.

Author Contributions: BB and ZAA contributed to the development of the study concept and design. BB and YX contributed to data acquisition. BB, YX, and ZAA contributed to data analysis and interpretation. BB and YX contributed to statistical analysis. BB, and ZAA drafted the manuscript. Critical revision of the manuscript was contributed to by BB, YX, EX, and ZAA. Administrative, technical, and material support was provided by ZAA. ZAA contributed supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ZAA takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained. All authors approved the final version of the report.

Funding: This research was funded by the United States Department of Veterans Affairs (for ZAA) and two American Society of Nephrology and KidneyCure Pre-doctoral fellowship awards (for BB and YX). The funders of this study had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Disclosures: Z. Al-Aly reports Research Funding from US Department of Veteran Affairs, Institute for Public Health, and Washington University in Saint Louis. All remaining authors have nothing to disclose.

Disclaimer: The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Data Sharing: All data is available by request from the US Department of Veterans Affairs.

Corresponding Author: Ziyad Al-Aly, MD, VA Saint Louis Health Care System, 915 North Grand Boulevard, 151-JC, Saint Louis, MO 63106; Telephone: (314) 289-6333; email: zalaly@gmail.com

References:

1. Xie Y, Bowe B, Maddukuri G, Al-Aly Z: Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza: cohort study. *Bmj*, 2021 http://dx.doi.org/10.1136/bmj.m4677
2. Al-Aly Z, Xie Y, Bowe B: High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*, 2021 10.1038/s41586-021-03553-9
3. Bowe B, Xie Y, Xian H, Lian M, Al-Aly Z: Geographic Variation and US County Characteristics Associated With Rapid Kidney Function Decline. *Kidney Int Rep,* 2**:** 5-17, 2017 10.1016/j.ekir.2016.08.016
4. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z: Higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus. *Kidney international,* 93**:** 741-752, 2018 10.1016/j.kint.2017.08.033
5. Bowe B, Xie Y, Yan Y, Al-Aly Z: Burden of Cause-Specific Mortality Associated With PM2.5 Air Pollution in the United States. *JAMA Netw Open,* 2**:** e1915834, 2019 10.1001/jamanetworkopen.2019.15834
6. Xie Y, Bowe B, Yan Y, Xian H, Li T, Al-Aly Z: Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. *Bmj,* 365**:** l1580, 2019 10.1136/bmj.l1580
7. Bowe B, Xie Y, Xian H, Li T, Al-Aly Z: Association between Monocyte Count and Risk of Incident CKD and Progression to ESRD. *Clin J Am Soc Nephrol,* 12**:** 603-613, 2017 10.2215/CJN.09710916
8. Al-Aly Z, Maddukuri G, Xie Y: Proton Pump Inhibitors and the Kidney: Implications of Current Evidence for Clinical Practice and When and How to Deprescribe. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 75**:** 497-507, 2020 10.1053/j.ajkd.2019.07.012
9. Xie Y BB, Gibson A, McGill J, Yan Y, Maddukuri G, Al-Aly Z.: Comparative Effectiveness of the Sodium-glucose Co-transporter-2 Inhibitor Empagliflozin vs. Other Antihyperglycemics on Risk of Major Adverse Kidney Events. *Diabetes Care,* 43, 2020 https://doi.org/10.2337/dc20-1231
10. Xie Y, Bowe B, Gibson AK, McGill JB, Maddukuri G, Al-Aly Z: Comparative Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors vs Sulfonylureas in Patients With Type 2 Diabetes. *JAMA internal medicine*, 2021 10.1001/jamainternmed.2021.2488
11. Department of Veterans Affairs: COVID-19:Shared Data Resource Available at: https://vhacdwdwhweb100.vha.med.va.gov/phenotype/index.php/COVID-19:Shared_Data_Resource#Acknowledgements_COVID-19_Shared_Data_Resource.
12. Kind AJ, Jencks S, Brock J, Yu M, Bartels C, Ehlenbach W, et al.: Neighborhood socioeconomic disadvantage and 30 day rehospitalizations: an analysis of Medicare data. *Ann Intern Med,* 161**:** 765, 2014
13. Kind AJ, Buckingham WR: Making Neighborhood-Disadvantage Metrics Accessible—The Neighborhood Atlas. *N Engl J Med,* 378**:** 2456-2458, 2018
14. Levey AS, Stevens LA: Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis,* 55**:** 622-627, 2010 10.1053/j.ajkd.2010.02.337
15. Bowe B, Cai M, Xie Y, Gibson AK, Maddukuri G, Al-Aly Z: Acute Kidney Injury in a National Cohort of Hospitalized US Veterans with COVID-19. *Clinical journal of the American Society of Nephrology : CJASN*, 2020 10.2215/CJN.09610620
16. Chertow GM, Lazarus JM, Christiansen CL, Cook EF, Hammermeister KE, Grover F, et al.: Preoperative renal risk stratification. *Circulation,* 95**:** 878-884, 1997
17. Klepser DG, Collier DS, Cochran GL: Proton pump inhibitors and acute kidney injury: a nested case–control study. *BMC Nephrol,* 14**:** 150, 2013
18. Leonard CE, Freeman CP, Newcomb CW, Reese PP, Herlim M, Bilker WB, et al.: Proton pump inhibitors and traditional nonsteroidal anti‐inflammatory drugs and the risk of acute interstitial nephritis and acute kidney injury. *Pharmacoepidemiol Drug Saf,* 21**:** 1155-1172, 2012
19. Okusa MD: The inflammatory cascade in acute ischemic renal failure. *Nephron,* 90**:** 133-138, 2002

20. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA: High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology (Cambridge, Mass),* 20**:** 512, 2009
21. Al-Aly Z, Xie Y, Bowe B: High-dimensional characterization of post-acute sequalae of COVID-19. *Nature***:** 1-8, 2021
22. Xie Y, Bowe B, Gibson AK, McGill JB, Yan Y, Maddukuri G, et al.: Comparative Effectiveness of the Sodium–Glucose Cotransporter 2 Inhibitor Empagliflozin Versus Other Antihyperglycemics on Risk of Major Adverse Kidney Events. *Diabetes Care,* 43**:** 2785-2795, 2020
23. Xie Y, Bowe B, Maddukuri G, Al-Aly Z: Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza: cohort study. *BMJ,* 371, 2020
24. Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity‐score matched samples. *Stat Med,* 28**:** 3083-3107, 2009
25. Rubin DB: Using Propensity Scores to Help Design Observational Studies: Application to the Tobacco Litigation. *Health Services and Outcomes Research Methodology,* 2**:** 169-188, 2001 10.1023/A:1020363010465
26. Breslow NE: Discussion of Professor Cox's paper. *J Royal Stat Soc B,* 34**:** 216-217, 1972
27. Xie Y, Bowe B, Gibson AK, McGill JB, Maddukuri G, Yan Y, et al.: Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of kidney outcomes: emulation of a target trial using health care databases. *Diabetes Care,* 43**:** 2859-2869, 2020
28. Lipsitch M, Tchetgen ET, Cohen T: Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology (Cambridge, Mass),* 21**:** 383, 2010
29. Daugherty SE, Guo Y, Heath K, Dasmarinas MC, Jubilo KG, Samranvedhya J, et al.: SARS-CoV-2 infection and risk of clinical sequelae during the post-acute phase: a retrospective cohort study. *BMJ*, 2021
30. Wickham H: *ggplot2: elegant graphics for data analysis*, Springer, 2016
31. Delorey TM, Ziegler CGK, Heimberg G, Normand R, Yang Y, Segerstolpe Å, et al.: COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. *Nature*, 2021 10.1038/s41586-021-03570-8
32. Figueroa JD, Brennan PM, Theodoratou E, Poon MTC, Purshouse K, Din FVN, et al.: Distinguishing between direct and indirect consequences of covid-19. *Bmj,* 369**:** m2377, 2020 10.1136/bmj.m2377
33. Townsend E: COVID-19 policies in the UK and consequences for mental health. *Lancet Psychiatry,* 7**:** 1014-1015, 2020 10.1016/S2215-0366(20)30457-0
34. Knipe D, Evans H, Marchant A, Gunnell D, John A: Mapping population mental health concerns related to COVID-19 and the consequences of physical distancing: a Google trends analysis. *Wellcome open research,* 5**:** 82, 2020 10.12688/wellcomeopenres.15870.2
35. Raker EJ, Zacher M, Lowe SR: Lessons from Hurricane Katrina for predicting the indirect health consequences of the COVID-19 pandemic. *Proceedings of the National Academy of Sciences of the United States of America,* 117**:** 12595-12597, 2020 10.1073/pnas.2006706117
36. Mahase E: Covid-19: Mental health consequences of pandemic need urgent research, paper advises. *Bmj,* 369**:** m1515, 2020 10.1136/bmj.m1515
37. Xie Y, Bowe B, Yan Y, Cai M, Al-Aly Z: County-Level Contextual Characteristics and Disparities in Life Expectancy. *Mayo Clinic proceedings,* 96**:** 92-104, 2021 10.1016/j.mayocp.2020.04.043
38. Bowe B, Xie Y, Gibson AK, Cai M, van Donkelaar A, Martin RV, et al.: Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: Cohort study. *Environment International,* 154**:** 106564, 2021 https://doi.org/10.1016/j.envint.2021.106564

Tables:

Table 1: Demographic and health characteristics of the overall cohort and by COVID-19 status at baseline

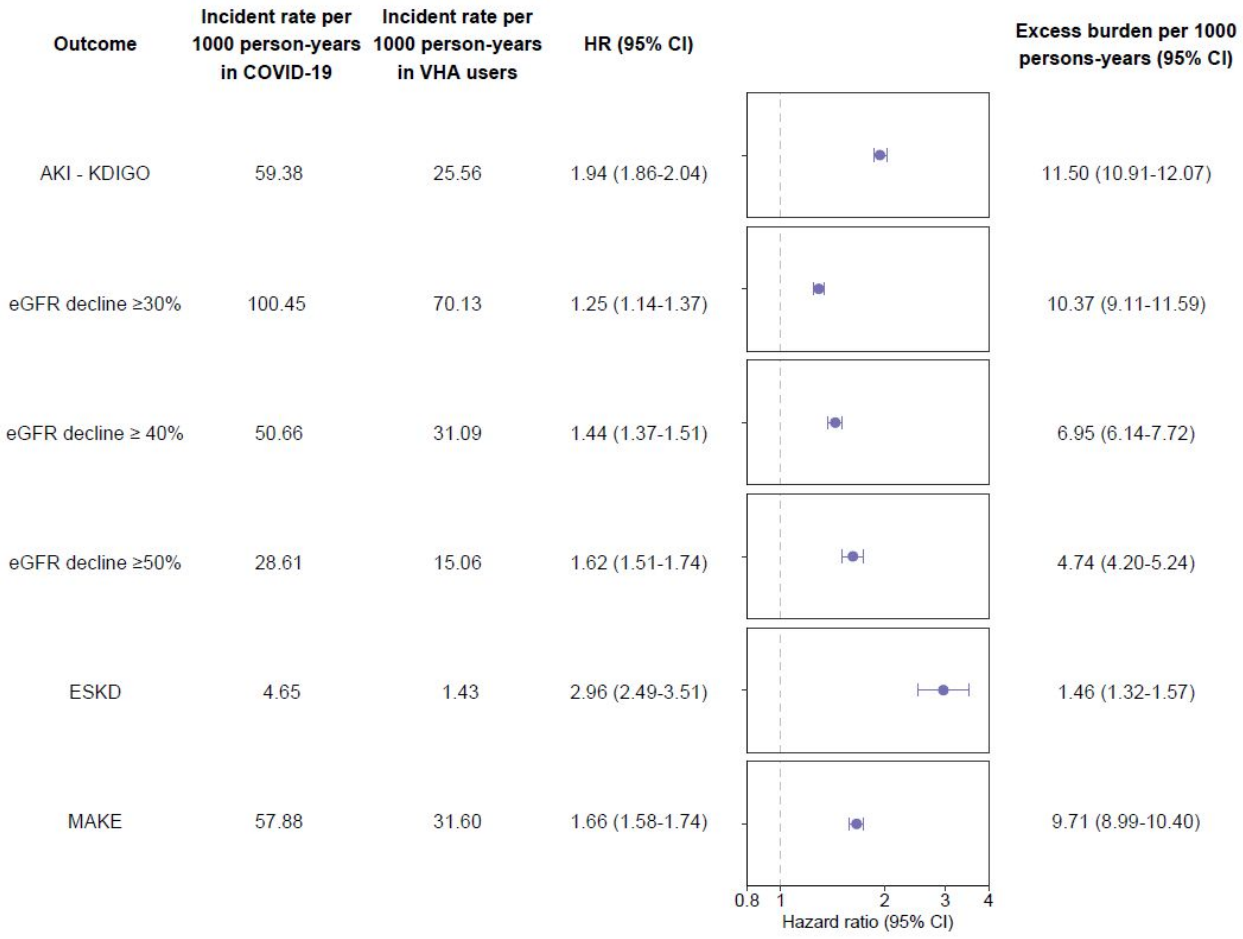
Characteristics	Overall	COVID-19	VHA Users
No. (%)	1726683	89216 (5.2%)	1637467 (94.8%)
Median follow-up (IQR)	172 (133-281)	164 (127-268)	172 (133-282)
Age, median (IQR), yr	68.5 (56.8-74.3)	65.5 (53.7-73.3)	68.7 (57.0-74.3)
Race, no. (%)			
White	1267091 (73.4)	60508 (67.8)	1206583 (73.7)
Black	329937 (19.1)	21934 (24.6)	308003 (18.8)
Other	129655 (7.5)	6774 (7.6)	122881 (7.5)
Sex, no. (%), men	1575385 (91.2)	80399 (90.1)	1494986 (91.3)
ADI[a], median (IQR)	55.0 (44.2-64.1)	54.6 (44.5-63.2)	55.0 (44.2-64.1)
Smoking status, no. (%)			
Never smoked	915783 (53.0)	51356 (57.6)	864427 (52.8)
Former smoker	413037 (23.9)	22607 (25.3)	390430 (23.8)
Current smoker	397863 (23.0)	15253 (17.1)	382610 (23.4)
Long-term care	15961 (0.9)	2982 (3.3)	12979 (0.8)
Clinical Characteristics			
eGFR (n=1672359)			
Median (IQR), ml/min/1.73m^2	76.9 (61.8-90.2)	77.9 (62.5-91.7)	76.9 (61.7-90.2)
>90, no. (%)	425597 (25.5)	24394 (27.9)	401203 (25.3)
60 to 90, no. (%)	870283 (52.0)	44182 (50.5)	826101 (52.1)
45 to 60, no. (%)	232074 (14.6)	12147 (13.9)	232074 (14.6)
30 to 45, no. (%)	101026 (6.0)	5332 (6.1)	95694 (6.0)
<30, no. (%)	31232 (1.9)	1513 (1.7)	29719 (1.9)
Serum creatinine, mean (%) (mg/dL) (n=1672359)	1.11 (0.4)	1.11 (0.3)	1.11 (0.4)
BMI category, no. (%) (n=1719839)			
Underweight/Normal	302216 (17.6)	11485 (12.9)	290731 (17.8)
Overweight	598159 (34.8)	27470 (30.9)	570689 (40.0)
Obese	819464 (47.7)	50027 (56.2)	769437 (47.2)
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.2 (13.2)	133.3 (12.5)	133.2 (13.2)
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	77.3 (7.9)	78.0 (7.7)	77.3 (8.0)
Number of eGFR measurements in the 2-years prior, median (IQR)	2 (1-3)	2 (1-4)	2 (1-3)
Cancer	164810 (9.5)	9487 (10.6)	155323 (9.5)
Cardiovascular disease	310297 (18.0)	18154 (20.4)	292143 (17.8)

Cerebrovascular disease	101276 (5.9)	6397 (7.2)	94879 (5.8)
Chronic lung disease	261646 (15.2)	15530 (17.4)	246116 (15.0)
Dementia	38853 (2.3)	3366 (3.8)	35487 (2.2)
Diabetes mellitus type 2	581080 (33.7)	35120 (39.4)	545960 (33.3)
HIV	11928 (0.7)	871 (1.0)	11057 (0.7)
Peripheral artery disease	25358 (1.5)	1654 (1.9)	23704 (1.5)
Medications			
ACE/ARB	682651 (39.5)	38337 (43.0)	644314 (39.4)
Antibiotics	109706 (6.4)	8169 (9.2)	101537 (6.2)
Antivirals	51059 (3.0)	3629 (4.1)	47430 (2.9)
Aspirin	257708 (14.9)	16475 (18.5)	241233 (14.7)
Beta-blockers	519867 (30.1)	29506 (33.1)	490361 (30.0)
Chemotherapeutic agents	19144 (1.1)	1151 (1.3)	17993 (1.1)
Diuretics	244845 (14.2)	14364 (16.1)	230481 (14.1)
Immunosuppressants	21488 (1.2)	1322 (1.5)	20166 (1.2)
NSAIDs	546424 (31.7)	35616 (39.9)	510808 (31.2)
PPI	495026 (28.7)	30583 (34.3)	46443 (28.4)

[a]ADI is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.
IQR, interquartile range; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Figure Legends

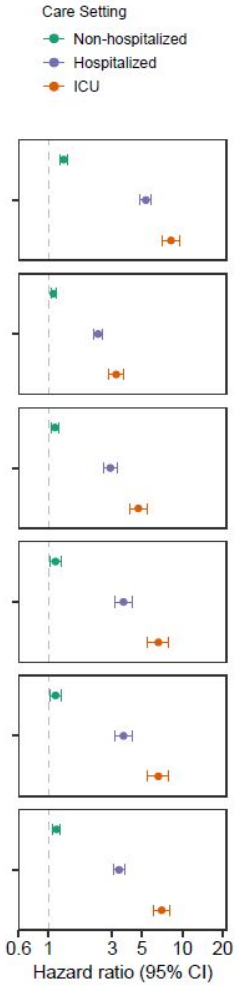
Figure 1: Risk and excess burden of post-acute COVID-19 kidney outcomes at 6 months.



