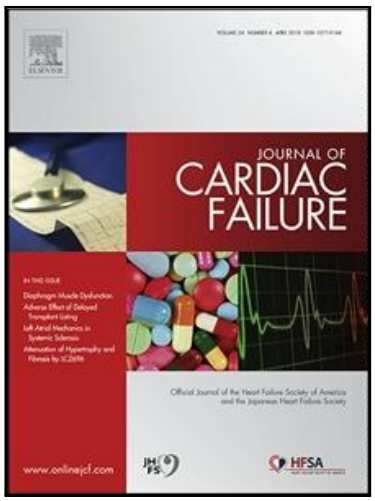

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Unique Patterns of Cardiovascular Involvement in COVID-19

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Key Words: Coronavirus Disease 2019, Acute COVID-19 Cardiovascular Syndrome

Non-standard Abbreviations and Acronyms:

ACovCS, Acute COVID-19 Cardiovascular Syndrome

ACE2, Angiotensin-Converting Enzyme 2

ADAM17, ADAM metallopeptidase domain 17

ARDS, Acute Respiratory Distress Syndrome

CAD, Coronary Artery Disease

COVID-19, Coronavirus Disease 2019

SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2

STEMI, ST-elevation myocardial infarction

TMPRSS2, Transmembrane Serine Protease 2

Coronavirus Disease 2019 (COVID-19) due to infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) remains a global pandemic. While COVID-19 was initially thought to be a disease largely characterized by respiratory disease and a fever, subsequent data have highlighted this clinical scope was too narrow. Indeed, the majority of individuals infected with SARS-CoV-2 may be asymptomatic, while others present with a variety of symptoms including cardiac, neurological, and hypercoagulable complications [1-4]. We recently have termed the broad spectrum of cardiovascular and thromboembolic complications the acute COVID-19 cardiovascular syndrome (ACovCS) [3]. These cardiac complications include acute coronary syndrome with obstructive coronary artery disease (CAD), acute myocardial injury with non-obstructive CAD, heart failure, cardiogenic shock, myocarditis, arrythmias, pericardial effusions, and cardiac tamponade, as well as thromboembolic complications such as stroke, pulmonary embolism, and deep vein thrombosis [3].

Recently, cardiac presentations of COVID-19 in the absence of significant pulmonary involvement have been described in case reports or case series (see Table 1). However, to our knowledge, a framework describing the variable presentations of cardiac involvement in COVID-19 within the broader spectrum of symptomatic SARS-CoV-2 infection has not been previously proposed. We attempt to fill this void by highlighting two patterns of cardiac presentations: the more common phenotype with cardiac involvement superimposed on top of the typical pulmonary predominate symptoms ("mixed pulmonary and cardiac"), or as an isolated or predominate cardiac presentation ("predominate cardiac"). Unquestionably there are patients where the distinctions between these patterns is blurred (e.g., a patient with STEMI who has mild pulmonary infiltrates); however, we believe this classification provides a useful framework for future research and therapeutic endeavors.

A contrast of the characteristics of the mixed pulmonary and cardiac versus predominate cardiac patterns is shown in Figure 1. First, the prevalence of mixed cardiopulmonary disease as assessed by elevated cardiac troponin levels, is variable, but occurs in 10-25% of patients hospitalized with COVID-19 [3, 4]. In contrast, the cardiac predominate phenotype appears to be much less common, likely well <5% of patients hospitalized with COVID-19 [5, 6]. Fever is a common manifestation of COVID-19 when there is typical pulmonary involvement but may be absent in the predominate cardiac phenotype. Both presentations can have elevated inflammatory and elevated cardiac biomarkers (e.g. cardiac troponin and natriuretic peptides); however, in the mixed presentations, the troponin is less likely to be severely elevated upon admission but can rise considerably during the hospitalization. In contrast, the troponin level with an isolated cardiac presentation can be absent or markedly elevated depending on the presentation (e.g., when presenting with a ST-elevation myocardial infarction or myocarditis). ACovCS with cardiac predominate disease may be more apparent at hospital presentation relative to mixed cardiopulmonary disease because the predominate cardiac manifestations (e.g. chest pain due to a myocardial infarction) often results in symptoms which lead patients to seek emergent care. In contrast, ACovCS superimposed on pulmonary disease is unpredictable and can occur at any time during hospital admission. Indeed, reports now suggest that this late complication can be seen in critically ill patients perhaps even after apparent respiratory stabilization [7]. Furthermore, in the minority of patients with COVID-19 who develop shock, patients with cardiac predominate disease would be anticipated to develop cardiogenic rather than distributive shock. In short, these two patterns of ACovCS presentation can be distinguished from each other by their associated clinical characteristics. We anticipate that future research will better characterize the differences in the disease course and outcomes between these two groups.

