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| **eMERGE Network: Manuscript Concept Sheet** | | |
| **Reference Number**  *(to be assigned by CC)* | NT446 | |
| **Submission Date** | 3/31/22 | |
| **Project Title** | Computed Algorithms for Multicentric Assessment of Myocardial Injury Subtypes in Acute COVID-19 | |
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| **Background / Significance** | **Myocardial injury and COVID-19**  Myocardial injury is common in patients hospitalized with COVID-191. Myocardial injury is defined by the Fourth Universal Definition of Myocardial Infarction2 as detection of a cardiac troponin measurement above the 99th percentile of upper normal limit; the injury is considered acute if there is a significant increase or decrease on repeat measurement. Among COVID-19 patients, an elevated troponin level is more likely in patients with a history of chronic cardiac diseases and in patients with more severe COVID-193. Multiple studies have demonstrated associations between myocardial injury in COVID-19 and worse short-term outcomes including a 5-fold increase in requiring invasive mechanical ventilation and an 11-fold increase in mortality compared to those without elevated troponin levels4-13. This highlights the need for early identification of such high-risk individuals, thus allowing for closer monitoring and earlier intervention where possible.  Myocardial injury can be seen with multiple cardiovascular conditions including acute myocardial infarction, myocarditis, pericarditis, stress cardiomyopathy, pulmonary embolism, and acute heart failure3. However, noncardiac conditions including severe respiratory involvement with hypoxia, acute or chronic renal failure, critical illness with systemic inflammation, and sepsis can also result in elevated troponin level3,14. It has been noted that in COVID-19, mild elevation (2-3 times the upper normal limit) in cardiac troponin level can be the result of acute stress due to COVID-191. Thus, it is important to determine the etiology of elevated troponin levels to risk-stratify for cardiovascular complications.  **Electronic health records (EHR)-based algorithms:**  Simplistic EHR-based algorithms use one or more International Classification of Diseases (ICD) diagnosis codes for the definition of cardiovascular diseases. However, the accuracy of these to identify high-risk patients is poor15. Sometimes patients who do not meet the definition of cardiovascular diseases are labeled with these codes – i.e. a patient with only a mild aortic ectasia may be labeled as an abdominal aortic aneurysm. Other times, ICD codes cannot differentiate cardiovascular diseases from other conditions – i.e. the ICD-9 code 433.1 (occlusion and stenosis of carotid artery) is widely used for those with mild atherosclerosis of carotid arteries and cannot differentiate these cases from obstructive carotid artery stenosis. The presence of an ICD code also has poor accuracy for determining whether a diagnosis is acute or chronic.  EHR-based algorithms using other EHR-derived data (i.e. CPT/ICD procedure codes, laboratory values, etc.) in addition to ICD-codes have been used previously with acceptable accuracy for identifying individuals with a high risk for a chronic certain phenotype, such as familial hypercholesterolemia16, abdominal aortic aneurysm17, and peripheral artery disease18. These algorithms help monitor for mid-term and long-term outcomes and could be part of an automated clinical decision support tool to flag high-risk individuals. Here, we propose the development of EHR-based algorithms to identify the underlying subtype of myocardial injury in patients with acute COVID-19. Our experience shows that using such algorithms are useful and accurate in detecting cardiovascular traits. Specifically, we propose algorithms for 5 myocardial injury subtypes, including stress cardiomyopathy, myocarditis, pericarditis, acute pulmonary embolism, and acute myocardial infarction. These subtypes are associated with elevated cardiac troponin measurements and adverse outcomes in patients with COVID-19 based on the previous studies. Challenges are anticipated with creating the algorithms to focus on only acute phenotypes occurring is temporal relationship to the acute COVID-19 infection.  We also propose to assess the short-term outcomes of these cohorts including need for intensive care unit (ICU) level of care, length of index hospitalization, 30-day re-hospitalization rate, and 30-day mortality rate. Once established, these cohorts can also be followed in the future to re-assess mid-term and long-term outcomes, as well as to compare outcomes of patients infected during various temporal waves of COVID-19 with different characteristics – i.e. Delta variant vs Omicron variant.    **Myocardial injury subtypes in acute COVID-19:**   1. *Stress Cardiomyopathy*   Stress cardiomyopathy, also called Takotsubo cardiomyopathy, is a type of acute, usually reversible, ventricular dysfunction that is brought about by an emotional or physical stressor. Classically this occurs more frequently is elderly women. Cardiac imaging typically shows a left ventricular apical ballooning pattern, although other subtypes exist. Obstructive coronary artery disease needs to be ruled out for the diagnosis to be made19. Many case reports exist for COVID related stress cardiomyopathy that have been reviewed by Moady *et al.*20 A few larger series have been reported in the literature which showed chest pain and ECG changes being present in a minority of cases and with mortality rates ranging from 19-57%21-24. For classical stress cardiomyopathy the InterTAK diagnostic score has been useful but this has not been examined in COVID cases25, therefore we will examine this within the COVID cohort. We built our approach to clinically define stress cardiomyopathy based on the Modified Mayo Clinic Diagnostic Criteria for stress cardiomyopathy26:  1. Left ventricular regional wall motion abnormalities (hypokinesis, akinesis, or dyskinesis) that are typically transient (<21 days) and typically extend beyond the distribution of a single coronary artery.  2. The absence of angiographic evidence of obstructive coronary artery disease or plaque rupture which is responsible for the respective wall motion abnormality.  3. Modestly increased troponin values or ECG abnormalities.  4. Exclude myocarditis and pheochromocytoma.\*  \*Pheochromocytomas are extremely rare and we did not include this requirement in our algorithm.   1. *Myocarditis*   Myocarditis is inflammation of the muscular tissue of the heart; this can lead to temporary or permanent ventricular dysfunction and scarring of the cardiac parenchyma. The gold standard for myocarditis diagnosis is an endomyocardial biopsy which is seldom performed in acute COVID-19. Cardiac MRI has good diagnostic yield, but this is also relatively infrequently performed during acute COVID-19, although it is becoming more frequently utilized shortly after the acute phase and these MRI results have been recently reviewed27. Additionally, a review of autopsy results showing myocarditis in COVID-19 patients who succumbed to the disease has been published28. Together these studies suggest that clinically relevant myocarditis is less frequent than was initially feared in the early alarming reports. One large EHR-based retrospective cohort study29 of 718,365 COVID-19 patients in the TriNetX network found that 5% developed new-onset myocarditis with a 6-month all-cause mortality of 3.9% compared to 2.9% of matched COVID-19 patients without myocarditis. However, the presence of Myocarditis was based purely on the presence of ICD codes, which is often inaccurate, and there is no mention of chart review to validate their phenotype.  Due to diagnostic limitations, clinical criteria for suspected myocarditis need to be employed. We utilized the criteria from the 2013 European Society of Cardiology position statement on clinically suspected myocarditis30. This includes either at least one clinical presentation and at least one diagnostic criteria, or at least 2 diagnostic criteria from the following list (in the absence of angiographically detectable obstructive coronary artery disease):  1. Clinical presentations  a. Acute chest pain, pericarditic, or pseudo-ischemic.  b. New-onset (days up to 3 months) or worsening of: dyspnea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs.  c. Subacute/chronic (>3 months) or worsening of: dyspnea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs.  d. Palpitations, and/or unexplained arrythmia symptoms and/or syncope, and/or aborted sudden cardiac death.  e. Unexplained cardiogenic shock.  2. Diagnostic criteria\*  a. Functional and structural abnormalities on cardiac imaging (echo/angiogram/cardiac MRI) including new, otherwise unexplained left and/or right ventricle structure and function abnormality, with or without ventricular dilatation, increased wall thickness, pericardial effusion, or endocavitary thrombi.  b. Tissue characterization by cardiac MRI including edema and/or late gadolinium enhancement of classical myocarditic pattern.  \*The published criteria also include elevated troponin which is moot since we are only examining cases with elevated troponin; they also include a criterion for electrocardiogram abnormalities that are extensive and would be very difficult to easily incorporate into the electronic algorithm.   1. *Pericarditis*   Pericarditis is inflammation of the pericardium, or sack around the heart. This can occur with or without elevated troponins, however, as we are assessing the cause of myocardial injury, we are only assessing the subset with elevated troponin values. Pericarditis can occur in isolation or in conjunction with myocarditis (myopericarditis). Myopericarditis behaves more like myocarditis, therefore we will focus on pericarditis in isolation and group myopericarditis with myocarditis.  