COVID-19 participants were compared to users of the Veteran Health Administration healthcare system with no record of a positive COVID-19 test (control group). Outcomes were ascertained starting from 30 days after the participants COVID-19 positive test through end of follow-up. Unadjusted incident rates in the COVID-19 and VHA users per 1000 person-years, hazard ratios, and excess burden per 1000 persons at 6 months are provided. Hazard ratios and corresponding 95% confidence intervals are plotted. Major adverse kidney events (MAKE) was defined as a composite of eGFR decline ≥50%, end-stage kidney disease, or all-cause mortality. All models were adjusted for a set of 29 predefined variables and 100 variables selected by a high dimensional variable selection algorithm.

Figure 2: Risk and excess burden of post-acute COVID-19 kidney outcomes at 6 months in mutually exclusive cohorts of Veterans with non-hospitalized COVID-19, hospitalized COVID-19, and those admitted to intensive care with COVID-19 during the first 30 days (acute phase) of the infection.

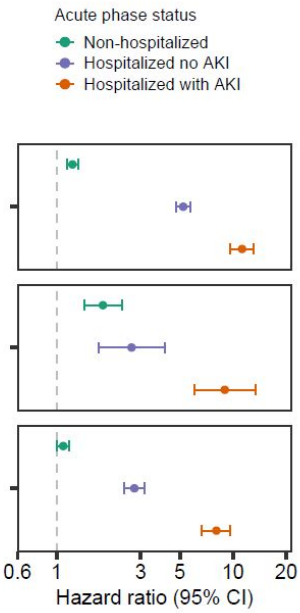
Outcome	Care Setting	Incident rate per 1000 person-years	HR (95% CI)	Excess burden per 1000 persons-years (95% CI)
AKI	Non-hospitalized	29.46	1.30 (1.21-1.39)	3.17 (2.39-3.90)
	Hospitalized	185.10	5.35 (4.85-5.90)	45.21 (44.43-45.94)
	ICU	244.54	8.24 (7.13-9.52)	74.19 (73.41-74.92)
eGFR decline ≥30%	Non-hospitalized	72.60	1.09 (1.04-1.14)	3.01 (1.48-4.47)
	Hospitalized	220.45	2.35 (2.16-2.55)	44.71 (43.18-46.18)
	ICU	275.78	3.21 (2.82-3.66)	72.23 (70.70-73.70)
eGFR decline ≥40%	Non-hospitalized	32.22	1.12 (1.05-1.20)	1.81 (0.78-2.78)
	Hospitalized	122.26	2.90 (2.59-3.24)	27.72 (26.69-28.69)
	ICU	184.30	4.70 (4.02-5.47)	53.23 (52.20-54.20)
eGFR decline ≥50%	Non-hospitalized	15.81	1.13 (1.02-1.24)	0.90 (0.17-1.56)
	Hospitalized	73.16	3.64 (3.14-4.21)	18.44 (17.72-19.10)
	ICU	124.95	6.63 (5.52-7.97)	39.02 (38.29-39.68)
ESKD	Non-hospitalized	2.52	2.15 (1.67-2.77)	0.78 (0.58-0.93)
	Hospitalized	12.44	5.72 (3.98-8.23)	3.20 (3.01-3.35)
	ICU	20.97	13.26 (8.28-21.23)	8.29 (8.09-8.44)
MAKE	Non-hospitalized	30.63	1.15 (1.07-1.23)	2.01 (1.03-2.93)
	Hospitalized	157.61	3.37 (3.04-3.73)	31.92 (30.94-32.84)
	ICU	267.75	7.02 (6.15-8.00)	79.13 (78.15-80.05)



COVID-19 participants were compared to users of the Veteran Health Administration healthcare system with no record of a positive COVID-19 test (control group). Outcomes were ascertained starting from 30 days after the participants COVID-19 positive test through end of follow-up. Unadjusted incident rates per 1000 person-years, hazard ratios, and excess burden per 1000 persons at 6 months are provided for each COVID-19 group (non-hospitalized, hospitalized, and those admitted to intensive care during the acute phase of the infection). Hazard ratios and corresponding 95% confidence intervals are plotted. Major adverse kidney events (MAKE) was defined as a composite of eGFR decline ≥50%, end-stage kidney disease, or all-cause mortality. All models were adjusted for a set of 29 predefined variables and 100 variables selected by a high dimensional variable selection algorithm.

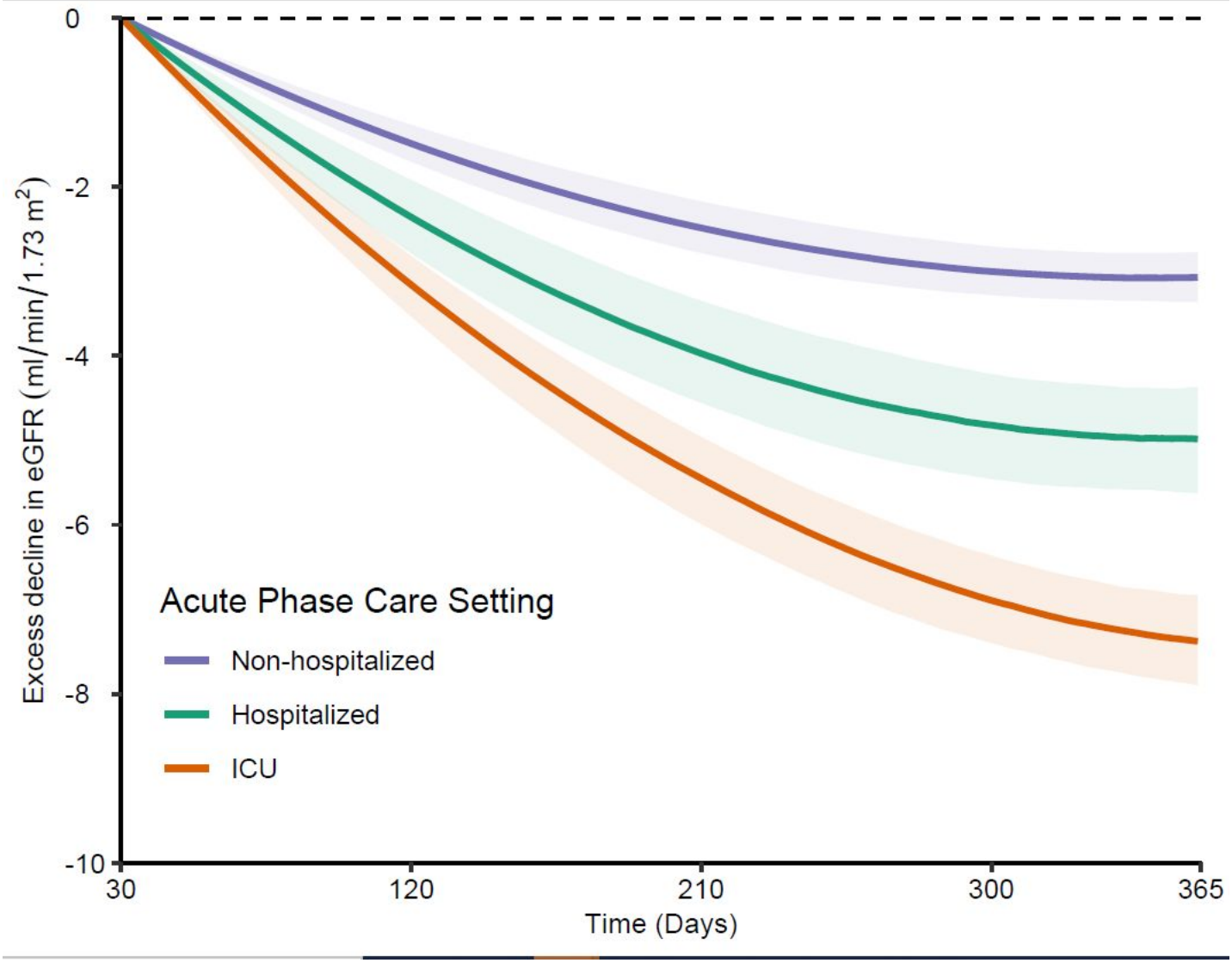
Figure 3: Risk and excess burden of post-acute COVID-19 kidney outcomes at 6 months in mutually exclusive cohorts of Veterans with non-hospitalized COVID-19, hospitalized COVID-19 with no evidence of an AKI, and those hospitalized with COVID-19 with an AKI during the first 30 days (acute phase) of the infection.

Outcome	Acute phase status	Incident rate	HR (95% CI)	Excess burden per 1000 persons-years (95% CI)
AKI	Non-hospitalized	32.35	1.23 (1.14, 1.32)	3.23 (2.03, 4.51)
	Hospitalized no AKI	213.56	5.22 (4.73, 5.75)	57.9 (51.45, 64.95)
	Hospitalized with AKI	462.41	11.26 (9.67, 13.12)	135.06 (115.35, 157.47)
ESKD	Non-hospitalized	2.52	1.83 (1.43, 2.34)	0.67 (0.35, 1.08)
	Hospitalized no AKI	5.68	2.66 (1.72, 4.12)	1.33 (0.58, 2.51)
	Hospitalized with AKI	49.99	8.98 (6.03, 13.37)	6.39 (4.03, 9.89)
MAKE	Non-hospitalized	25.47	1.09 (1.01, 1.18)	1.12 (0.08, 2.24)
	Hospitalized no AKI	118.68	2.76 (2.43, 3.13)	21.35 (17.37, 25.86)
	Hospitalized with AKI	289.00	8.05 (6.68, 9.69)	82.84 (67.37, 101.12)



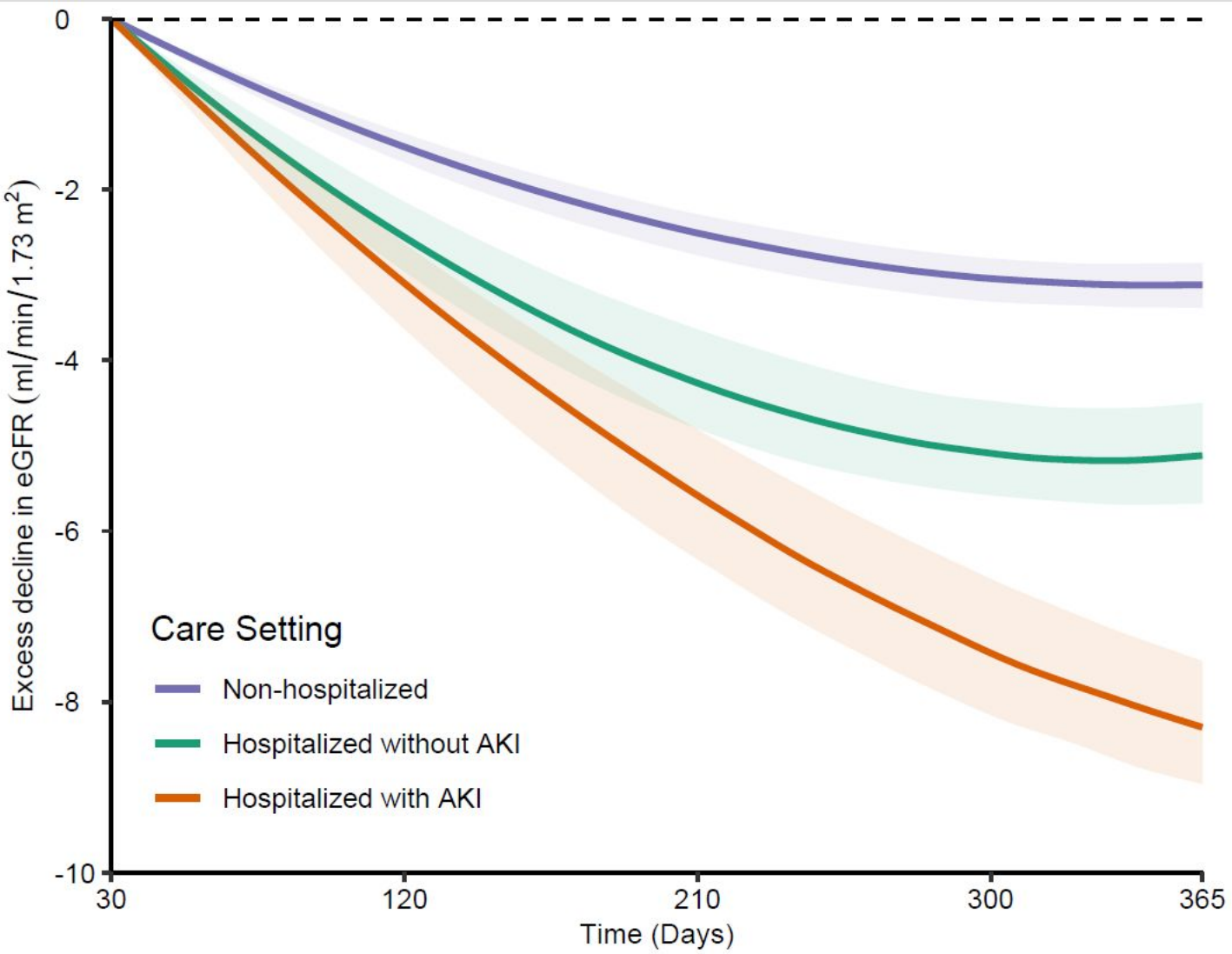
COVID-19 participants were compared to users of the Veteran Health Administration healthcare system with no record of a positive COVID-19 test (control group). Outcomes were ascertained starting from 30 days after the participants COVID-19 positive test through end of follow-up. Unadjusted incident rates per 1000 person-years, hazard ratios, and excess burden per 1000 persons at 6 months are provided for each COVID-19 group (non-hospitalized, hospitalized without an AKI, and hospitalized with an AKI during the acute phase of the infection). Hazard ratios and corresponding 95% confidence intervals are plotted. Major adverse kidney events (MAKE) was defined as a composite of eGFR decline ≥50%, end-stage kidney disease, or all-cause mortality. All models were adjusted for a set of 29 predefined variables and 100 variables selected by a high dimensional variable selection algorithm.

Figure 4: Excess decline in eGFR in post-acute COVID-19.



Differences in the trajectory of eGFR by day of follow-up compared to users of the Veteran Health Administration healthcare system with no record of a positive COVID-19 test (control group), estimated after adjustment for baseline characteristics. Changes are estimated starting from 30 days after a COVID-19 positive test. Bands represent the 95%CI.

Figure 5: Excess decline in eGFR in post-acute COVID-19 by AKI status during the acute phase of the illness.



Differences in the trajectory of eGFR by day of follow-up compared to users of the Veteran Health Administration healthcare system with no record of a positive COVID-19 test (control group), estimated after adjustment for baseline characteristics. Changes are estimated starting from 30 days after a COVID-19 positive test. Bands represent the 95% CI.