Just as there is variability in cardiac presentations of COVID-19, SARS-CoV-2 infection overall has a wide spectrum of disease penetrance with many patients displaying few to no symptoms, while an unfortunate minority develop severe life limiting disease. The basis of such disease variability, including why the cardiac system is involved in only a minority of patients, is entirely unknown at this juncture but there are some putative risk factors to consider (see Figure 2). SARS-CoV-2 is the seventh coronavirus known to infect humans and strongly binds to the Angiotensin-Converting Enzyme 2 (ACE2) receptor which is expressed by pericytes and cardiomyocytes [8]. Further analysis has determined that the receptor binding domain on the SARS-CoV-2 spike protein, the host ACE2 receptor and host cell transmembrane serine protease 2 (TMPRSS2) are all essential for host cell infection [3, 8]. In addition, the host cell ADAM metallopeptidase domain 17 (ADAM17) participates in ACE2 receptor cleavage from the cell membrane leading to release into the circulation [9]. Cleaved ACE2 has the potential to influence clotting cascades and feedback to the renin-angiotensin system which may impact vascular, cardiac and renal pathophysiology [4]. As such, it is reasonable to speculate that genetic variations within the host, whether that be the ACE2 receptor, TMPRSS2, or ADAM17, may influence variability of presentation clinical presentations, the prevalence of ACovCS and COVID-19 clinical outcomes. Whether such genetic differences contribute to the disparities in COVID-19 outcomes between races is unknown. Finally, rare genetic mutations that lead to familial cardiomyopathy may predispose a subset of patients to developing fulminant myocarditis in the setting of a COVID-19 infection, a so-called 'two-hit hypothesis'. Support for this possibility comes from prior observations in children of an association of certain genetic mutations with an increased risk for developing acquired myocarditis in the setting of acute viral infections [10].

Whether or not a two-hit hypothesis contributes to the rarely described cases of biopsy-proven fulminant COVID-19 myocarditis is also unknown.

Other factors which may influence the variable presentation of COVID-19 include mutations in the circulating SARS-CoV-2 virus though it remains uncertain whether such observations explain the regional differences in the outcomes of COVID-19. Likewise, antecedent patient characteristics including age, race, gender, and comorbid health conditions, particularly diabetes, chronic lung disease, and cardiovascular diseases such as hypertension, CAD, heart failure may impact disease severity and penetrance not only through baseline risk but also potentially through differential ACE2 tissue expression. Additionally, the powerful influences of lower socioeconomic status and unfavorable environmental factors likely contribute to racial COVID-19 health disparities [11]. Other factors that may influence disease variability in the overall population include a history of smoking, e-cigarette use, illicit drug use, the route of infection (inhaled versus direct mucosal contact), viral inoculation dose, healthcare delivery systems, and host immune status among others. Urgent investigation is needed to understand the basis of this variability of disease progression, including those that predispose to cardiac involvement. We suspect that gaining such knowledge may also provide insights into the pathophysiology and progression of cardiomyopathy and heart failure that extends beyond COVID-19.