In the previously mentioned TriNetX study29 on myocarditis, they also examined pericarditis, and found 1.5% prevalence of pericarditis in COVID-19 patients, but with a strikingly high mortality rate of 15.5% compared to 6.7% of matched controls. Pericarditis again was determined based purely on a few ICD codes and no mention is made of verifying the phenotype with manual chart review.  In our manual chart review, acute pericarditis is diagnosed when at least two of the following four criteria were present31:  1. Pericardial chest pain  2. Pericardial friction rub  3. Suggestive ECG changes (typically widespread ST-segment elevation, PR depression)  4. New or worsening pericardial effusion on imaging (typically echocardiogram)  \*Although some authors will use C-reactive protein levels, these are frequently high in acute COVID-19 and would be very non-specific for pericarditis in this population.   1. *Acute Pulmonary Embolism*   Acute pulmonary embolism occurs when a blood clot (thrombus) becomes lodged in the pulmonary arteries. This thrombus is typically formed in the deep venous system of the lower extremities and migrates to the pulmonary arteries. Due to the thrombogenic state in acute COVID-19, pulmonary emboli are frequently occurring complications. In one retrospective multicentric study32 of 1,240 hospitalized COVID-19 patients, 8.3% had pulmonary embolism confirmed by CT pulmonary angiography, the gold standard test for diagnosis. The need for ICU transfer (31.1% vs 13.5%) and mechanical ventilation (24.3% vs 7.3%) were significantly higher among these patients than COVID matched controls without pulmonary emboli. Another study33 of 224 hospitalized COVID-19 patients found 14% with pulmonary embolism by CT pulmonary angiography and this was associated with increased length of hospital stay (7 vs 3 days), higher mortality rate (50% vs 27%) and higher rates of cardiogenic shock (37% vs 14%).  Given that acute pulmonary embolism is a diagnosis on imaging, the largest obstacle in detecting acute event when using ICD codes has been old diagnoses being carried forward when someone had a previous pulmonary embolism unrelated to COVID-19; therefore, we will use an exclusion period prior to the COVID diagnosis where pulmonary embolism has been previously mentioned. Manual chart review consists simply of examining the CT imaging reports.     1. *Acute Myocardial Infarction:*   Acute myocardial infarction occurs when a coronary artery becomes acutely occluded, typically due to a ruptured atherothrombotic plaque causing thrombus formation. This is a frequent finding in COVID-19 patients, likely secondary to the altered inflammatory milieu. Acute myocardial infarction consists of ST-segment elevation myocardial infarction (STEMI) and non- ST-segment elevation myocardial infarction (NSTEMI). One study34 found that among COVID patients with a STEMI, 85.7% had the STEMI as the first symptoms of COVID-19.  Results of the international COVID-ACS registry35 revealed that COVID-19 patients had a prolonged symptom-to-admission time (339 min vs 173 min for STEMI and 417 min vs 295 min for NSTEMI) and higher in-hospital mortality (22.9% vs 5.7% in STEMI and 6.6% vs 1.2% in NSTEMI) in comparison to pre-COVID-19 myocardial infarction population.  In a retrospective cohort study36 consisting of 509 US centers in the Vizient clinical database, 76,434 out-of-hospital and 4,015 in-hospital STEMI patients were assessed. Among patients with out-of-hospital STEMI, the rate of in-hospital mortality was significantly higher in COVID-19 positive than COVID-19 negative patients (15% vs 11%). In-hospital mortality was also significantly higher in COVID-19 positive patients among the in-hospital STEMI patients (78.5% vs 46.1%).  Identifying acute myocardial infarction by ICD code is challenging since many old codes are carried forward in the chart, and the label “type 2 NSTEMI” or “demand ischemia” will often be given to patients simply because of an elevated troponin, when “acute myocardial injury” would be more appropriate because there is no evidence of ischemia. For chart review, we will utilize the definition for the Fourth Universal Definition of Myocardial Infarction2; in addition to an elevated troponin we require at least one of the following:  1. Symptoms of myocardial ischemia (ischemic pain or dyspnea, etc)  2. New ischemic ECG changes  3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities in a patterns consistent with an ischemic etiology  4. Identification of a coronary thrombus by angiography or autopsy  5. The development of new pathological Q waves on ECG  REFERENCES   1. Baigent C, Windecker S, Andreini D, Arbelo E, Barbato E, Bartorelli AL, et al. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1—epidemiology, pathophysiology, and diagnosis. Cardiovascular Research. 