Supplemental Table of Contents:

Supplemental Table 15: Characteristics and standardized mean differences of predefined covariates in COVID-19 non-hospitalized and COVID-19 hospitalized with no AKI groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Supplemental Table 16: Characteristics and standardized mean differences of predefined covariates in COVID-19 non-hospitalized and COVID-19 hospitalized with an AKI groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Supplemental Table 17: Characteristics and standardized mean differences of predefined covariates in COVID-19 hospitalized with no AKI and COVID-19 hospitalized with an AKI groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Supplemental Table 18: Pairwise comparisons of risk and excess burden of adverse risks by AKI status during the acute COVID-19 infection.

Supplemental Table 19a: Pairwise comparisons of risk and excess burden of adverse kidney outcomes to VHA users risks by AKI status during the acute COVID-19 infection adjusting only for predefined covariates.

Supplemental Table 19b: Pairwise comparisons of risk and excess burden of adverse kidney outcomes to VHA users by AKI status during the acute COVID-19 infection adjusting only for predefined covariates.

Supplemental Table 20: Outcome controls for the comparison of COVID-19 positive Veterans vs. VHA users.

Supplemental Figure 1: Cohort flow chart

Supplemental Figure 2: Covariate balance in the comparison of COVID-19 positive Veterans with VHA users.

Supplemental Figure 3: Covariate balance in the comparison of COVID-19 positive Veterans by severity of the acute infection with non-hospitalized VHA users.

Supplemental Figure 4: Covariate balance in the comparison of COVID-19 positive Veterans by severity AKI status during the acute phase of the illness.

Supplemental Figure 5: Excess decline in eGFR in post-acute COVID-19 adjusting for predefined covariates.

Supplemental Figure 6: Excess decline in eGFR in post-acute COVID-19 by AKI status during the acute phase of the illness adjusting for only predefined covariates.

Supplemental material

Kidney Outcomes in Long COVID

Benjamin Bowe, Yan Xie, Evan Xu, and Ziyad Al-Aly

Supplemental Material Table of Contents

Supplemental Table 16: Characteristics and standardized mean differences of predefined covariates in COVID-19 non-hospitalized and COVID-19 hospitalized with an AKI groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.
Supplemental Table 17: Characteristics and standardized mean differences of predefined covariates in COVID-19 hospitalized with no AKI and COVID-19 hospitalized with an AKI groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.
Supplemental Table 18: Pairwise comparisons of risk and excess burden of adverse risks by AKI status during the acute COVID-19 infection.
Supplemental Table 19a: Pairwise comparisons of risk and excess burden of adverse kidney outcomes to VHA users risks by AKI status during the acute COVID-19 infection adjusting only for predefined covariates.
Supplemental Table 19b: Pairwise comparisons of risk and excess burden of adverse kidney outcomes to VHA users by AKI status during the acute COVID-19 infection adjusting only for predefined covariates.
Supplemental Table 20: Outcome controls for the comparison of COVID-19 positive Veterans vs. VHA users.
Supplemental Figure 1: Cohort flow chart
Supplemental Figure 2: Covariate balance in the comparison of COVID-19 positive Veterans with VHA users.
Supplemental Figure 3: Covariate balance in the comparison of COVID-19 positive Veterans by severity of the acute infection with non-hospitalized VHA users.
Supplemental Figure 4: Covariate balance in the comparison of COVID-19 positive Veterans by severity AKI status during the acute phase of the illness.
Supplemental Figure 5: Excess decline in eGFR in post-acute COVID-19 adjusting for predefined covariates.
Supplemental Figure 6: Excess decline in eGFR in post-acute COVID-19 by AKI status during the acute phase of the illness adjusting for only predefined covariates.

Supplemental Table 1: Median time to outcomes (days) in the VHA user group, those with COVID-19, and those with COVID-19 that were non-hospitalized, hospitalized, and admitted to the ICU.

Outcome	VHA Users	COVID-19	COVID-19 non-Hospitalized	COVID-19 Hospitalized	COVID-19 ICU
Median time to outcome (IQR) (days)					
AKI	106 (67-166)	84 (45-1467)	107 (65-174)	75 (41-136)	48 (32-110)
eGFR decline 30	106 (67-167)	98 (55-158)	107 (67-169)	85 (44-146)	68 (35-127)
eGFR decline 40	109 (69-172)	95 (52-160)	109 (69-175)	85 (43-144)	59 (35-123)
eGFR decline 50	112 (70-176)	92 (46-161)	114 (70-182)	81 (40-144)	56 (35-122)
ESKD	112 (73-176)	92 (57-146)	108 (77-160)	88 (60-151)	54 (36-110)
MAKE	134 (86-208)	99 (56-164)	119 (78-192)	94 (54-155)	62 (37-117)

AKI, acute kidney injury; ESKD, end-stage kidney disease; MAKE, major adverse kidney events; IQR, inter-quartile range.
Time to outcomes were assessed as days from T_0.

Supplemental Table 2: Characteristics and standardized mean differences of predefined covariates between COVID-19 and VHA user groups before and after weighting.

Characteristics	Before Weighting			After Weighting		
	COVID-19	VHA Users	Standardized Mean Difference	COVID-19	VHA Users	Standardized Mean Difference
Age, mean (std), yr	65.5 (14.3)	68.7 (14.3)	0.152	66.0 (12.6)	66.1 (13.2)	0.008
Race, no. (%)						
White	60508 (67.8)	1206583 (73.7)	0.129	47542 (71.6)	891316 (72.1)	0.012
Black	21934 (24.6)	308003 (18.8)	0.141	13830 (20.8)	251888 (20.4)	0.011
Other	6774 (7.6)	122881 (7.5)	0.003	5055 (7.6)	93361 (7.6)	0.002
Sex, no. (%), men	80399 (90.1)	1494986 (91.3)	0.041	60675 (91.3)	1133559 (91.7)	0.012
ADI, mean (std)	54.6 (15.1)	55.0 (15.6)	0.006	53.7 (14.8)	53.7 (15.7)	<0.001
Smoking status, no. (%)						
Never smoked	51356 (57.6)	864427 (52.8)	0.096	34190 (51.5)	637944 (51.6)	0.002
Former smoker	22607 (25.3)	390430 (23.8)	0.035	16527 (24.9)	306545 (24.8)	0.002
Current smoker	15253 (17.1)	382610 (23.4)	0.157	15710 (23.7)	292077 (23.6)	0.001
Long-term care	2982 (3.3)	12979 (0.8)	0.180	757 (1.1)	12118 (1.0)	0.016
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	77.9 (21.5)	76.9 (21.1)	0.046	74.9 (20.1)	74.9 (21.1)	<0.001
BMI (std) (n=1719839)	32.4 (6.4)	31.3 (6.1)	0.006	31.3 (5.8)	31.8 (6.2)	0.003
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.3 (12.5)	133.2 (13.2)	0.008	134.0 (12.3)	134.1 (13.1)	0.006
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	78.0 (7.7)	77.3 (8.0)	0.096	77.5 (7.5)	77.5 (7.9)	0.002
Number of eGFR measurements in the 2-years prior, mean (std)	2.0 (6.1)	2.0 (4.1)	0.208	3.0 (4.6)	3.0 (4.6)	0.029
Cancer	9487 (10.6)	155323 (9.5)	0.038	7287 (11.0)	130705 (10.6)	0.013
Cardiovascular disease	18154 (20.4)	292143 (17.8)	0.064	14408 (21.7)	262275 (21.2)	0.012
Cerebrovascular disease	6397 (7.2)	94879 (5.8)	0.056	4690 (7.1)	84705 (6.9)	0.008
Chronic lung disease	15530 (17.4)	246116 (15.0)	0.065	11791 (17.8)	210711 (17.0)	0.019
Dementia	3366 (3.8)	35487 (2.2)	0.094	1641 (2.5)	29307 (2.4)	0.007

Diabetes mellitus type 2	35120 (39.4)	545960 (33.3)	0.126	25933 (39.0)	479787 (38.8)	0.005
HIV	871 (1.0)	11057 (0.7)	0.033	518 (0.8)	9398 (0.8)	0.002
Peripheral artery disease	1654 (1.9)	23704 (1.5)	0.031	1242 (1.9)	22135 (1.8)	0.006
Medications						
ACE/ARB	38337 (43.0)	644314 (39.4)	0.074	34609 (52.1)	647466 (52.4)	0.005
Antibiotics	8169 (9.2)	101537 (92.6)	0.111	5879 (8.9)	104119 (8.4)	0.015
Antivirals	3629 (4.1)	47430 (2.9)	0.064	2690 (4.1)	48473 (3.9)	0.007
Aspirin	16475 (18.5)	241233 (14.7)	0.101	13418 (20.2)	244593 (19.8)	0.011
Beta-blockers	29506 (33.1)	490361 (30.0)	0.067	26803 (40.4)	493142 (39.9)	0.010
Chemotherapeutic agents	1151 (1.3)	17993 (1.1)	0.017	1016 (1.5)	18178 (1.5)	0.005
Diuretics	14364 (16.1)	230481 (14.1)	0.056	12535 (18.9)	232227 (18.8)	0.002
Immunosuppressants	1322 (1.5)	20166 (1.2)	0.022	1149 (1.7)	20403 (1.7)	0.006
NSAIDs	35616 (39.9)	510808 (31.2)	0.183	28252 (42.5)	518368 (41.9)	0.012
PPI	30583 (34.3)	46443 (28.4)	0.128	25668 (38.6)	469647 (38.0)	0.014

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 3: Risk and excess burden of post-acute COVID-19 adverse kidney events in models adjusted for only predefined covariates.

Outcome	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)
AKI	1.80 (1.71-1.89)	37.52 (37.12-37.89)
eGFR decline ≥ 30%	1.27 (1.23-1.32)	31.54 (30.45-32.60)
eGFR decline ≥ 40%	1.40 (1.33-1.47)	21.17 (20.54-21.78)
eGFR decline ≥ 50%	1.54 (1.44-1.65)	14.41 (14.03-14.77)
ESKD	2.52 (2.14-2.98)	5.30 (5.23-5.35)
MAKE	1.54 (1.47-1.62)	28.21 (27.68-28.72)

Adjusted for age, Area Deprivation Index, race, sex, smoking status, baseline eGFR, systolic and diastolic blood pressure, body mass index, and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, peripheral artery disease, angiotensin converting enzyme inhibitors /angiotensin II receptor blockers, antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, residence at a long-term care facility, and the number of eGFR measurements in the year prior to T_0.

[a]Burden estimated at 6 months following a COVID-19 positive test.

AKI, acute kidney injury; ESKD, end-stage kidney disease; MAKE, major adverse kidney outcomes; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval

Supplemental Table 4: Characteristics and standardized mean differences of predefined covariates by COVID-19 non-hospitalized and VHA user groups before and after weighting.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Positive	VHA Users	Standardized Mean Difference	COVID-19 Positive	VHA Users	Standardized Mean Difference
Age, mean (std), yr	61.8 (14.4)	68.7 (14.3)	0.242	66.1 (12.7)	66.1 (13.2)	0.002
Race, no. (%)						
White	50235 (69.1)	1206583 (73.7)	0.102	39079 (71.7)	891436 (72.1)	0.008
Black	17021 (23.4)	308003 (18.8)	0.113	11289 (20.7)	252276 (20.4)	0.008
Other	5438 (7.5)	122881 (7.5)	0.001	4131 (7.6)	93457 (7.6)	0.001
Sex, no. (%), men	64816 (89.2)	1494986 (91.3)	0.072	49834 (91.4)	1134069 (91.7)	0.009
ADI, mean (std)	53.5 (15.2)	55.0 (15.6)	0.008	53.8 (14.9)	53.7 (15.7)	0.001
Smoking status, no. (%)						
Never smoked	42506 (58.5)	864427 (52.8)	0.115	27987 (51.4)	638325 (51.6)	0.005
Former smoker	18011 (24.8)	390430 (23.8)	0.022	13577 (24.9)	306751 (24.8)	0.003
Current smoker	12177 (16.8)	382610 (23.4)	0.166	12935 (23.7)	292092 (23.6)	0.003
Long-term care	1419 (2.0)	12979 (0.8)	0.100	649 (1.2)	12267 (1.0)	0.019
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	78.5 (21.1)	76.9 (21.1)	0.110	74.8 (20.2)	74.9 (21.1)	0.004
BMI (std) (n=1719839)	32.4 (6.2)	31.3 (6.1)	0.006	31.5 (5.8)	31.8 (6.2)	0.002
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.1 (12.4)	133.2 (13.2)	0.008	134 (12.4)	134.1 (13.1)	0.007
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	78.3 (7.7)	77.3 (8.0)	0.135	77.4 (7.5)	77.5 (7.9)	0.006
Number of eGFR measurements in the 2-years prior, mean (std)	3.0 (4.4)	2 (4.1)	0.085	3.2 (4.6)	3.0 (4.6)	0.032
Cancer	6838 (9.4)	155323 (9.5)	0.003	5972 (11.0)	130787 (10.6)	0.013
Cardiovascular disease	12879 (17.7)	292143 (17.8)	0.003	11794 (21.6)	262601 (21.2)	0.010
Cerebrovascular disease	4272 (5.9)	94879 (5.8)	0.004	3856 (7.1)	84812 (6.9)	0.008

Chronic lung disease	11218 (15.4)	246116 (15.0)	0.011	9671 (17.7)	210951 (17.1)	0.018
Dementia	1929 (2.7)	35487 (2.2)	0.031	1389 (2.6)	29385 (2.4)	0.011
Diabetes mellitus type 2	27030 (37.2)	545960 (33.3)	0.080	21273 (39.0)	480172 (38.8)	0.004
HIV	669 (0.9)	11057 (0.7)	0.027	419 (0.8)	9378 (0.8)	0.001
Peripheral artery disease	1065 (1.5)	23704 (1.5)	0.002	1036 (1.9)	22168 (1.8)	0.008
Medications						
ACE/ARB	30364 (41.8)	644314 (39.4)	0.049	28411 (52.1)	647771 (52.4)	0.005
Antibiotics	6008 (8.3)	101537 (92.6)	0.080	4755 (8.7)	104308 (8.4)	0.011
Antivirals	3015 (4.2)	47430 (2.9)	0.068	2179 (4.0)	48517 (3.9)	0.004
Aspirin	12083 (16.6)	241233 (14.7)	0.052	11008 (20.2)	244861 (19.8)	0.010
Beta-blockers	22427 (30.9)	490361 (30.0)	0.020	22005 (40.4)	493494 (39.9)	0.010
Chemotherapeutic agents	889 (1.2)	17993 (1.1)	0.011	835 (1.5)	18237 (1.5)	0.005
Diuretics	11196 (15.4)	230481 (14.1)	0.037	10249 (18.8)	232452 (18.8)	0.001
Immunosuppressants	1059 (1.5)	20166 (1.2)	0.020	941 (1.7)	20434 (1.7)	0.006
NSAIDs	29329 (40.4)	510808 (31.2)	0.192	23082 (42.4)	518859 (42.0)	0.008
PPI	24341 (33.5)	46443 (28.4)	0.111	21016 (38.6)	470163 (38.0)	0.011

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 5: Characteristics and standardized mean differences of predefined covariates by COVID-19 hospitalized and VHA user groups before and after weighting.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Hospitalized	VHA Users	Standardized Mean Difference	COVID-19 Hospitalized	VHA Users	Standardized Mean Difference
Age, mean (std), yr	68.7 (12.8)	68.7 (14.3)	0.255	66.7 (6.8)	66.1 (13.2)	0.045
Race, no. (%)						
White	7715 (62.3)	1206583 (73.7)	0.245	1999 (69.4)	891436 (72.1)	0.058
Black	3666 (29.6)	308003 (18.8)	0.254	648 (22.5)	252276 (20.4)	0.051
Other	995 (8)	122881 (7.5)	0.020	232 (8.1)	93457 (7.6)	0.018
Sex, no. (%), men	11656 (94.2)	1494986 (91.3)	0.111	2638 (91.7)	1134069 (91.7)	0.001
ADI, mean (std)	52.1 (15)	55.0 (15.6)	0.086	53.5 (8.1)	53.7 (15.7)	0.016
Smoking status, no. (%)						
Never smoked	6607 (53.4)	864427 (52.8)	0.012	1511 (52.5)	638325 (51.6)	0.017
Former smoker	3438 (27.8)	390430 (23.8)	0.090	718 (25.0)	306751 (24.8)	0.004
Current smoker	2331 (18.8)	382610 (23.4)	0.111	649 (22.6)	292092 (23.6)	0.025
Long-term care	1214 (9.8)	12979 (0.8)	0.411	42 (1.5)	12267 (1.0)	0.044
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	71.3 (22.8)	76.9 (21.1)	0.221	74.2 (11.2)	74.9 (21.1)	0.033
BMI (std) (n=1719839)	32.7 (6.8)	31.3 (6.1)	0.008	31.3 (3.5)	31.8 (6.2)	0.003
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	134.3 (12.5)	133.2 (13.2)	0.089	134.6 (6.7)	134.1 (13.1)	0.041
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	76.8 (7.7)	77.3 (8.0)	0.065	77.5 (4.1)	77.5 (7.9)	0.004
Number of eGFR measurements in the 2-years prior, mean (std)	6.9 (10.2)	2.0 (4.1)	0.536	3.4 (2.8)	3.0 (4.6)	0.068
Cancer	2007 (16.2)	155323 (9.5)	0.202	339 (11.8)	130787 (10.6)	0.038
Cardiovascular disease	3867 (31.3)	292143 (17.8)	0.315	676 (23.5)	262601 (21.2)	0.054
Cerebrovascular disease	1646 (13.3)	94879 (5.8)	0.258	225 (7.8)	84812 (6.9)	0.036

