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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT440 |
| **Submission Date** | 1/11/2022 |
| **Project Title** | Multi-Center Description, Validation and Outcomes of Acute Kidney Injury Phenotypes during Coronavirus-19 Disease Hospitalizations |
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| **Sites Participating** | 1. Geisinger Health: 3 investigators
2. Massachusetts General Hospital: 2 investigators
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| **Background / Significance** | Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has been responsible for an ongoing global pandemic of coronavirus disease 2019 (COVID-19), resulting in significant morbidity and mortality 1. Acute Kidney Injury (AKI) is a common association of COVID-19 hospitalizations, with global prevalence around 12% 2. In a national cohort of hospitalized US veterans, 32% had AKI, and almost half of them did not recover to baseline serum creatinine by discharge. COVID-19 associated AKI was also associated with a higher risk of death and other poor outcomes 3. When COVID-19-associated AKI patients hospitalized in a New York City health system were compared with historical hospitalized AKI patients, they were found to have a 5-fold higher risk ratio of requiring dialysis and lower chances of renal recovery by discharge 4. Analyses pre-dating the SARS-CoV-2 pandemic show that long-term consequences of AKI in hospitalized patients include up to 40% re-hospitalization, up to 30% recurrent AKI, and similar increase in adverse kidney events like death, decrease in estimated glomerular filtration rate (EGFR), and end-stage kidney disease (ESKD) 5. In a high-dimensional characterization of post-acute sequelae of COVID-19 in US veterans, the 6-month excess burden was 4 per 1000 for AKI and 25 per 1000 for CKD among participants hospitalized for COVID-196. However, this analysis was performed using International Classification of Diseases, Tenth Revision (ICD-10) codes. This approach has been shown to have significant limitations. In a cohort of more than 500,000 hospitalized patients, ICD-10 coding had a sensitivity of only 25 to 35% in identifying biochemically defined AKI. Moreover, the positive predictive value was also poor, and varied from 45% to 76% 7. The Kidney Disease: Improving Global Outcomes (KDIGO) AKI definitions are well validated and near- universally accepted 8. CKD as a pre-existing co-morbid condition is reported in close to 10% of COVID-19 hospitalizations, and multiple associated phenotypes have been associated with high risk of COVID-19 hospitalization 2 9. Both AKI and CKD are intimately interconnected, and patients with one of these entities is predisposed to develop the other 10. Simple, pragmatic phenotypes of CKD have been validated for use in electronic database research 11. In this multi-center study, we will validate various CKD and AKI phenotypes by manual chart review and used these to describe intermediate-term outcomes after COVID-19 hospitalizations.REFERENCESREFERENCES1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-534.2. Singh J, Malik P, Patel N, et al. Kidney disease and COVID-19 disease severity-systematic review and meta-analysis. Clin Exp Med. 2021. 3. 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. Clin J Am Soc Nephrol. 2020;16(1):14-25. 4. Fisher M, Neugarten J, Bellin E, et al. AKI in Hospitalized Patients with and without COVID-19: A Comparison Study. J Am Soc Nephrol. 2020;31(9):2145-2157. 5. Gameiro J, Marques F, Lopes JA. Long-term consequences of acute kidney injury: a narrative review. Clin Kidney J. 2021;14(3):789-804..6. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021. 7. Logan R, Davey P, De Souza N, Baird D, Guthrie B, Bell S. Assessing the accuracy of ICD-10 coding for measuring rates of and mortality from acute kidney injury and the impact of electronic alerts: an observational cohort study. Clin Kidney J. 2020;13(6):1083-1090. 8. Joyce EL, DeAlmeida DR, Fuhrman DY, Priyanka P, Kellum JA. eResearch in acute kidney injury: a primer for electronic health record research. Nephrology, dialysis, transplantation. 2019;34(3):401-407. 9. Oetjens MT, Luo JZ, Chang A, et al. Electronic health record analysis identifies kidney disease as the leading risk factor for hospitalization in confirmed COVID-19 patients. PLoS One. 2020;15(11):e0242182.10. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58-66. 11. Norton JM, Ali K, Jurkovitz CT, et al. Development and Validation of a Pragmatic Electronic Phenotype for CKD. Clin J Am Soc Nephrol. 2019;14(9):1306-1314. |
| **Outline of Project** | **Methodology:**1. Pull admissions between April 1, 2020 and September 30, 2021
2. Exclude patients with ESKD or kidney transplant (see below for detailed description). Record how many patients were excluded for each.
3. Define COVID as: ICD code U07.1 (billing/diagnosis/hospital problem list) AND Positive COVID PCR within 14 days before or 7 days after admission
4. Classify patients as COVID index admission Yes or no. If a patient had any admission which met the above definition of COVID, that admission counts as an index COVID admission. For patients who didn’t have any COVID admissions during the year, the first admission counts as the index admission.
5. Data from readmissions will not be analyzed for further analysis. Each patient will have either 1 COVID index admission or 1 non-COVID index admission.
6. Create dialysis and CRRT variables:

Dialysis: codes during admissionICD-9 code: 39.95ICD-10 code: 5A1D70Z: Performance of Urinary Filtration, Intermittent, Less than 6 Hours Per DayCRRT: ICD-10 codes during admission5A1D80Z: Performance of Urinary Filtration, Prolonged Intermittent, 6-18 hours Per Day5A1D90Z: Performance of Urinary Filtration, Continuous, Greater than 18 hours Per Day1. Create variable baseline creatinine (see detailed table 1 below) and pull data.
2. Pull highest creatinine for index admission and create variables AKI, and AKI stages 1, 2, and 3. See detailed algorithm below.
3. Create variables: Baseline proteinuria: see below
4. Create variable: Last f/u proteinuria: see below
5. Extract data for problem list diagnoses of hypertension, diabetes, coronary artery disease (CAD), congestive heart failure (CHF). Using ICD codes are fine.
6. Extract admission BMI: either from system values or =Weight (in kg)/ ((Height in meters)^2)
7. Extract other admission variables and mortality data as described in excel spreadsheet
8. Create variable AKI ICD code. This will not be used to define any AKI but demonstrates the futility of using ICD codes to define AKI as many groups have done. This variable will be “yes” for any index admissions with the following ICD codes:

N17.0: Acute kidney failure with tubular necrosisN17.1: Acute kidney failure with cortical necrosisN17.2: Acute kidney failure with medullary necrosisN17.8: Other acute kidney failureN17.9: Acute Kidney Injury, unspecifiedN99.0: Postprocedural kidney failure1. All creatinine values can be converted to eGFR by using the following equation:

eGFR = 142 X min(Scr/k,1)α X max(Scr/k,1)-1.2 X 0.9938age X 1.012 [if female]where Scr is serum creatinine,k is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 11. Please double check and note that the different creatinine values being extracted are: baseline (algorithm), peak creatinine during admission, discharge creatinine, close to 90-day post discharge creatinine, last follow-up creatinine.
2. Please double check and note that the different proteinuria values being extracted are: baseline proteinuria(algorithm), and last follow-up proteinuria (algorithm).
3. Check for patients who met the aforementioned definition for ESKD after discharge and label them as such
4. Pull mortality data post-discharge and cite source: electronic medical record or social security death index or other.

**EXCLUSION CRITERIA****ESKD**: Existence of any of these ever before admission:1. **USRDS label for ESKD/ ESRD (if available)**
2. **Any of these CPT codes:**

36818 – 36820 Arteriovenous anastomosis, open…36821, 36831 Thrombectomy, open, arteriovenous fistula…36832, 36833 Revision, open, arteriovenous fistula…90940 Hemodialysis access flow study to determine blood flow…90951 – 90962 ESRD related services monthly…90963 – 90966 ESRD related services for home dialysis per full month…90967 – 90970 ESRD related services for dialysis less than a full month…90989, 90993 Dialysis training, patient, including helper…G0257 Unscheduled or emergency dialysis treatment for an ESRD…G9231 Documentation of ESRD, dialysis, renal transplant…S9339 Home therapy; peritoneal dialysis, administrative…36147 Introduction of needle and/or catheter, arteriovenous shunt created for dialysis…90918 – 90921 ESRD related services per full month…90925 ESRD related services (less than full month)…G0308 – G0319 ESRD related services during the course of treatment…G0320 – G0323 ESRD related services for home dialysis patients per full month…G0324 – G0327 ESRD related services for home dialysis (less than full month)…G0392, G0393 Transluminal balloon angioplasty, percutaneous; for maintenance of hemodialysis access… 1. **Any of these ICD codes**:

ICD-9 Codes:39.27 Arteriovenostomy for renal dialysis39.42 Revision of arteriovenous shunt for renal dialysis39.53 Repair of arteriovenous fistula39.54 Re-entry operation (aorta)585.6 End stage renal diseaseV45.11 Renal dialysis statusV45.12 Noncompliance with renal dialysisV56.1 Fitting and adjustment of extracorporeal dialysis catheterV56.2 Fitting and adjustment of peritoneal dialysis catheterV56.31 Encounter for adequacy testing for hemodialysisV56.32 Encounter for adequacy testing for peritoneal dialysisV56.8 Encounter for other dialysisV45.1 Postprocedural; renal dialysis statusICD-10 Codes:N18.6 End stage renal diseaseZ91.15 Patient’s noncompliance with renal dialysisN18.5 + Z99.2 Dependence on renal dialysis**Kidney transplant:** Existence of any of these at any point prior to admission:1. **USRDS label for ESKD/ ESRD/ transplant (if available)**
2. **Any of these CPT codes:**