2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Journal of the American College of Cardiology. 2018;72(18):2231-64. 3. Sandoval Y, Januzzi JL, Jr., Jaffe AS. Cardiac Troponin for Assessment of Myocardial Injury in COVID-19: JACC Review Topic of the Week. J Am Coll Cardiol. 2020;76(10):1244-58. 4. Huang, C. et al. 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| **Outline of Project** | **Methodology:**  The population being examined are inpatients identified as having acute COVID-19 that have an elevated serum troponin level within the window period (3 days before and 30 days after the index COVID-19 diagnosis as determined by positive PCR swab. We will compare this to the definition developed by our eMERGE colleagues defining acute COVID-19 infection as the presence of an ICD code U07.1 and a positive COVID-19 PCR within 14 days before or 7 days after admission.  For each subtype of acute myocardial injury, the presence of a single ICD diagnosis code from a predefined list of codes (Table 1) within the window period qualified the patient as having a “possible” cardiovascular complication of the indicated phenotype. Chart review was then performed on a subset of “possible” cases within the Mayo Clinic enterprise database, and algorithms were iterated to optimize sensitivity and specificity (Table 1).   |  |  | | --- | --- | | **Table 1. Algorithms for myocardial injury subtypes from the Mayo Clinic Enterprise** | | | **Phenotype** | Algorithm\* | | **Stress cardiomyopathy** | a. At least 1 instance of ICD-10 code: I51.81  b. At least 1 instance of a troponin >2x ULN | | **Myocarditis** | a. At least 2 instances of ICD-10 codes on different dates: B33.2, B33.20, B33.22, B33.24, I40, I40.0, I40.1, I40.8, I40.9, I41, I51.4  b. At least 1 instance of a troponin >3x ULN  c. None of the ICD-10 codes within 30 days prior to window period  d. Not detected by stress cardiomyopathy algorithm | | **Pericarditis** | a. At least 2 instances of ICD-10 codes on different dates: I30, I30.0, I30.1, I30.8, I30.9, I31, I31.8, I31.9, I32, I33.23  b. At least 1 instance of a troponin >1x ULN  c. None of the ICD-10 codes within 120 days prior to the window period  d. Not detected by the myocarditis algorithm | | **Pulmonary embolism** | a. At least 1 instance of any of the ICD-10 diagnosis codes: I26, I26.0, I26.02, I26.09, I26.9, I26.92, I26.93, I26.94, I26.99  b. At least 1 instance of a troponin >1x ULN  c. None of the ICD-10 codes within 730 days (2 years) prior to the window period | | **Myocardial infarction** | a. At least 1 instance of CPT/ICD procedure code: extensive list, provided in chart review excel file  b. At least 1 instance of a troponin >1x ULN  OR  a. At least 1 instance of ICD-10 codes: I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8  b. At least 1 instance of a tronopin >3 ULN  c. No severe CKD ICD-10 codes: N18.4, N18.5, N18.6, I12.0, I13.11, I13.2  d. No Muscular Dystrophy ICD-10 codes: G71.0, G71.00, G71.01, G71.02, G71.09, G71.1, G71.11, G71.12, G71.13, G71.14, G71.19, G71.3  e. Not detected by the stress cardiomyopathy, myocarditis, pericarditis, or pulmonary embolism algorithms | | **\* Detection of ICD-10/CPT codes and troponin had to occur within the window period of -3 through +30 days from the first positive SARS-CoV-2 PCR test**  **CPT: current procedural terminology, CKD: chronic kidney disease, ICD-10 (Internation Classification of Diseases 10th edition)** | |   Specific data extraction forms will be sent to additional sites who will also perform validation chart review on a subset of “possible” patients. Based on performance at these additional sites the algorithms may then undergo additional iterations to further optimize performance among the diverse EHR datasets.  The final algorithms will then be sent to all participating sites to implement on their full datasets without the need for additional chart review, and the data will be pooled for analyses.  Step by step instructions:   1. **Data pull** 2. Pull admission between April 1, 2020 and October 31, 2021 with a positive COVID-19 PCR/NAAT test and/or a U07.1 ICD-10 diagnosis code 3. The index date will be listed as the date of the positive PCR test if one is available, if not it will be the date of the first U07.1 ICD code 4. Within the window period (3 days before or up to 30 days after the index date) pull all phenotype ICD/CPT codes (attached spreadsheet, 6th page) including the codes that will only be used for exclusion 5. Within the window period pull troponin values for these patients and exclude any patients without a troponin value greater than upper limit of normal for your test within the window period 6. Determine how many patients have at least one ICD/CPT code for each phenotype in addition to the elevated troponin (i.e. stress cardiomyopathy n=X, myocarditis n=X, etc) 7. **Chart review for validating site(s):** 8. An excel file is being provided to the validating site(s) that contains 6 pages: one for each of the 5 cardiovascular phenotypes, and one containing all ICD/CPT codes that should be extracted to determine inclusion/exclusion into one of the 5 cardiovascular phenotypes. 