Chronic lung disease	3138 (25.4)	246116 (15.0)	0.259	552 (19.2)	210951 (17.1)	0.055
Dementia	1155 (9.3)	35487 (2.2)	0.311	85 (3.0)	29385 (2.4)	0.036
Diabetes mellitus type 2	5973 (48.3)	545960 (33.3)	0.307	1186 (41.2)	480172 (38.8)	0.049
HIV	162 (1.3)	11057 (0.7)	0.064	26 (0.9)	9378 (0.8)	0.016
Peripheral artery disease	445 (3.6)	23704 (1.5)	0.137	60 (2.1)	22168 (1.8)	0.022
Medications						
ACE/ARB	5880 (47.5)	644314 (39.4)	0.165	1524 (53)	647771 (52.4)	0.012
Antibiotics	1655 (13.4)	101537 (92.6)	0.243	282 (9.8)	104308 (8.4)	0.047
Antivirals	485 (3.9)	47430 (2.9)	0.056	116 (4.0)	48517 (3.9)	0.005
Aspirin	3337 (27.0)	241233 (14.7)	0.305	628 (21.8)	244861 (19.8)	0.050
Beta-blockers	5252 (42.4)	490361 (30.0)	0.262	1213 (42.2)	493494 (39.9)	0.046
Chemotherapeutic agents	197 (1.6)	17993 (1.1)	0.043	46 (1.6)	18237 (1.5)	0.011
Diuretics	2282 (18.4)	230481 (14.1)	0.118	573 (19.9)	232452 (18.8)	0.028
Immunosuppressants	200 (1.6)	20166 (1.2)	0.033	50 (1.8)	20434 (1.7)	0.008
NSAIDs	4785 (38.7)	510808 (31.2)	0.157	1249 (43.4)	518859 (42.0)	0.029
PPI	4685 (37.9)	46443 (28.4)	0.203	1147 (39.8)	470163 (38.0)	0.037

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 6: Characteristics and standardized mean differences of predefined covariates by COVID-19 admitted to ICU and VHA user groups before and after weighting.

Characteristics	Before Weighting			After Weighting		
	COVID-19 ICU	VHA Users	Standardized Mean Difference	COVID-19 ICU	VHA Users	Standardized Mean Difference
Age, mean (std), yr	68.9 (11.6)	68.7 (14.3)	0.277	67.1 (20.1)	66.1 (13.2)	0.071
Race, no. (%)						
White	2558 (61.7)	1206583 (73.7)	0.259	6126 (71.4)	891436 (72.1)	0.016
Black	1247 (30.1)	308003 (18.8)	0.265	1775 (20.7)	252276 (20.4)	0.007
Other	341 (8.2)	122881 (7.5)	0.027	682 (8.0)	93457 (7.6)	0.015
Sex, no. (%), men	3927 (94.7)	1494986 (91.3)	0.134	7941 (92.5)	1134069 (91.7)	0.031
ADI, mean (std)	53.0 (14.8)	55.0 (15.6)	0.023	53.2 (23.9)	53.7 (15.7)	0.036
Smoking status, no. (%)						
Never smoked	2243 (54.1)	864427 (52.8)	0.026	4575 (53.3)	638325 (51.6)	0.034
Former smoker	1158 (27.9)	390430 (23.8)	0.093	2171 (25.3)	306751 (24.8)	0.012
Current smoker	745 (18)	382610 (23.4)	0.134	1837 (21.4)	292092 (23.6)	0.053
Long-term care	349 (8.4)	12979 (0.8)	0.370	150 (1.8)	12267 (1.0)	0.065
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	71.0 (22.1)	76.9 (21.1)	0.236	73.8 (33.4)	74.9 (21.1)	0.053
BMI (std) (n=1719839)	31.7 (6.8)	31.3 (6.1)	0.003	32.3 (10.3)	31.8 (6.2)	0.003
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.8 (12.9)	133.2 (13.2)	0.046	134.6 (20.3)	134.1 (13.1)	0.036
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	76.5 (7.8)	77.3 (8.0)	0.104	77.4 (12.3)	77.5 (7.9)	0.014
Number of eGFR measurements in the 2-years prior, mean (std)	7.2 (10.8)	2.0 (4.1)	0.558	3.5 (8.7)	3.0 (4.6)	0.082
Cancer	642 (15.5)	155323 (9.5)	0.182	1010 (11.8)	130787 (10.6)	0.038
Cardiovascular disease	1408 (34)	292143 (17.8)	0.374	2037 (23.7)	262601 (21.2)	0.060
Cerebrovascular disease	479 (11.6)	94879 (5.8)	0.206	675 (7.9)	84812 (6.9)	0.039

Chronic lung disease	1174 (28.3)	246116 (15.0)	0.327	1693 (19.7)	210951 (17.1)	0.069
Dementia	282 (6.8)	35487 (2.2)	0.225	256 (3.0)	29385 (2.4)	0.037
Diabetes mellitus type 2	2117 (51.1)	545960 (33.3)	0.365	3519 (41)	480172 (38.8)	0.045
HIV	40 (1.0)	11057 (0.7)	0.031	58 (0.7)	9378 (0.8)	0.011
Peripheral artery disease	144 (3.5)	23704 (1.5)	0.131	150 (1.7)	22168 (1.8)	0.004
Medications						
ACE/ARB	2093 (50.5)	644314 (39.4)	0.225	4684 (54.6)	647771 (52.4)	0.044
Antibiotics	506 (12.2)	101537 (92.6)	0.209	875 (10.2)	104308 (8.4)	0.061
Antivirals	129 (3.1)	47430 (2.9)	0.012	362 (4.2)	48517 (3.9)	0.015
Aspirin	1055 (25.5)	241233 (14.7)	0.270	1860 (21.7)	244861 (19.8)	0.046
Beta-blockers	1827 (44.1)	490361 (30.0)	0.296	3658 (42.6)	493494 (39.9)	0.055
Chemotherapeutic agents	65 (1.6)	17993 (1.1)	0.041	134 (1.6)	18237 (1.5)	0.007
Diuretics	886 (21.4)	230481 (14.1)	0.192	1705 (19.9)	232452 (18.8)	0.027
Immunosuppressants	63 (1.5)	20166 (1.2)	0.025	125 (1.5)	20434 (1.7)	0.015
NSAIDs	1502 (36.2)	510808 (31.2)	0.107	3609 (42.1)	518859 (42.0)	0.002
PPI	1557 (37.6)	46443 (28.4)	0.196	3399 (39.6)	470163 (38.0)	0.033

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 7: Characteristics and standardized mean differences of predefined covariates by COVID-19 non-hospitalized and COVID-19 hospitalized groups before and after weighting.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Positive	COVID-19 Hospitalized	Standardized Mean Difference	COVID-19 Positive	COVID-19 Hospitalized	Standardized Mean Difference
Age, mean (std), yr	61.8 (14.4)	68.7 (12.8)	0.508	66.1 (12.7)	66.7 (6.8)	0.047
Race, no. (%)						
White	50235 (69.1)	7715 (62.3)	0.143	39079 (71.7)	1999 (69.4)	0.050
Black	17021 (23.4)	3666 (29.6)	0.141	11289 (20.7)	648 (22.5)	0.044
Other	5438 (7.5)	995 (8)	0.021	4131 (7.6)	232 (8.1)	0.018
Sex, no. (%), men	64816 (89.2)	11656 (94.2)	0.182	49834 (91.4)	2638 (91.7)	0.008
ADI, mean (std)	53.5 (15.2)	52.1 (15)	0.096	53.8 (14.9)	53.5 (8.1)	0.017
Smoking status, no. (%)						
Never smoked	42506 (58.5)	6607 (53.4)	0.102	27987 (51.4)	1511 (52.5)	0.023
Former smoker	18011 (24.8)	3438 (27.8)	0.068	13577 (24.9)	718 (25.0)	0.001
Current smoker	12177 (16.8)	2331 (18.8)	0.054	12935 (23.7)	649 (22.6)	0.028
Long-term care	1419 (2.0)	1214 (9.8)	0.339	649 (1.2)	42 (1.5)	0.025
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	78.5 (21.1)	71.3 (22.8)	0.327	74.8 (20.2)	74.2 (11.2)	0.028
BMI (std) (n=1719839)	32.4 (6.2)	32.7 (6.8)	0.004	31.5 (5.8)	31.3 (3.5)	0.004
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.1 (12.4)	134.3 (12.5)	0.101	134 (12.4)	134.6 (6.7)	0.048
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	78.3 (7.7)	76.8 (7.7)	0.204	77.4 (7.5)	77.5 (4.1)	0.010
Number of eGFR measurements in the 2-years prior, mean (std)	3.0 (4.4)	6.9 (10.2)	0.485	3.2 (4.6)	3.4 (2.8)	0.036
Cancer	6838 (9.4)	2007 (16.2)	0.205	5972 (11.0)	339 (11.8)	0.025
Cardiovascular disease	12879 (17.7)	3867 (31.3)	0.319	11794 (21.6)	676 (23.5)	0.044
Cerebrovascular disease	4272 (5.9)	1646 (13.3)	0.254	3856 (7.1)	225 (7.8)	0.028

Chronic lung disease	11218 (15.4)	3138 (25.4)	0.248	9671 (17.7)	552 (19.2)	0.037
Dementia	1929 (2.7)	1155 (9.3)	0.284	1389 (2.6)	85 (3.0)	0.025
Diabetes mellitus type 2	27030 (37.2)	5973 (48.3)	0.225	21273 (39.0)	1186 (41.2)	0.044
HIV	669 (0.9)	162 (1.3)	0.037	419 (0.8)	26 (0.9)	0.015
Peripheral artery disease	1065 (1.5)	445 (3.6)	0.136	1036 (1.9)	60 (2.1)	0.014
Medications						
ACE/ARB	30364 (41.8)	5880 (47.5)	0.116	28411 (52.1)	1524 (53)	0.017
Antibiotics	6008 (8.3)	1655 (13.4)	0.165	4755 (8.7)	282 (9.8)	0.037
Antivirals	3015 (4.2)	485 (3.9)	0.012	2179 (4.0)	116 (4.0)	0.001
Aspirin	12083 (16.6)	3337 (27.0)	0.252	11008 (20.2)	628 (21.8)	0.040
Beta-blockers	22427 (30.9)	5252 (42.4)	0.242	22005 (40.4)	1213 (42.2)	0.036
Chemotherapeutic agents	889 (1.2)	197 (1.6)	0.031	835 (1.5)	46 (1.6)	0.006
Diuretics	11196 (15.4)	2282 (18.4)	0.081	10249 (18.8)	573 (19.9)	0.028
Immunosuppressants	1059 (1.5)	200 (1.6)	0.013	941 (1.7)	50 (1.8)	0.002
NSAIDs	29329 (40.4)	4785 (38.7)	0.035	23082 (42.4)	1249 (43.4)	0.021
PPI	24341 (33.5)	4685 (37.9)	0.092	21016 (38.6)	1147 (39.8)	0.026

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 8: Characteristics and standardized mean differences of predefined covariates by COVID-19 non-hospitalized and COVID-19 admitted to ICU groups before and after weighting.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Positive	COVID-19 ICU	Standardized Mean Difference	COVID-19 Positive	COVID-19 ICU	Standardized Mean Difference
Age, mean (std), yr	61.8 (14.4)	68.9 (11.6)	0.275	66.1 (12.7)	67.1 (20.1)	0.070
Race, no. (%)						
White	50235 (69.1)	2558 (61.7)	0.156	39079 (71.7)	6126 (71.4)	0.008
Black	17021 (23.4)	1247 (30.1)	0.151	11289 (20.7)	1775 (20.7)	0.001
Other	5438 (7.5)	341 (8.2)	0.028	4131 (7.6)	682 (8.0)	0.014
Sex, no. (%), men	64816 (89.2)	3927 (94.7)	0.205	49834 (91.4)	7941 (92.5)	0.040
ADI, mean (std)	53.5 (15.2)	53.0 (14.8)	0.023	53.8 (14.9)	53.2 (23.9)	0.036
Smoking status, no. (%)						
Never smoked	42506 (58.5)	2243 (54.1)	0.088	27987 (51.4)	4575 (53.3)	0.039
Former smoker	18011 (24.8)	1158 (27.9)	0.072	13577 (24.9)	2171 (25.3)	0.009
Current smoker	12177 (16.8)	745 (18)	0.032	12935 (23.7)	1837 (21.4)	0.056
Long-term care	1419 (2.0)	349 (8.4)	0.295	649 (1.2)	150 (1.8)	0.047
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	78.5 (21.1)	71.0 (22.1)	0.236	74.8 (20.2)	73.8 (33.4)	0.053
BMI (std) (n=1719839)	32.4 (6.2)	31.7 (6.8)	0.011	31.5 (5.8)	32.3 (10.3)	0.011
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.1 (12.4)	133.8 (12.9)	0.047	134 (12.4)	134.6 (20.3)	0.036
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	78.3 (7.7)	76.5 (7.8)	0.106	77.4 (7.5)	77.4 (12.3)	0.014
Number of eGFR measurements in the 2-years prior, mean (std)	3.0 (4.4)	7.2 (10.8)	0.552	3.2 (4.6)	3.5 (8.7)	0.080
Cancer	6838 (9.4)	642 (15.5)	0.185	5972 (11.0)	1010 (11.8)	0.026
Cardiovascular disease	12879 (17.7)	1408 (34)	0.378	11794 (21.6)	2037 (23.7)	0.050
Cerebrovascular disease	4272 (5.9)	479 (11.6)	0.202	3856 (7.1)	675 (7.9)	0.030

Chronic lung disease	11218 (15.4)	1174 (28.3)	0.316	9671 (17.7)	1693 (19.7)	0.051
Dementia	1929 (2.7)	282 (6.8)	0.197	1389 (2.6)	256 (3.0)	0.026
Diabetes mellitus type 2	27030 (37.2)	2117 (51.1)	0.282	21273 (39.0)	3519 (41)	0.040
HIV	669 (0.9)	40 (1.0)	0.004	419 (0.8)	58 (0.7)	0.012
Peripheral artery disease	1065 (1.5)	144 (3.5)	0.129	1036 (1.9)	150 (1.7)	0.012
Medications						
ACE/ARB	30364 (41.8)	2093 (50.5)	0.175	28411 (52.1)	4684 (54.6)	0.049
Antibiotics	6008 (8.3)	506 (12.2)	0.130	4755 (8.7)	875 (10.2)	0.050
Antivirals	3015 (4.2)	129 (3.1)	0.056	2179 (4.0)	362 (4.2)	0.011
Aspirin	12083 (16.6)	1055 (25.5)	0.218	11008 (20.2)	1860 (21.7)	0.036
Beta-blockers	22427 (30.9)	1827 (44.1)	0.276	22005 (40.4)	3658 (42.6)	0.045
Chemotherapeutic agents	889 (1.2)	65 (1.6)	0.030	835 (1.5)	134 (1.6)	0.002
Diuretics	11196 (15.4)	886 (21.4)	0.155	10249 (18.8)	1705 (19.9)	0.027
Immunosuppressants	1059 (1.5)	63 (1.5)	0.005	941 (1.7)	125 (1.5)	0.022
NSAIDs	29329 (40.4)	1502 (36.2)	0.085	23082 (42.4)	3609 (42.1)	0.006
PPI	24341 (33.5)	1557 (37.6)	0.085	21016 (38.6)	3399 (39.6)	0.021