00868 Anesthesia for extraperitoneal procedures in lower abdomen, including urinary tract; renal transplant (recipient) (units: 10)50340 Recipient nephrectomy (separate procedure)50360, 50365 Renal allotransplantation; implantation of graft…50380 Renal autotransplantation, reimplantation of kidneyS2065 Simultaneous pancreas kidney transplantationG9231 Documentation of ESRD, dialysis, renal transplant1. **Any of these ICD codes**:

ICD-9 Codes00.91 Transplant from live related donor…00.92 Transplant from live non-related donor…00.93 Transplant from cadaver…55.53 Removal of transplanted or rejected kidney55.69 Other kidney transplantationV42.0 Transplant; kidneyICD-10 Codes0TY\*\*\*\* Surgical or Medical / Urinary System / Transplantation / KidneyZ94.0 Kidney transplant status**BASELINE CREATININE**Initial look-back period: 7-365 days before index admissionTable 1: Hierarchy for reference creatinine calculation

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| --- | --- | --- |
|  | Creatinine values available prior to admission | Reference creatinine |
| Preference 1 | 3 or more outpatient values available in 7- 365 days prior to admission (PTA) | Mean of all outpatient creatinine values |
| Preference 2 | 2 outpatient values available in 7- 365 days PTA + some prior inpatient values | Mean of 2 outpatient values and lowest inpatient creatinine from prior admissions |
| Preference 3 | 1 or fewer outpatient creatinine values in 7- 365 days PTA but more outpatient values available within 18 months PTA | Mean of any outpatient creatinine values available in 18 months prior to admission |
| Preference 4 | No outpatient creatinine values in 18 months PTA but patient had prior inpatient admissions | Mean of 3 lowest inpatient creatinine values over the past 18 months |
| Preference 5 | No prior inpatient or outpatient creatinine available  | If no dialysis/CRRT: lowest creatinine during admissionIf needed dialysis/CRRT: Creatinine at admission  |

**BASELINE PROTEINURIA DETERMINATION**

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|  | Proteinuria values available prior to admission | Reference proteinuria |
| Preference 1 | Urine albumin creatinine ratio (UACR) values available in 7- 365 days prior to admission (PTA) | Use most recent UACR in mg/g |
| Preference 2 | No albumin creatinine ratios available but protein creatinine ratio (UPCR) available in 7- 365 days PTA | Convert most recent UPCR value to UACR in mg/g  |
| Preference 3 | Neither UACR nor UPCR available in 7-365 days PTA but available in 7 d to 18 months PTA | Most recent UACR or UPCR converted to UACR |
| Preference 4 | No UACR or UPCR in 18 months PTA but >2 dipstick or urinalyses available in 7-365 days prior to admission | Convert up to 3 most recent urinalyses protein values to UACR and use mean value in mg/g |
| Preference 5 | Only 1 dipstick or urinalysis available in 7-365 days prior to admission | Convert to UACR and use value in mg/g |

**UPCR conversion to UACR:**UACR = exp (5.3920 + 0.3072×log (min (UPCR/50, 1)) + 1.5793×log (max(min(UPCR/500, 1) , 0.1)) + 1.1266×log (max (UPCR/500, 1)))**Dipstick/Urinalysis conversion to UACR:**Dipstick or urinalysis results are usually negative, Trace, + (or 1+), ++ (or 2+), +++ (or 3+) and so on.If negative, UACR value 0 otherwise,UACR = exp (2.4738 + 0.7539×(if trace) + 1.7243×(if +) + 3.3475×(if ++) + 4.6399×(if >++))**LAST FOLLOW-UP PROTEINURIA DETERMINATION**

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|  | Proteinuria values available prior to admission | Reference proteinuria |
| Preference 1 | Urine albumin creatinine ratio (UACR) values available post discharge? | Use most recent UACR in mg/g |
| Preference 2 | No albumin creatinine ratios available but protein creatinine ratio (UPCR) available post discharge | Convert most recent UPCR value to UACR in mg/g  |
| Preference 3 | No UACR or UPCR post discharge but >2 dipstick or urinalyses available  | Convert up to 3 most recent urinalyses protein values to UACR and use mean value in mg/g |
| Preference 4 | Only 1 dipstick or urinalysis available post discharge | Convert to UACR and use value in mg/g |