9. Specific instructions are as follows:  * Stress cardiomyopathy: Columns A-M contain data that can be directly pulled and entered. Columns N-V contain data that need to be manually abstracted by chart review. Column W is for any comments the abstractor wishes to enter. Column X contains the diagnostic criteria needed for the abstractor to determine the answer for column N. * Myocarditis: Columns A-N contain data that can be directly pulled and entered. Columns O-R contain data that need to be manually abstracted by chart review. Column S is for any comments the abstractor wishes to enter. Column T contains the diagnostic criteria needed for the abstractor to determine the answer for column O. * Pericarditis: Columns A-N contain data that can be directly pulled and entered. Columns O-P contain data that need to be manually abstracted by chart review. Column Q is for any comments the abstractor wishes to enter. Column R contains the diagnostic criteria needed for the abstractor to determine the answer for column O. * Acute pulmonary embolism: Columns A-M contain data that can be directly pulled and entered. Column N contains data that need to be manually abstracted by chart review. Column O is for any comments the abstractor wishes to enter. * Acute myocardial infarction: Columns A-S contain data that can be directly pulled and entered. Columns T-V contain data that need to be manually abstracted by chart review. Column W is for any comments the abstractor wishes to enter. Column X contains the diagnostic criteria needed for the abstractor to determine the answer for column T-U.  1. The phenotypes and number of charts to be reviewed per phenotype can be determined on the institutional level depending on manpower/bandwidth to perform chart review. Several of the phenotypes are likely to only have a limited number of “possible” charts to review (stress cardiomyopathy, myocarditis, pericarditis) and it may be possible to review all charts for these phenotypes, while others are likely to have many charts (acute pulmonary embolism and acute myocardial infarction) and only reviewing a limited number would be sufficient (perhaps as many as 50 per phenotype, although any chart review, even at a smaller number, will be helpful). 2. For the stress cardiomyopathy phenotype, this includes gathering information to compare the commonly used InterTAK diagnostic score compared to the algorithm’s identification of stress cardiomyopathy. 3. The completed (deidentified data) excel sheets for each participating site will then be returned to the Mayo Clinic team for data analysis and final iterations of the algorithms. 4. **Algorithm implementation and analysis** 5. Once the final iterations of the algorithms are complete, pseudocode and/or R code will be distributed to all participating sites (including those that are interested that could not contribute to the chart review). 6. These sites will implement the algorithms on their entire EHR datasets and will provide the deidentified results that can be combined between sites (data format will be provided in the supplied code). 7. A variety of outcomes will be assessed. These can be further determined by the group but will include at least the short-term outcomes of these cohorts including need for intensive care unit (ICU) level of care, length of index hospitalization, 30-day re-hospitalization rate, and 30-day mortality rate. Once established, these cohorts can also be followed in the future to re-assess mid-term and long-term outcomes. | |
| **Desired Data - Common Variables\***  *(Available from the CC)* | Demographics  ICD9/10 codes  CPT codes  Phecodes  BMI | Common Variable Labs  Common Variable Meds  ☐ Geocoding 2015 ACS variables  Other: Case/Control status |
| **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)* | |
| **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  No | |
| **Planned Statistical Analyses** |  | |
| **Ethical Considerations** |  | |
| **Available Funding or Resources** |  | |
| **Target Journal** | JAMA Cardiology | |
| **Milestones**  *(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | March 31, 2022: Determine validating site(s) specific chart review plan / initial data pull  April 15, 2022: Discuss issues with initial chart review  May 15, 2022: Deadline to submit chart reviews  June 15, 2022: Code for final algorithm iterations will be supplied to all participating sites  July 15, 2022: All data will be returned to the Mayo Clinic group  August 15, 2022: Data analysis and manuscript draft complete | |

**\*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