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 9: Characteristics and standardized mean differences of predefined covariates by COVID-19 hospitalized and COVID-19 ICU admitted to groups before and after weighting.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Hospitalized	COVID-19 ICU	Standardized Mean Difference	COVID-19 Hospitalized	COVID-19 ICU	Standardized Mean Difference
Age, mean (std), yr	68.7 (12.8)	68.9 (11.6)	0.012	66.7 (6.8)	67.1 (20.1)	0.026
Race, no. (%)						
White	7715 (62.3)	2558 (61.7)	0.013	1999 (69.4)	6126 (71.4)	0.042
Black	3666 (29.6)	1247 (30.1)	0.010	648 (22.5)	1775 (20.7)	0.044
Other	995 (8)	341 (8.2)	0.007	232 (8.1)	682 (8.0)	0.004
Sex, no. (%), men	11656 (94.2)	3927 (94.7)	0.024	2638 (91.7)	7941 (92.5)	0.033
ADI, mean (std)	52.1 (15)	53.0 (14.8)	0.065	53.5 (8.1)	53.2 (23.9)	0.020
Smoking status, no. (%)						
Never smoked	6607 (53.4)	2243 (54.1)	0.014	1511 (52.5)	4575 (53.3)	0.016
Former smoker	3438 (27.8)	1158 (27.9)	0.003	718 (25.0)	2171 (25.3)	0.008
Current smoker	2331 (18.8)	745 (18)	0.022	649 (22.6)	1837 (21.4)	0.028
Long-term care	1214 (9.8)	349 (8.4)	0.048	42 (1.5)	150 (1.8)	0.021
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	71.3 (22.8)	71.0 (22.1)	0.010	74.2 (11.2)	73.8 (33.4)	0.020
BMI (std) (n=1719839)	32.7 (6.8)	31.7 (6.8)	0.015	31.3 (3.5)	32.3 (10.3)	0.036
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	134.3 (12.5)	133.8 (12.9)	0.044	134.6 (6.7)	134.6 (20.3)	0.005
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	76.8 (7.7)	76.5 (7.8)	0.040	77.5 (4.1)	77.4 (12.3)	0.018
Number of eGFR measurements in the 2-years prior, mean (std)	6.9 (10.2)	7.2 (10.8)	0.028	3.4 (2.8)	3.5 (8.7)	0.015
Cancer	2007 (16.2)	642 (15.5)	0.020	339 (11.8)	1010 (11.8)	0.000
Cardiovascular disease	3867 (31.3)	1408 (34)	0.058	676 (23.5)	2037 (23.7)	0.006
Cerebrovascular disease	1646 (13.3)	479 (11.6)	0.053	225 (7.8)	675 (7.9)	0.002

Chronic lung disease	3138 (25.4)	1174 (28.3)	0.067	552 (19.2)	1693 (19.7)	0.014
Dementia	1155 (9.3)	282 (6.8)	0.093	85 (3.0)	256 (3.0)	0.001
Diabetes mellitus type 2	5973 (48.3)	2117 (51.1)	0.056	1186 (41.2)	3519 (41)	0.004
HIV	162 (1.3)	40 (1.0)	0.033	26 (0.9)	58 (0.7)	0.027
Peripheral artery disease	445 (3.6)	144 (3.5)	0.007	60 (2.1)	150 (1.7)	0.026
Medications						
ACE/ARB	5880 (47.5)	2093 (50.5)	0.059	1524 (53)	4684 (54.6)	0.032
Antibiotics	1655 (13.4)	506 (12.2)	0.035	282 (9.8)	875 (10.2)	0.013
Antivirals	485 (3.9)	129 (3.1)	0.044	116 (4.0)	362 (4.2)	0.010
Aspirin	3337 (27.0)	1055 (25.5)	0.034	628 (21.8)	1860 (21.7)	0.004
Beta-blockers	5252 (42.4)	1827 (44.1)	0.033	1213 (42.2)	3658 (42.6)	0.009
Chemotherapeutic agents	197 (1.6)	65 (1.6)	0.002	46 (1.6)	134 (1.6)	0.004
Diuretics	2282 (18.4)	886 (21.4)	0.073	573 (19.9)	1705 (19.9)	0.001
Immunosuppressants	200 (1.6)	63 (1.5)	0.008	50 (1.8)	125 (1.5)	0.023
NSAIDs	4785 (38.7)	1502 (36.2)	0.050	1249 (43.4)	3609 (42.1)	0.027
PPI	4685 (37.9)	1557 (37.6)	0.006	1147 (39.8)	3399 (39.6)	0.005

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 10: Pairwise comparison among COVID-19 positive individuals of excess burden of PASC kidney disease by severity of the acute COVID-19 infection

Outcome	COVID-19 non-hospitalized vs. COVID hospitalized (reference)		COVID-19 non-hospitalized vs. COVID admitted to the ICU (reference)		COVID-19 hospitalized vs. COVID admitted to the ICU (reference)	
	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)
AKI	4.12 (3.66-4.64)	42.04 (35.93,48.88)	6.35 (5.41-7.45)	71.02 (58.95,84.97)	1.54 (1.3-1.83)	28.97 (15.95-44.23)
eGFR decline ≥ 30%	2.16 (1.96-2.37)	41.7 (34.89,49.13)	2.95 (2.57-3.38)	69.23 (56.19,83.95)	1.37 (1.17-1.6)	27.52 (12.97-44.21)
eGFR decline ≥ 40%	2.58 (2.27-2.94)	25.91 (20.85,31.36)	4.18 (3.53, 4.94	51.42 (41.20, 63.37)	1.62 (1.34-1.96)	25.51 (14.06, 39.16)
eGFR decline ≥ 50%	3.23 (2.71-3.84)	17.55 (13.51,22.33)	5.89 (4.79-7.23)	38.12 (29.7,48.37)	1.82 (1.45-2.3)	20.57 (11.16-32.32)
ESKD	2.66 (1.72-4.11)	2.42 (1.05,4.53)	6.16 (3.63-10.45)	7.51 (3.83,13.72)	2.32 (1.28-4.18)	5.09 (1.1-12.23)
MAKE	2.94 (2.6-3.31)	29.91 (24.79,35.65)	6.12 (5.28-7.09)	77.12 (64.88,91.1)	2.08 (1.77-2.46)	47.21 (33.63-62.98)

Adjusted for age, Area Deprivation Index, race, sex, smoking status, baseline eGFR, systolic and diastolic blood pressure, body mass index, and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, peripheral artery disease, angiotensin converting enzyme inhibitors /angiotensin II receptor blockers, antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, residence at a long-term care facility, and the number of eGFR measurements in the year prior to T_0, as well as 100 high dimensional variables.

[a]Burden estimated at 6 months following a COVID-19 positive test.

AKI, acute kidney injury; ESKD, end-stage kidney disease; MAKE, major adverse kidney outcomes; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval

Supplemental Table 11a: Pairwise comparison among COVID-19 positive individuals of excess burden of PASC kidney disease by severity of the acute COVID-19 infection adjusting for predefined covariates only.

Outcome	COVID-19 non-hospitalized vs. VHA users (reference)		COVID-19 non-hospitalized vs. VHA users (reference)		COVID admitted to the ICU vs. VHA users (reference)	
	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)
AKI	1.28 (1.19-1.37)	2.59 (1.65-3.60)	5.26 (4.78-5.78)	46.1 (41.02-51.73)	8.34 (7.30-9.55)	77.25 (66.72-89.12)
eGFR decline ≥ 30%	1.09 (1.04-1.13)	2.88 (1.37-4.46)	2.32 (2.14-2.51)	43.73 (37.86-50.04)	3.20 (2.83-3.63)	71.96 (60.19-85.09)
eGFR decline ≥ 40%	1.10 (1.03-1.17)	1.44 (0.44-2.50)	2.80 (2.51-3.12)	26.27 (22.10-30.91)	4.78 (4.13-5.55)	54.49 (45.22-65.13)
eGFR decline ≥ 50%	1.11 (1.01-1.21)	0.75 (0.07-1.50)	3.48 (3.02-4.02)	17.31 (14.10-20.99)	6.76 (5.68-8.05)	39.73 (32.39-48.41)
ESKD	2.01 (1.58-2.55)	0.69 (0.40-1.06)	5.36 (3.81-7.52)	2.96 (1.92-4.44)	11.91 (7.77-18.25)	7.41 (4.6-11.69)
MAKE	1.13 (1.06-1.20)	1.74 (0.75-2.79)	3.28 (2.97-3.62)	30.67 (26.61-35.13)	6.91 (6.09-7.85)	77.62 (67.19-89.32)

Adjusted for age, Area Deprivation Index, race, sex, smoking status, baseline eGFR, systolic and diastolic blood pressure, body mass index, and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, peripheral artery disease, angiotensin converting enzyme inhibitors /angiotensin II receptor blockers, antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, residence at a long-term care facility, and the number of eGFR measurements in the year prior to T_0.

[a]Burden estimated at 6 months following a COVID-19 positive test.

AKI, acute kidney injury; ESKD, end-stage kidney disease; MAKE, major adverse kidney outcomes; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval

Supplemental Table 11b: Pairwise comparison among COVID-19 positive individuals of excess burden of PASC kidney disease by severity of the acute COVID-19 infection adjusting for predefined covariates only.

Outcome	COVID-19 non-hospitalized vs. COVID hospitalized (reference)		COVID-19 non-hospitalized vs. COVID admitted to the ICU (reference)		COVID-19 hospitalized vs. COVID admitted to the ICU (reference)	
	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)
AKI	4.11 (3.66-4.61)	41.15 (35.35-47.65)	6.53 (5.61-7.59)	71.91 (60.42-85.09)	1.59 (1.35-1.87)	30.76 (18.24-45.31)
eGFR decline ≥ 30%	2.14 (1.95-2.34)	40.85 (34.32-47.94)	2.95 (2.59-3.36)	69.07 (56.72-82.94)	1.38 (1.19-1.60)	28.23 (14.34-44.06)
eGFR decline ≥ 40%	2.55 (2.25-2.89)	24.84 (20.08-30.20)	4.36 (3.71-5.12)	53.06 (43.07-64.65)	1.71 (1.42-2.05)	28.22 (16.93-41.60)
eGFR decline ≥ 50%	3.15 (2.66-3.72)	16.56 (12.83-20.95)	6.11 (5.02-7.43)	38.98 (30.82-48.82)	1.94 (1.55-2.43)	22.43 (13.20-33.85)
ESKD	2.67 (1.77-4.01)	2.28 (1.06-4.11)	5.93 (3.65-9.62)	6.72 (3.62-11.72)	2.22 (1.30-3.82)	4.44 (1.07-10.20)
MAKE	2.91 (2.59-3.27)	28.93 (24.12-34.30)	6.13 (5.32-7.07)	75.88 (64.27-89.09)	2.11 (1.80-2.47)	46.95 (34.03-61.89)

Adjusted for age, Area Deprivation Index, race, sex, smoking status, baseline eGFR, systolic and diastolic blood pressure, body mass index, and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, peripheral artery disease, angiotensin converting enzyme inhibitors /angiotensin II receptor blockers, antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, residence at a long-term care facility, and the number of eGFR measurements in the year prior to T_0.

[a]Burden estimated at 6 months following a COVID-19 positive test.

AKI, acute kidney injury; ESKD, end-stage kidney disease; MAKE, major adverse kidney outcomes; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval

Supplemental Table 12: Characteristics and standardized mean differences of predefined covariates in COVID-19 non-hospitalized and VHA user groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Positive	VHA Users	Standardized Mean Difference	COVID-19 Positive	VHA Users	Standardized Mean Difference
Age, mean (std), yr	61.8 (14.4)	68.7 (14.3)	0.239	66.1 (13.3)	66.1 (13.2)	0.002
Race, no. (%)						
White	50235 (69.1)	1206583 (73.7)	0.103	38991.8 (71.8)	880045.2 (72.1)	0.008
Black	17021 (23.4)	308003 (18.8)	0.114	11232.7 (20.7)	248039.5 (20.3)	0.008
Other	5438 (7.5)	122881 (7.5)	0.001	4119.8 (7.6)	92224.0 (7.6)	0.001
Sex, no. (%), men	64816 (89.2)	1494986 (91.3)	0.071	49667.2 (91.4)	1118331 (91.6)	0.009
ADI, mean (std)	53.5 (15.2)	55.0 (15.6)	0.007	53.8 (15.6)	53.8 (15.6)	0.002
Smoking status, no. (%)						
Never smoked	42506 (58.5)	864427 (52.8)	0.112	27992.7 (51.5)	631099.5 (51.7)	0.004
Former smoker	18011 (24.8)	390430 (23.8)	0.022	13542.2 (24.9)	302484.8 (24.8)	0.003
Current smoker	12177 (16.8)	382610 (23.4)	0.163	12809.5 (23.6)	286724.4 (23.5)	0.002
Long-term care	1419 (2.0)	12979 (0.8)	0.107	597.2 (1.1)	11122.5 (0.9)	0.019
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	78.6 (21.8)	76.2 (21.2)	0.113	75.1 (21.7)	75.1 (21.1)	0.000
BMI (std) (n=1719839)	32.4 (6.2)	31.3 (6.1)	0.006	31.4 (6.0)	31.8 (6.2)	0.002
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.1 (12.4)	133.2 (13.2)	0.007	134.0 (13.0)	134.1 (13.1)	0.007
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	78.3 (7.7)	77.3 (8.0)	0.134	77.4 (7.9)	77.5 (7.9)	0.006
Number of eGFR measurements in the 2-years prior, mean (std)	3.0 (4.4)	2 (4.1)	0.109	3.1 (4.6)	2.9 (4.3)	0.033
Cancer	6838 (9.4)	155323 (9.5)	0.002	5865.1 (10.8)	127117.3 (10.4)	0.012
Cardiovascular disease	12879 (17.7)	292143 (17.8)	0.003	11597.8 (21.3)	255609.4 (21.0)	0.01
Cerebrovascular disease	4272 (5.9)	94879 (5.8)	0.008	3780.3 (7.0)	82279.2 (6.7)	0.009

Chronic lung disease	11218 (15.4)	246116 (15.0)	0.016	9519.3 (17.5)	205394.2 (16.8)	0.018
Dementia	1929 (2.7)	35487 (2.2)	0.035	1344.5 (2.5)	28168.1 (2.3)	0.01
Diabetes mellitus type 2	27030 (37.2)	545960 (33.3)	0.083	21159.3 (38.9)	472287.4 (38.7)	0.005
HIV	669 (0.9)	11057 (0.7)	0.028	413.5 (0.8)	9179.0 (0.8)	0.001
Peripheral artery disease	1065 (1.5)	23704 (1.5)	0.007	993.3 (1.8)	21079.2 (1.7)	0.008
Medications						
ACE/ARB	30364 (41.8)	644314 (39.4)	0.052	28305.2 (52.1)	638472.8 (52.3)	0.005
Antibiotics	6008 (8.3)	101537 (92.6)	0.085	4669.9 (8.6)	101213.5 (8.3)	0.011
Antivirals	3015 (4.2)	47430 (2.9)	0.069	2171.1 (4.0)	47727.32 (3.9)	0.005
Aspirin	12083 (16.6)	241233 (14.7)	0.057	10882.1 (20.0)	239358.2 (19.6)	0.01
Beta-blockers	22427 (30.9)	490361 (30.0)	0.024	21826.0 (40.2)	484325.9 (39.7)	0.01
Chemotherapeutic agents	889 (1.2)	17993 (1.1)	0.012	830.3 (1.5)	17888.18 (1.5)	0.005
Diuretics	11196 (15.4)	230481 (14.1)	0.040	10186.0 (18.7)	228474.2 (18.7)	0.001
Immunosuppressants	1059 (1.5)	20166 (1.2)	0.020	939.3 (1.7)	20081.03 (1.7)	0.006
NSAIDs	29329 (40.4)	510808 (31.2)	0.193	23024.1 (42.4)	511511.9 (41.9)	0.009
PPI	24341 (33.5)	46443 (28.4)	0.115	20878.7 (38.4)	461728.9 (37.8)	0.012