**Evaluate outcomes per the following:** |
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| **Prior status** |  | AKI in COVID |
|  | Stage 1 | Stage 2 | Stage 3 | RRT no USRDS | RRT with outpt USRDS |
| Non proteinuric/ unknown | eGFR>=60 |  |  |  |  |  |
| eGFR <60, >30 |  |  |  |  |  |
| eGFR <30 |  |  |  |  |  |
| Unknown |  |  |  |  |  |
| Proteinuric<3 gm | eGFR>=60 |  |  |  |  |  |
| eGFR <60, >30 |  |  |  |  |  |
| eGFR <30 |  |  |  |  |  |
| Unknown |  |  |  |  |  |
| Nephrotic rangeProteinuric | eGFR>=60 |  |  |  |  |  |
| eGFR <60, >30 |  |  |  |  |  |
| eGFR <30 |  |  |  |  |  |
| Unknown |  |  |  |  |  |

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| **Prior status** |  | 3-9 month follow-up (last 2 creatinines) |
|  | Full reco very | eGFR loss <25% | eGFR loss 25-50% | eGFR loss >50% | ESRD |
| Non proteinuric/ unknown | eGFR>=60 |  |  |  |  |  |
| eGFR <60, >30 |  |  |  |  |  |
| eGFR <30 |  |  |  |  |  |
| Unknown |  |  |  |  |  |
| Proteinuric<3 gm | eGFR>=60 |  |  |  |  |  |
| eGFR <60, >30 |  |  |  |  |  |
| eGFR <30 |  |  |  |  |  |
| Unknown |  |  |  |  |  |
| Nephrotic rangeProteinuric | eGFR>=60 |  |  |  |  |  |
| eGFR <60, >30 |  |  |  |  |  |
| eGFR <30 |  |  |  |  |  |
| Unknown |  |  |  |  |  |

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| **Prior status** |  | 3-9 month follow-up (last 2 urines) |
|  | No proteinuria/ unknown | <3 gm | Nephrotic range |
| Non proteinuric/ unknown | eGFR>=60 |  |  |  |
| eGFR <60, >30 |  |  |  |
| eGFR <30 |  |  |  |
| Unknown |  |  |  |
| Proteinuric<3 gm | eGFR>=60 |  |  |  |
| eGFR <60, >30 |  |  |  |
| eGFR <30 |  |  |  |
| Unknown |  |  |  |
| Nephrotic rangeProteinuric | eGFR>=60 |  |  |  |
| eGFR <60, >30 |  |  |  |
| eGFR <30 |  |  |  |
| Unknown |  |  |  |

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| **Desired Data - Common Variables\*** *(Available from the CC)* | [ ] Demographics [ ] ICD9/10 codes[ ] CPT codes[ ] Phecodes[ ] BMI |
| **Other Desired Data *(Available from participating sites)*** | *Please specifically list out any data elements that participating sites would collect or extract from clinical or other sources for this project (i.e. not common variables above)*  | [ ] Common Variable Labs[ ] Common Variable Meds☐ Geocoding 2015 ACS variables[ ] Other: Case/Control status  |
| **Desired Genetic Data** | [ ] eMERGE I-III Merged set (HRC imputed, GWAS)[ ] eMERGE PGx/PGRNseq data set [ ] eMERGEseq data set (Phase III)[ ] eMERGE Whole Genome sequencing data set[ ] eMERGE Exome chip data set[ ] eMERGE Whole Exome sequencing data set[ ] Other (not listed above): |
| **Does project pertain to an existing eMERGE Phenotype?** | [ ] Yes, if so please list [x] No |
| **Planned Statistical Analyses** |  |
| **Ethical Considerations** |  |
| **Available Funding or Resources** |  |
| **Target Journal** | JAMA/ JAMA Network Open/ JASN |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | July 1, 2021: Determine site specific chart review plan/ initial data pullJuly 15,2021: Discuss issues with initial chart reviewAug 1, 2021: Deadline to submit chart reviewsAugust 15, 2021: Data analysis |
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**\*Common Variables available across all datasets:**

* Demographics: sex, year of birth, decade of birth, race, ethnicity
* Codes: (repeated values & age at event): ICD, CPT, Phecodes
* BMI: (repeated value & age at event) height, weight, BMI
* Labs: (lab name, repeated lab value & age at event) Serum total cholesterol, LDL, HDL, Triglycerides, Glucose fasting/non-fasting/unknown, & White Blood Cell count
* Medications: (medication name, repeated, & age at event) Cerivastatin sodium, Rosuvastatin, Simvastatin, Fluvastatin, Pravastatin, Lovastatin, Atorvastatin, & Pitavastatin
* Other: Case/Control status on Phase I and Phase II phenotype: only on GWAS dataset participants