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 13: Characteristics and standardized mean differences of predefined covariates in COVID-19 hospitalized with no AKI and VHA user groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Hospitalized non-AKI	VHA Users	Standardized Mean Difference	COVID-19 Hospitalized non-AKI	VHA Users	Standardized Mean Difference
Age, mean (std), yr	68.3(12.8)	68.7 (14.3)	0.223	66.4 (13.0)	66.1 (13.2)	0.019
Race, no. (%)						
White	8596 (64.3)	1206583 (73.7)	0.205	6122.1 (67.1)	880045.2 (72.1)	0.108
Black	3673 (27.5)	308003 (18.8)	0.208	2246.5 (24.6)	248039.5 (20.3)	0.103
Other	1093 (8.2)	122881 (7.5)	0.025	749.3 (8.2)	92224.0 (7.6)	0.024
Sex, no. (%), men	12534 (93.8)	1494986 (91.3)	0.096	8335.3 (91.4)	1118331 (91.6)	0.008
ADI, mean (std)	53.5 (14.9)	55.0 (15.6)	0.069	53.5 (15.6)	53.8 (15.6)	0.020
Smoking status, no. (%)						
Never smoked	7198 (53.9)	864427 (52.8)	0.019	4807.6 (52.7)	631099.5 (51.7)	0.020
Former smoker	3643 (27.3)	390430 (23.8)	0.079	2286.6 (25.1)	302484.8 (24.8)	0.007
Current smoker	2521 (18.9)	382610 (23.4)	0.108	2023.7 (22.2)	286724.4 (23.5)	0.031
Long-term care	1196 (9.0)	12979 (0.8)	0.391	134.7 (1.5)	11122.5 (0.9)	0.052
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	83.0 (21.5)	76.2 (21.2)	0.317	74.6 (21.5)	75.1 (21.1)	0.021
BMI (std) (n=1719839)	31.8 (6.8)	31.3 (6.1)	0.003	31.5 (6.5)	31.8 (6.2)	0.001
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.6 (12.3)	133.2 (13.2)	0.035	134.9 (13.0)	134.1 (13.1)	0.064
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	76.9 (12.3)	77.3 (8.0)	0.058	77.7 (8.0)	77.5 (7.9)	0.023
Number of eGFR measurements in the 2-years prior, mean (std)	6.7 (9.9)	2.0 (4.1)	0.553	3.4 (5.2)	2.9 (4.3)	0.095
Cancer	2133 (16.0)	155323 (9.5)	0.200	1080.1 (11.9)	127117.3 (10.4)	0.045
Cardiovascular disease	4046 (30.3)	292143 (17.8)	0.300	2105.0 (23.1)	255609.4 (21.0)	0.052
Cerebrovascular disease	1639 (12.3)	94879 (5.8)	0.232	696.0 (7.6)	82279.2 (6.7)	0.034

Chronic lung disease	3490 (26.1)	246116 (15.0)	0.282	1742.0 (19.1)	205394.2 (16.8)	0.059
Dementia	1142 (8.6)	35487 (2.2)	0.290	247.3 (2.7)	28168.1 (2.3)	0.026
Diabetes mellitus type 2	6214 (46.5)	545960 (33.3)	0.274	3778.9 (41.4)	472287.4 (38.7)	0.056
HIV	165 (1.2)	11057 (0.7)	0.058	95.7 (1.1)	9179.0 (0.8)	0.032
Peripheral artery disease	469 (3.5)	23704 (1.5)	0.137	189.9 (2.1)	21079.2 (1.7)	0.026
Medications						
ACE/ARB	6133 (45.9)	644314 (39.4)	0.135	4943.4 (54.2)	638472.8 (52.3)	0.038
Antibiotics	1749 (13.1)	101537 (92.6)	0.240	885.1 (9.7)	101213.5 (8.3)	0.05
Antivirals	518 (3.9)	47430 (2.9)	0.055	363.7 (4.0)	47727.32 (3.9)	0.004
Aspirin	3439 (25.7)	241233 (14.7)	0.281	1998.8 (21.9)	239358.2 (19.6)	0.057
Beta-blockers	5466 (40.9)	490361 (30.0)	0.236	3806.7 (41.8)	484325.9 (39.7)	0.042
Chemotherapeutic agents	209 (1.6)	17993 (1.1)	0.041	149.7 (1.6)	17888.18 (1.5)	0.014
Diuretics	2342 (17.5)	230481 (14.1)	0.097	1858.0 (20.4)	228474.2 (18.7)	0.042
Immunosuppressants	211 (1.6)	20166 (1.2)	0.030	158.0 (1.7)	20081.03 (1.7)	0.006
NSAIDs	5265 (39.4)	510808 (31.2)	0.174	3950.1 (43.3)	511511.9 (41.9)	0.028
PPI	5110 (38.2)	46443 (28.4)	0.215	3580.3 (39.3)	461728.9 (37.8)	0.029

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 14: Characteristics and standardized mean differences of predefined covariates in COVID-19 hospitalized with AKI and VHA user groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Hospitalized AKI	VHA Users	Standardized Mean Difference	COVID-19 Hospitalized AKI	VHA Users	Standardized Mean Difference
Age, mean (std), yr	70.9 (10.9)	68.7 (14.3)	0.445	67.7 (11.9)	66.1 (13.2)	0.149
Race, no. (%)						
White	1677 (53.1)	1206583 (73.7)	0.439	1357.6 (69.2)	880045.2 (72.1)	0.063
Black	1240 (39.2)	308003 (18.8)	0.464	434.5 (22.2)	248039.5 (20.3)	0.045
Other	243 (7.7)	122881 (7.5)	0.007	168.8 (8.6)	92224.0 (7.6)	0.039
Sex, no. (%), men	3049 (96.5)	1494986 (91.3)	0.219	1857.6 (94.7)	1118331 (91.6)	0.123
ADI, mean (std)	52.14 (15.2)	55.0 (15.6)	0.081	53.3 (15.1)	53.8 (15.6)	0.028
Smoking status, no. (%)						
Never smoked	1652 (52.3)	864427 (52.8)	0.013	1023.6 (52.2)	631099.5 (51.7)	0.010
Former smoker	953 (30.2)	390430 (23.8)	0.143	507.8 (25.9)	302484.8 (24.8)	0.026
Current smoker	555 (17.6)	382610 (23.4)	0.142	429.4 (21.9)	286724.4 (23.5)	0.038
Long-term care	367 (11.6)	12979 (0.8)	0.465	35.6 (1.8)	11122.5 (0.9)	0.078
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	60.3 (26.5)	76.2 (21.2)	0.664	73.6 (22.2)	75.1 (21.1)	0.068
BMI (std) (n=1719839)	35.4 (7.0)	31.3 (6.1)	0.021	30.8 (6.9)	31.8 (6.2)	0.006
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	136.6 (13.6)	133.2 (13.2)	0.255	134.8 (13.0)	134.1 (13.1)	0.053
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	76.1 (8.2)	77.3 (8.0)	0.150	77.0 (7.7)	77.5 (7.9)	0.065
Number of eGFR measurements in the 2-years prior, mean (std)	8.1 (12.9)	2.0 (4.1)	0.587	3.4 (5.2)	2.9 (4.3)	0.105
Cancer	516 (16.3)	155323 (9.5)	0.210	255.2 (13.0)	127117.3 (10.4)	0.081
Cardiovascular disease	1229 (38.9)	292143 (17.8)	0.487	495.8 (25.3)	255609.4 (21.0)	0.103
Cerebrovascular disease	486 (15.4)	94879 (5.8)	0.320	167.2 (8.5)	82279.2 (6.7)	0.067

Chronic lung disease	822 (26.0)	246116 (15.0)	0.280	396.3 (20.2)	205394.2 (16.8)	0.087
Dementia	295 (9.3)	35487 (2.2)	0.315	76.8 (3.9)	28168.1 (2.3)	0.093
Diabetes mellitus type 2	1876 (59.4)	545960 (33.3)	0.543	902.8 (46.0)	472287.4 (38.7)	0.149
HIV	37 (1.2)	11057 (0.7)	0.052	19.9 (1.0)	9179.0 (0.8)	0.029
Peripheral artery disease	120 (3.8)	23704 (1.5)	0.152	36.1 (1.8)	21079.2 (1.7)	0.008
Medications						
ACE/ARB	1840 (58.2)	644314 (39.4)	0.387	1158.7 (59.1)	638472.8 (52.3)	0.137
Antibiotics	412 (13.0)	101537 (92.6)	0.238	222.9 (11.4)	101213.5 (8.3)	0.104
Antivirals	96 (3.0)	47430 (2.9)	0.009	71.4 (3.6)	47727.32 (3.9)	0.014
Aspirin	953 (30.2)	241233 (14.7)	0.381	448.0 (22.9)	239358.2 (19.6)	0.079
Beta-blockers	1613 (51.0)	490361 (30.0)	0.445	915.8 (46.7)	484325.9 (39.7)	0.142
Chemotherapeutic agents	53 (1.7)	17993 (1.1)	0.051	32.0 (1.6)	17888.18 (1.5)	0.013
Diuretics	826 (26.1)	230481 (14.1)	0.307	423.6 (21.6)	228474.2 (18.7)	0.072
Immunosuppressants	52 (1.7)	20166 (1.2)	0.035	29.2 (1.5)	20081.03 (1.7)	0.013
NSAIDs	1022 (32.3)	510808 (31.2)	0.026	818.7 (41.8)	511511.9 (41.9)	0.003
PPI	1132 (35.8)	46443 (28.4)	0.164	784.0 (40.0)	461728.9 (37.8)	0.044

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 15: Characteristics and standardized mean differences of predefined covariates in COVID-19 non-hospitalized and COVID-19 hospitalized with no AKI groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Positive	COVID-19 Hospitalized non-AKI	Standardized Mean Difference	COVID-19 Positive	COVID-19 Hospitalized non-AKI	Standardized Mean Difference
Age, mean (std), yr	61.8 (14.4)	68.3(12.8)	0.474	66.1 (13.3)	66.4 (13.0)	0.022
Race, no. (%)						
White	50235 (69.1)	8596 (64.3)	0.101	38991.8 (71.8)	6122.1 (67.1)	0.100
Black	17021 (23.4)	3673 (27.5)	0.094	11232.7 (20.7)	2246.5 (24.6)	0.095
Other	5438 (7.5)	1093 (8.2)	0.026	4119.8 (7.6)	749.3 (8.2)	0.024
Sex, no. (%), men	64816 (89.2)	12534 (93.8)	0.167	49667.2 (91.4)	8335.3 (91.4)	0.001
ADI, mean (std)	53.5 (15.2)	53.5 (14.9)	0.078	53.8 (15.6)	53.5 (15.6)	0.022
Smoking status, no. (%)						
Never smoked	42506 (58.5)	7198 (53.9)	0.093	27992.7 (51.5)	4807.6 (52.7)	0.024
Former smoker	18011 (24.8)	3643 (27.3)	0.057	13542.2 (24.9)	2286.6 (25.1)	0.004
Current smoker	12177 (16.8)	2521 (18.9)	0.055	12809.5 (23.6)	2023.7 (22.2)	0.033
Long-term care	1419 (2.0)	1196 (9.0)	0.312	597.2 (1.1)	134.7 (1.5)	0.034
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	78.6 (21.8)	83.0 (21.5)	0.205	75.1 (21.7)	74.6 (21.5)	0.020
BMI (std) (n=1719839)	32.4 (6.2)	31.8 (6.8)	0.010	31.4 (6.0)	31.5 (6.5)	0.002
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.1 (12.4)	133.6 (12.3)	0.044	134.0 (13.0)	134.9 (13.0)	0.071
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	78.3 (7.7)	76.9 (12.3)	0.197	77.4 (7.9)	77.7 (8.0)	0.029
Number of eGFR measurements in the 2-years prior, mean (std)	3.0 (4.4)	6.7 (9.9)	0.482	3.1 (4.6)	3.4 (5.2)	0.063
Cancer	6838 (9.4)	2133 (16.0)	0.198	5865.1 (10.8)	1080.1 (11.9)	0.033
Cardiovascular disease	12879 (17.7)	4046 (30.3)	0.297	11597.8 (21.3)	2105.0 (23.1)	0.042

Cerebrovascular disease	4272 (5.9)	1639 (12.3)	0.224	3780.3 (7.0)	696.0 (7.6)	0.026
Chronic lung disease	11218 (15.4)	3490 (26.1)	0.266	9519.3 (17.5)	1742.0 (19.1)	0.041
Dementia	1929 (2.7)	1142 (8.6)	0.259	1344.5 (2.5)	247.3 (2.7)	0.015
Diabetes mellitus type 2	27030 (37.2)	6214 (46.5)	0.190	21159.3 (38.9)	3778.9 (41.4)	0.051
HIV	669 (0.9)	165 (1.2)	0.030	413.5 (0.8)	95.7 (1.1)	0.031
Peripheral artery disease	1065 (1.5)	469 (3.5)	0.131	993.3 (1.8)	189.9 (2.1)	0.018
Medications						
ACE/ARB	30364 (41.8)	6133 (45.9)	0.083	28305.2 (52.1)	4943.4 (54.2)	0.043
Antibiotics	6008 (8.3)	1749 (13.1)	0.157	4669.9 (8.6)	885.1 (9.7)	0.039
Antivirals	3015 (4.2)	518 (3.9)	0.014	2171.1 (4.0)	363.7 (4.0)	0.001
Aspirin	12083 (16.6)	3439 (25.7)	0.225	10882.1 (20.0)	1998.8 (21.9)	0.047
Beta-blockers	22427 (30.9)	5466 (40.9)	0.211	21826.0 (40.2)	3806.7 (41.8)	0.032
Chemotherapeutic agents	889 (1.2)	209 (1.6)	0.029	830.3 (1.5)	149.7 (1.6)	0.009
Diuretics	11196 (15.4)	2342 (17.5)	0.057	10186.0 (18.7)	1858.0 (20.4)	0.041
Immunosuppressants	1059 (1.5)	211 (1.6)	0.010	939.3 (1.7)	158.0 (1.7)	0.000
NSAIDs	29329 (40.4)	5265 (39.4)	0.019	23024.1 (42.4)	3950.1 (43.3)	0.019
PPI	24341 (33.5)	5110 (38.2)	0.099	20878.7 (38.4)	3580.3 (39.3)	0.017

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 16: Characteristics and standardized mean differences of predefined covariates in COVID-19 non-hospitalized and COVID-19 hospitalized with an AKI groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Positive	COVID-19 Hospitalized AKI	Standardized Mean Difference	COVID-19 Positive	COVID-19 Hospitalized AKI	Standardized Mean Difference
Age, mean (std), yr	61.8 (14.4)	70.9 (10.9)	0.711	66.1 (13.3)	67.7 (11.9)	0.147
Race, no. (%)						
White	50235 (69.1)	1677 (53.1)	0.333	38991.8 (71.8)	1357.6 (69.2)	0.055
Black	17021 (23.4)	1240 (39.2)	0.346	11232.7 (20.7)	434.5 (22.2)	0.036
Other	5438 (7.5)	243 (7.7)	0.008	4119.8 (7.6)	168.8 (8.6)	0.038
Sex, no. (%), men	64816 (89.2)	3049 (96.5)	0.287	49667.2 (91.4)	1857.6 (94.7)	0.132
ADI, mean (std)	53.5 (15.2)	52.14 (15.2)	0.089	53.8 (15.6)	53.3 (15.1)	0.029
Smoking status, no. (%)						
Never smoked	42506 (58.5)	1652 (52.3)	0.125	27992.7 (51.5)	1023.6 (52.2)	0.014
Former smoker	18011 (24.8)	953 (30.2)	0.121	13542.2 (24.9)	507.8 (25.9)	0.023
Current smoker	12177 (16.8)	555 (17.6)	0.021	12809.5 (23.6)	429.4 (21.9)	0.040
Long-term care	1419 (2.0)	367 (11.6)	0.392	597.2 (1.1)	35.6 (1.8)	0.060
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	78.6 (21.8)	60.3 (26.5)	0.763	75.1 (21.7)	73.6 (22.2)	0.067
BMI (std) (n=1719839)	32.4 (6.2)	35.4 (7.0)	0.032	31.4 (6.0)	30.8 (6.9)	0.013
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.1 (12.4)	136.6 (13.6)	0.270	134.0 (13.0)	134.8 (13.0)	0.060
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	78.3 (7.7)	76.1 (8.2)	0.285	77.4 (7.9)	77.0 (7.7)	0.059
Number of eGFR measurements in the 2-years prior, mean (std)	3.0 (4.4)	8.1 (12.9)	0.532	3.1 (4.6)	3.4 (5.2)	0.073
Cancer	6838 (9.4)	516 (16.3)	0.208	5865.1 (10.8)	255.2 (13.0)	0.069
Cardiovascular disease	12879 (17.7)	1229 (38.9)	0.483	11597.8 (21.3)	495.8 (25.3)	0.094

Cerebrovascular disease	4272 (5.9)	486 (15.4)	0.312	3780.3 (7.0)	167.2 (8.5)	0.059
Chronic lung disease	11218 (15.4)	822 (26.0)	0.263	9519.3 (17.5)	396.3 (20.2)	0.069
Dementia	1929 (2.7)	295 (9.3)	0.285	1344.5 (2.5)	76.8 (3.9)	0.083
Diabetes mellitus type 2	27030 (37.2)	1876 (59.4)	0.455	21159.3 (38.9)	902.8 (46.0)	0.144
HIV	669 (0.9)	37 (1.2)	0.025	413.5 (0.8)	19.9 (1.0)	0.028
Peripheral artery disease	1065 (1.5)	120 (3.8)	0.146	993.3 (1.8)	36.1 (1.8)	0.001
Medications						
ACE/ARB	30364 (41.8)	1840 (58.2)	0.334	28305.2 (52.1)	1158.7 (59.1)	0.142
Antibiotics	6008 (8.3)	412 (13.0)	0.155	4669.9 (8.6)	222.9 (11.4)	0.093
Antivirals	3015 (4.2)	96 (3.0)	0.060	2171.1 (4.0)	71.4 (3.6)	0.019
Aspirin	12083 (16.6)	953 (30.2)	0.324	10882.1 (20.0)	448.0 (22.9)	0.069
Beta-blockers	22427 (30.9)	1613 (51.0)	0.420	21826.0 (40.2)	915.8 (46.7)	0.132
Chemotherapeutic agents	889 (1.2)	53 (1.7)	0.038	830.3 (1.5)	32.0 (1.6)	0.008
Diuretics	11196 (15.4)	826 (26.1)	0.267	10186.0 (18.7)	423.6 (21.6)	0.071
Immunosuppressants	1059 (1.5)	52 (1.7)	0.015	939.3 (1.7)	29.2 (1.5)	0.019
NSAIDs	29329 (40.4)	1022 (32.3)	0.167	23024.1 (42.4)	818.7 (41.8)	0.013
PPI	24341 (33.5)	1132 (35.8)	0.049	20878.7 (38.4)	784.0 (40.0)	0.032

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 17: Characteristics and standardized mean differences of predefined covariates in COVID-19 hospitalized with no AKI and COVID-19 hospitalized with an AKI groups before and after weighting in analyses of risks by AKI status during the acute COVID-19 infection.

Characteristics	Before Weighting			After Weighting		
	COVID-19 Hospitalized non-AKI	COVID-19 Hospitalized AKI	Standardized Mean Difference	COVID-19 Hospitalized non-AKI	COVID-19 Hospitalized AKI	Standardized Mean Difference
Age, mean (std), yr	68.3(12.8)	70.9 (10.9)	0.222	66.4 (13.0)	67.7 (11.9)	0.142
Race, no. (%)						
White	8596 (64.3)	1677 (53.1)	0.230	6122.1 (67.1)	1357.6 (69.2)	0.045
Black	3673 (27.5)	1240 (39.2)	0.251	2246.5 (24.6)	434.5 (22.2)	0.059
Other	1093 (8.2)	243 (7.7)	0.018	749.3 (8.2)	168.8 (8.6)	0.014
Sex, no. (%), men	12534 (93.8)	3049 (96.5)	0.125	8335.3 (91.4)	1857.6 (94.7)	0.131
ADI, mean (std)	53.5 (14.9)	52.14 (15.2)	0.013	53.5 (15.6)	53.3 (15.1)	0.007
Smoking status, no. (%)						
Never smoked	7198 (53.9)	1652 (52.3)	0.032	4807.6 (52.7)	1023.6 (52.2)	0.011
Former smoker	3643 (27.3)	953 (30.2)	0.064	2286.6 (25.1)	507.8 (25.9)	0.019
Current smoker	2521 (18.9)	555 (17.6)	0.034	2023.7 (22.2)	429.4 (21.9)	0.007
Long-term care	1196 (9.0)	367 (11.6)	0.088	134.7 (1.5)	35.6 (1.8)	0.027
Clinical Characteristics						
eGFR, mean (std) (ml/min/1.73m^2) (n=1672359)	83.0 (21.5)	60.3 (26.5)	0.940	74.6 (21.5)	73.6 (22.2)	0.047
BMI (std) (n=1719839)	31.8 (6.8)	35.4 (7.0)	0.038	31.5 (6.5)	30.8 (6.9)	0.026
Systolic blood pressure, mean (std) (mmHG) (n=1709598)	133.6 (12.3)	136.6 (13.6)	0.229	134.9 (13.0)	134.8 (13.0)	0.011
Diastolic blood pressure, mean (std) (mmHG) (n=1709598)	76.9 (12.3)	76.1 (8.2)	0.096	77.7 (8.0)	77.0 (7.7)	0.088
Number of eGFR measurements in the 2-years prior, mean (std)	6.7 (9.9)	8.1 (12.9)	0.122	3.4 (5.2)	3.4 (5.2)	0.009
Cancer	2133 (16.0)	516 (16.3)	0.010	1080.1 (11.9)	255.2 (13.0)	0.035
Cardiovascular disease	4046 (30.3)	1229 (38.9)	0.182	2105.0 (23.1)	495.8 (25.3)	0.051

Cerebrovascular disease	1639 (12.3)	486 (15.4)	0.090	696.0 (7.6)	167.2 (8.5)	0.033
Chronic lung disease	3490 (26.1)	822 (26.0)	0.003	1742.0 (19.1)	396.3 (20.2)	0.028
Dementia	1142 (8.6)	295 (9.3)	0.028	247.3 (2.7)	76.8 (3.9)	0.068
Diabetes mellitus type 2	6214 (46.5)	1876 (59.4)	0.260	3778.9 (41.4)	902.8 (46.0)	0.093
HIV	165 (1.2)	37 (1.2)	0.006	95.7 (1.1)	19.9 (1.0)	0.003
Peripheral artery disease	469 (3.5)	120 (3.8)	0.015	189.9 (2.1)	36.1 (1.8)	0.017
Medications						
ACE/ARB	6133 (45.9)	1840 (58.2)	0.249	4943.4 (54.2)	1158.7 (59.1)	0.099
Antibiotics	1749 (13.1)	412 (13.0)	0.001	885.1 (9.7)	222.9 (11.4)	0.054
Antivirals	518 (3.9)	96 (3.0)	0.046	363.7 (4.0)	71.4 (3.6)	0.018
Aspirin	3439 (25.7)	953 (30.2)	0.099	1998.8 (21.9)	448.0 (22.9)	0.022
Beta-blockers	5466 (40.9)	1613 (51.0)	0.204	3806.7 (41.8)	915.8 (46.7)	0.1
Chemotherapeutic agents	209 (1.6)	53 (1.7)	0.010	149.7 (1.6)	32.0 (1.6)	0.001
Diuretics	2342 (17.5)	826 (26.1)	0.210	1858.0 (20.4)	423.6 (21.6)	0.03
Immunosuppressants	211 (1.6)	52 (1.7)	0.006	158.0 (1.7)	29.2 (1.5)	0.019
NSAIDs	5265 (39.4)	1022 (32.3)	0.148	3950.1 (43.3)	818.7 (41.8)	0.032
PPI	5110 (38.2)	1132 (35.8)	0.050	3580.3 (39.3)	784.0 (40.0)	0.015

std, standard deviation; ADI, Area Deprivation Index; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Supplemental Table 18: Pairwise comparisons of risk and excess burden of adverse kidney by AKI status during the acute COVID-19 infection.

Outcome	COVID-19 hospitalized with no AKI vs. COVID-19 non-hospitalized (reference)		COVID-19 hospitalized with an AKI vs. COVID-19 non-hospitalized (reference)		COVID-19 hospitalized with AKI vs. COVID-19 hospitalized with no AKI (reference)	
	HR (95% CI)	**Excess Burden per 1000 persons[a] (95% CI)**	**HR (95% CI)**	**Excess Burden per 1000 persons[a] (95% CI)**	**HR (95% CI)**	**Excess Burden per 1000 persons[a] (95% CI)**
AKI	4.25 (3.77, 4.78)	54.67 (46.85, 63.39)	9.17 (7.76, 10.84)	131.84 (110.36, 156.55)	2.16 (1.80, 2.59)	77.17 (54.21, 103.86)
ESKD	1.45 (0.90, 2.39)	0.67 (-0.17, 2.03)	4.91 (3.10, 7.77)	5.72 (3.07, 9.90)	3.37 (1.88, 6.06)	5.05 (1.87, 10.74)
MAKE	2.53 (2.18, 2.94)	20.23 (15.62, 25.57)	7.37 (6.03, 9.02)	81.72 (65.05, 101.69)	2.92 (2.33, 3.650	61.48 (43.10, 83.98)

Adjusted for age, Area Deprivation Index, race, sex, smoking status, baseline eGFR, systolic and diastolic blood pressure, body mass index, and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, peripheral artery disease, angiotensin converting enzyme inhibitors /angiotensin II receptor blockers, antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, residence at a long-term care facility, and the number of eGFR measurements in the year prior to T_0, as well as 100 high dimensional variables.

[a]Burden estimated at 6 months following a COVID-19 positive test.

AKI, acute kidney injury; ESKD, end-stage kidney disease; MAKE, major adverse kidney outcomes; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval

Supplemental Table 19a: Pairwise comparisons of risk and excess burden of adverse kidney outcomes to VHA users by AKI status during the acute COVID-19 infection adjusting only for predefined covariates.

Outcome	COVID-19 non-hospitalized vs. VHA users (reference)		COVID-19 hospitalized with no AKI vs. VHA users (reference)		COVID-19 hospitalized with AKI vs. VHA users (reference)	
	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)	HR (95% CI)	Excess Burden per 1000 persons[a] (95% CI)
AKI	1.22 (1.14, 1.31)	3.12 (1.97, 4.34)	5.17 (4.71, 5.69)	57.28 (51.07, 64.06)	11.52 (9.91, 13.39)	138.06 (118.28. 160.48)
ESKD	1.78 (1.40, 2.25)	0.63 (0.32, 1.01)	2.55 (1.66, 3.92)	1.25 (0.53, 2.35)	8.77 (6.03, 12.76)	6.23 (4.04, 9.42)
MAKE	1.08 (1.01, 1.17)	1.01 (0.01, 2.08)	2.76 (2.43, 3.13)	21.32 (17.41, 25.74)	7.87 (6.59, 9.40)	80.69 (66.14, 97.77)

Adjusted for age, Area Deprivation Index, race, sex, smoking status, baseline eGFR, systolic and diastolic blood pressure, body mass index, and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, peripheral artery disease, angiotensin converting enzyme inhibitors /angiotensin II receptor blockers, antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, residence at a long-term care facility, and the number of eGFR measurements in the year prior to $T_{0.}$

[a]Burden estimated at 6 months following a COVID-19 positive test.

AKI, acute kidney injury; ESKD, end-stage kidney disease; MAKE, major adverse kidney outcomes; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval

Supplemental Table 19b: Pairwise comparisons of risk and excess burden of adverse kidney outcomes by AKI status during the acute COVID-19 infection adjusting only for predefined covariates.

Outcome	COVID-19 hospitalized with no AKI vs. COVID-19 non-hospitalized (reference)		COVID-19 hospitalized with an AKI vs. COVID-19 non-hospitalized (reference)		COVID-19 hospitalized with AKI vs. COVID-19 hospitalized with no AKI (reference)	
	HR (95% CI)	**Excess Burden per 1000 persons[a] (95% CI)**	**HR (95% CI)**	**Excess Burden per 1000 persons[a] (95% CI)**	**HR (95% CI)**	**Excess Burden per 1000 persons[a] (95% CI)**
AKI	4.24 (3.78, 4.76)	54.17 (46.65, 62.52)	9.44 (8.01, 11.12)	134.94 (113.46, 159.57)	2.23 (1.87, 2.66)	80.77 (57.83, 107.35)
ESKD	1.44 (0.89, 2.32)	0.62 (-0.16, 1.89)	4.93 (3.19, 7.62)	5.61 (3.13, 9.42)	3.44 (1.96, 6.04)	4.99 (1.96, 10.27)
MAKE	2.55 (2.20, 2.95)	20.31 (15.80, 25.52)	7.27 (5.99, 8.82)	79.68 (63.98, 98.38)	2.85 (2.30, 3.54)	59.37 (41.94, 80.56)

Adjusted for age, Area Deprivation Index, race, sex, smoking status, baseline eGFR, systolic and diastolic blood pressure, body mass index, and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, peripheral artery disease, angiotensin converting enzyme inhibitors /angiotensin II receptor blockers, antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, residence at a long-term care facility, and the number of eGFR measurements in the year prior to T_0.

[a]Burden estimated at 6 months following a COVID-19 positive test.

AKI, acute kidney injury; ESKD, end-stage kidney disease; MAKE, major adverse kidney outcomes; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval

Supplemental Table 20: Outcome controls for the comparison of COVID-19 positive Veterans vs. VHA users.

Outcome	HR (95% CI)	Excess burden per 1000 persons[a] (95% CI)
Positive outcome controls		
All-cause mortality	1.76 (1.66, 1.87)	6.00 (5.50, 6.48)
Hospitalization	1.77 (1.72, 1.81)	42.49 (41.12, 43.82)
Negative outcome controls		
Fitting or adjustment of casts and bandages	0.97 (0.89, 1.06)	-0.24 (-0.98, 0.43)
Atopic dermatitis	0.99 (0.83, 1.18)	-0.02 (-0.44, 0.33)

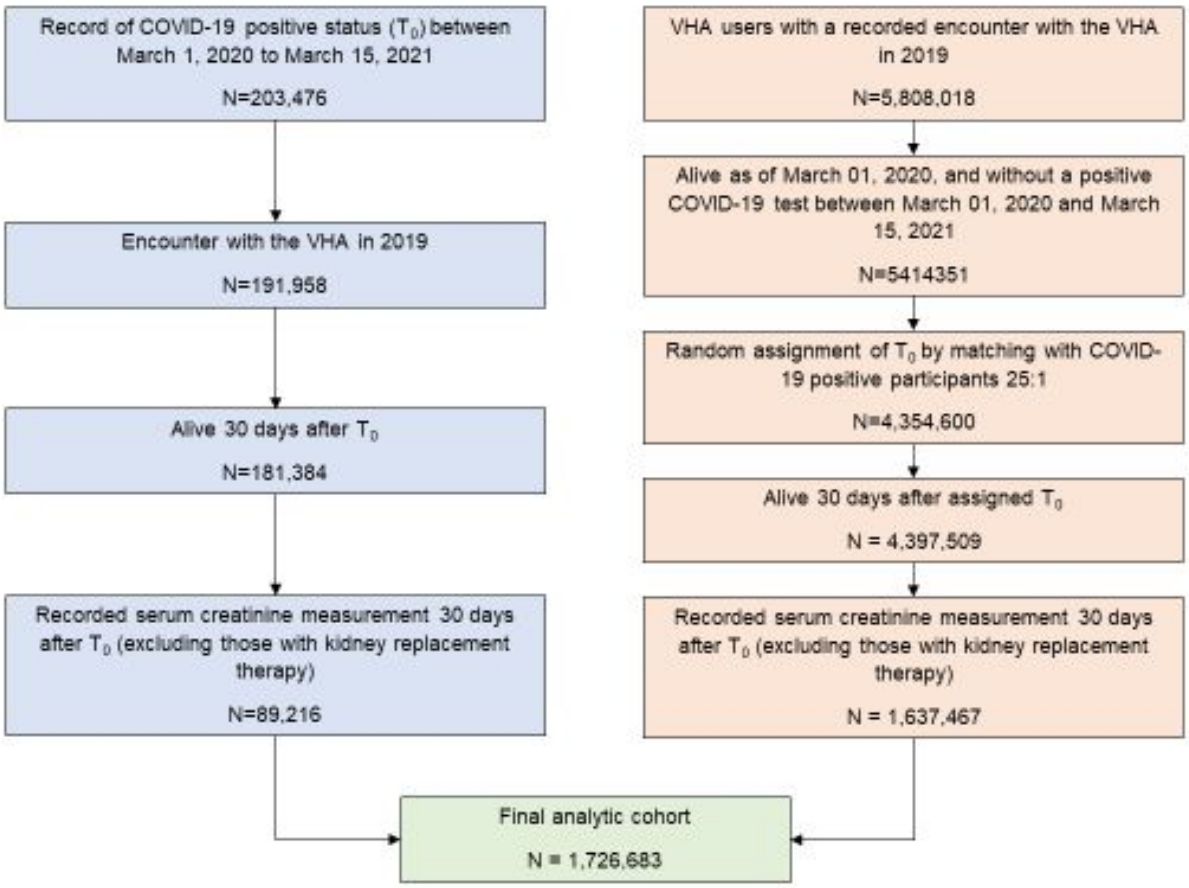
All models are adjusted for age, Area Deprivation Index, race, sex, smoking status, baseline eGFR, systolic and diastolic blood pressure, body mass index, and history of cancer, cardiovascular disease, cerebrovascular disease, chronic lung disease, dementia, diabetes mellitus type 2, peripheral artery disease, angiotensin converting enzyme inhibitors /angiotensin II receptor blockers, antibiotics, anticoagulants, antivirals, aspirin, beta-blockers, chemotherapeutic agents, diuretics, immunosuppressants, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, residence at a long-term care facility, and the number of eGFR measurements in the year prior to T_0, as well as 100 high dimensional variables.

[a]Burden estimated at 6 months following a COVID-19 positive test

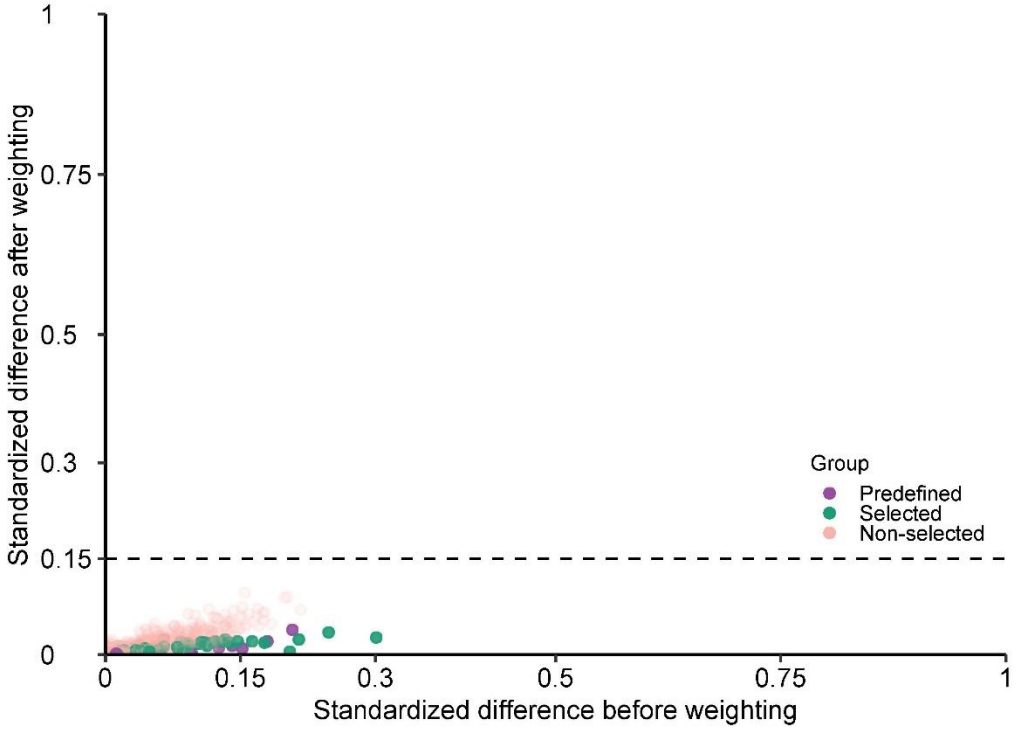
HR, hazard ratio; CI, confidence interval

Supplemental Figures

Supplemental Figure 1: Cohort flow chart

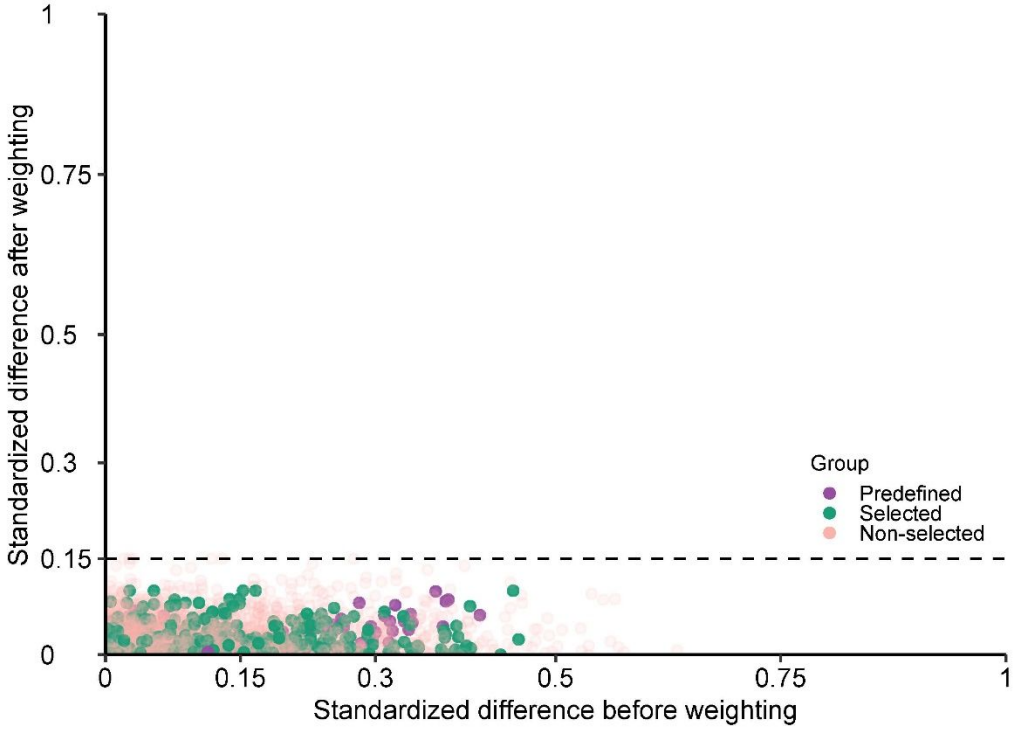


Supplemental Figure 2: Covariate balance in the comparison of COVID-19 positive Veterans with VHA users.



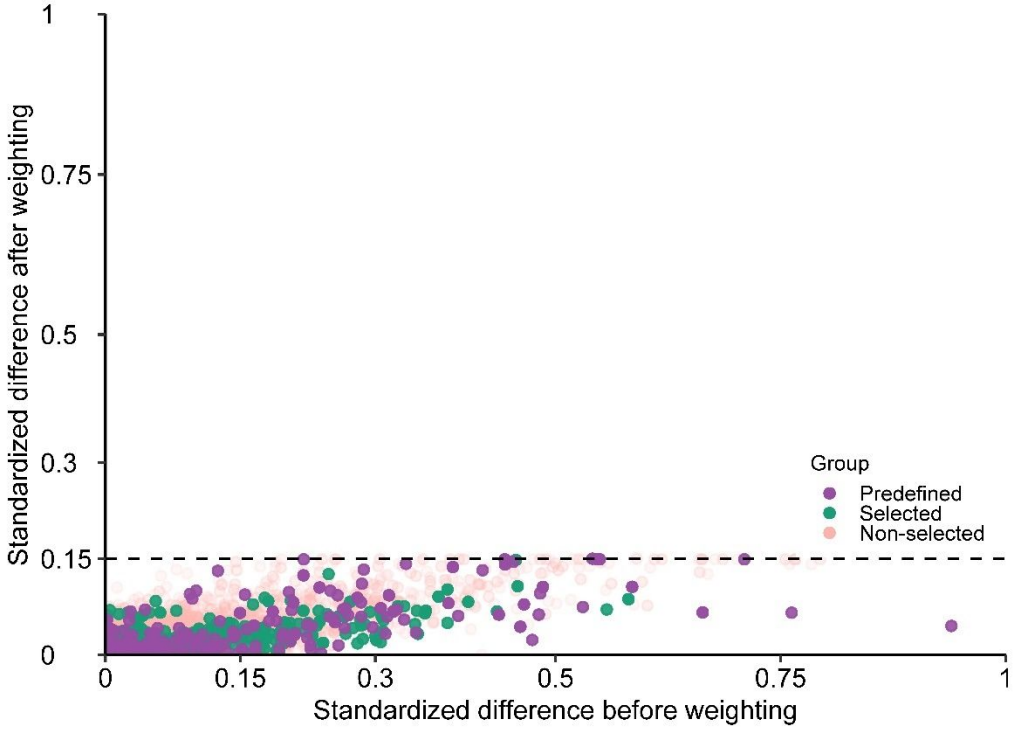
Standardized differences before and after inverse probability of treatment weighting are plotted, where a standardized difference less than 0.15 (reference line) was taken as evidence of covariate balance. Standardized differences are colored to denote if covariates examined were: 1) 30 predefined; 2) 100 selected by the high dimensional variable section (HDVS) algorithm; or 3) 734 tested as potential covariates, but were not selected by the HDVS algorithm.

Supplemental Figure 3: Covariate balance in the comparison of COVID-19 positive Veterans by severity of the acute infection with VHA users.



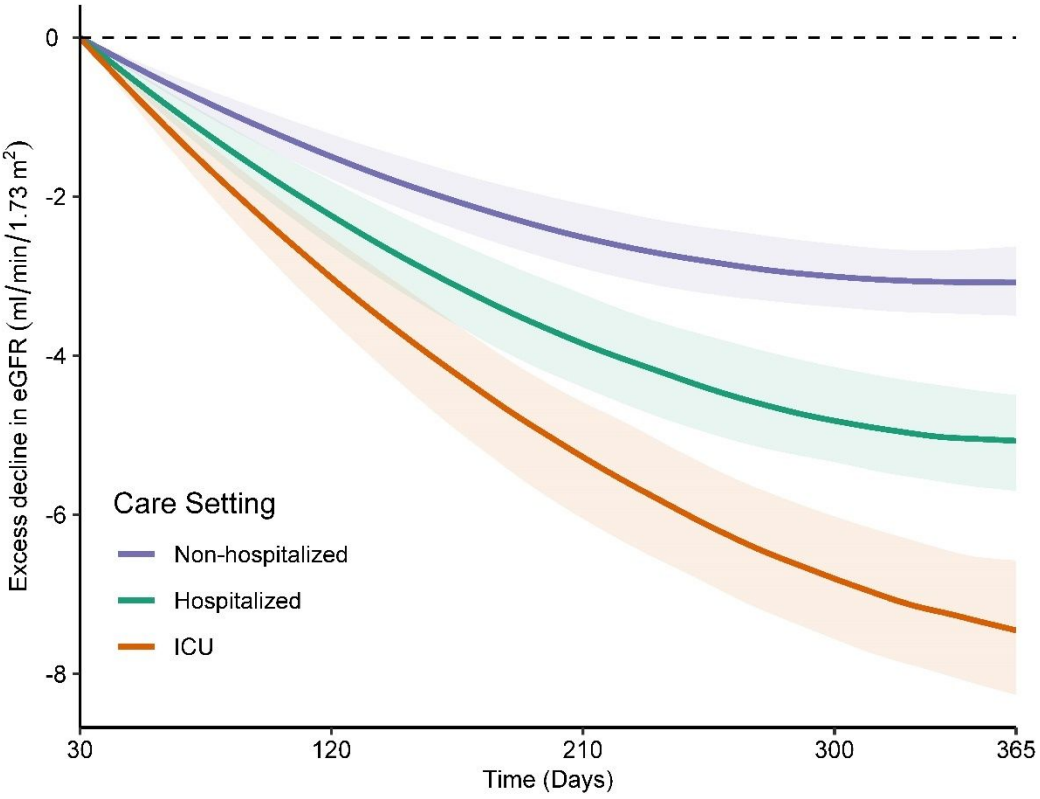
Standardized differences before and after inverse probability of treatment weighting are plotted, where a standardized difference less than 0.15 (reference line) was taken as evidence of covariate balance. Standardized differences are colored to denote if covariates examined were: 1) 30 predefined; 2) 100 selected by the high dimensional variable section (HDVS) algorithm; or 3) 734 tested as potential covariates, but were not selected by the HDVS algorithm.

Supplemental Figure 4: Covariate balance in the comparisons of COVID-19 positive Veterans by AKI status during the acute phase of care with VHA users.



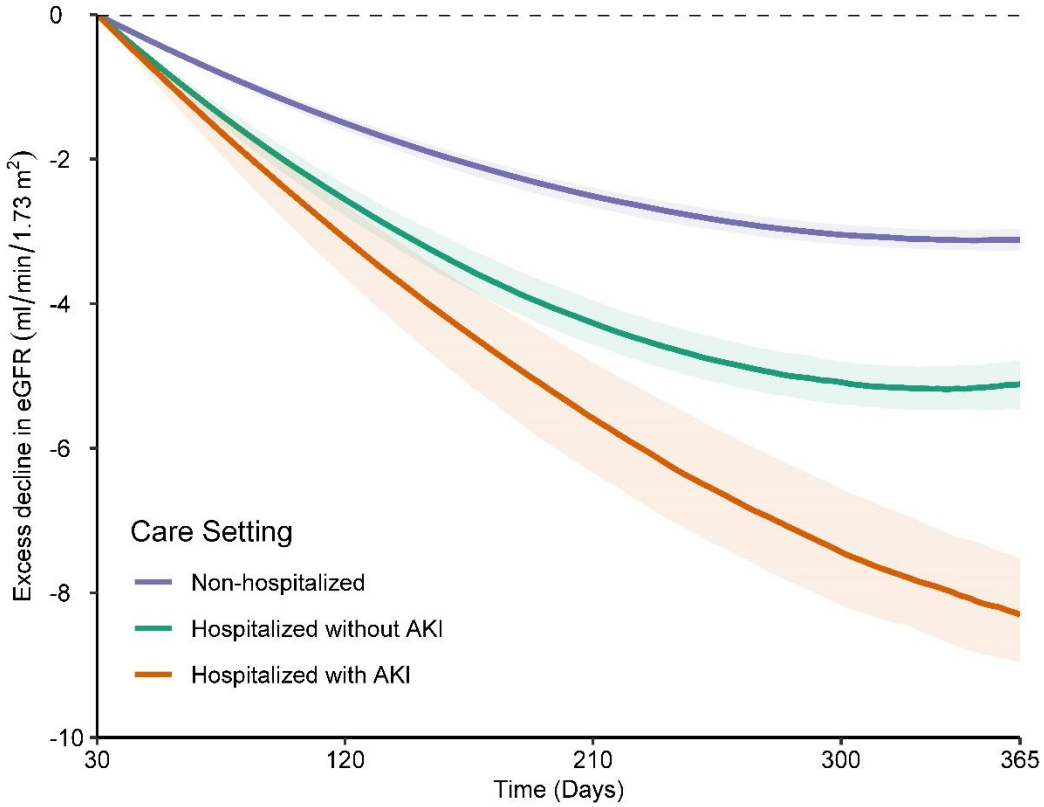
Standardized differences before and after inverse probability of treatment weighting are plotted, where a standardized difference less than 0.15 (reference line) was taken as evidence of covariate balance. Standardized differences are colored to denote if covariates examined were: 1) 30 predefined; 2) 100 selected by the high dimensional variable section (HDVS) algorithm; or 3) 734 tested as potential covariates, but were not selected by the HDVS algorithm.

Supplemental Figure 5:



Excess decline in eGFR in post-acute COVID-19 adjusting for predefined covariates. Differences in the trajectory of eGFR by day of follow-up compared to users of the Veteran Health Administration healthcare system with no record of a positive COVID-19 test (control group), estimated after adjustment for baseline characteristics. Changes are estimated starting from 30 days after a COVID-19 positive test. Bands represent the 95% CI.

Supplemental Figure 6:



Excess decline in eGFR in post-acute COVID-19 by AKI status during the acute phase of the illness adjusting for only predefined covariates. Differences in the trajectory of eGFR by day of follow-up compared to users of the Veteran Health Administration healthcare system with no record of a positive COVID-19 test (control group), estimated after adjustment for baseline characteristics. Changes are estimated starting from 30 days after a COVID-19 positive test. Bands represent the 95% CI.