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Works Cited:

1. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S and Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. *Radiology*. 2020:201187.
2. Bendavid E, Mulaney B, Sood N, Shah S, Ling E, Bromley-Dulfano R, Lai C, Weissberg Z, Saavedra R, Tedrow J, Tversky D, Bogan A, Kupiec T, Eichner D, Gupta R, Ioannidis J and Bhattacharya J. COVID-19 Antibody Seroprevalence in Santa Clara County, California. *medRxiv*. 2020:2020.04.14.20062463.
3. Hendren NS, Drazner MH, Bozkurt B and Cooper LT, Jr. Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome. *Circulation*. 2020.
4. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G and Winterton D. Elevated Troponin in Patients With Coronavirus Disease 2019: Possible Mechanisms. *J Card Fail*. 2020.
5. Ruan Q, Yang K, Wang W, Jiang L and Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020.
6. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N and Hochman JS. ST-Segment Elevation in Patients with Covid-19 - A Case Series. *N Engl J Med*. 2020.
7. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, Kritek PA, West TE, Luks A, Gerbino A, Dale CR, Goldman JD, O'Mahony S and Mikacenic C. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med*. 2020.
8. Andersen KG, Rambaut A, Lipkin WI, Holmes EC and Garry RF. The proximal origin of SARS-CoV-2. *Nat Med*. 2020;26:450-452.
9. Heurich A, Hofmann-Winkler H, Gierer S, Liepold T, Jahn O and Pohlmann S. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. *J Virol*. 2014;88:1293-307.
10. Belkaya S, Kontorovich AR, Byun M, Mulero-Navarro S, Bajolle F, Cobat A, Josowitz R, Itan Y, Quint R, Lorenzo L, Boucherit S, Stoven C, Di Filippo S, Abel L, Zhang SY, Bonnet D, Gelb BD and Casanova JL. Autosomal Recessive Cardiomyopathy Presenting as Acute Myocarditis. *J Am Coll Cardiol*. 2017;69:1653-1665.
11. Haynes N, Cooper LA, Albert MA and Association of Black C. At the Heart of the Matter: Unmasking and Addressing COVID-19's Toll on Diverse Populations. *Circulation*. 2020.
12. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D and Gavazzi E. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiology*. .
13. Fried JA, Ramasubbu K, Bhatt R, Topkara VK, Clerkin KJ, Horn E, Rabbani L, Brodie D, Jain SS and Kirtane A. The Variety of Cardiovascular Presentations of COVID-19. *Circulation*. 2020.
14. Paul JF, Charles P, Richaud C, Caussin C and Diakov C. Myocarditis revealing COVID-19 infection in a young patient. *Eur Heart J Cardiovasc Imaging*. 2020.
15. Stefanini GG, Montorfano M, Trabattoni D, Andreini D, Ferrante G, Ancona M, Metra M, Curello S, Maffeo D, Pero G, Cacucci M, Assanelli E, Bellini B, Russo F, Ielasi A, Tespili M, Danzi GB, Vandoni P, Bollati M, Barbieri L, Oreglia J, Lettieri C, Cremonesi A, Carugo S,

Reimers B, Condorelli G and Chieffo A. ST-Elevation Myocardial Infarction in Patients with COVID-19: Clinical and Angiographic Outcomes. *Circulation*. 2020.
16. Meyer P, Degrauwe S, Delden CV, Ghadri JR and Templin C. Typical takotsubo syndrome triggered by SARS-CoV-2 infection. *Eur Heart J*. 2020.
17. Dabbagh MF, Aurora L, D'Souza P, Weinmann AJ, Bhargava P and Basir MB. Cardiac Tamponade Secondary to COVID-19. *JACC Case Rep*. 2020.
18. Hua A, O'Gallagher K, Sado D and Byrne J. Life-threatening cardiac tamponade complicating myo-pericarditis in COVID-19. *European Heart Journal*. 2020.

Figures.

Figure 1.

Title: Spectrum of Symptomatic COVID-19 Clinical Presentations

Caption: Spectrum of pulmonary, cardiac and non-cardiopulmonary disease for hospitalized patients within the spectrum of the acute COVID-19 cardiovascular syndrome (ACovCS). Notably asymptomatic SARS-CoV-2 infection may represent that greatest prevalence of infected patients; however, the majority of symptomatic patients have respiratory symptoms without cardiac involvement. Predominate cardiac syndromes in patients hospitalized with COVID-19 represent a less common clinical phenotype while patients with mixed pulmonary and cardiac disease represent a phenotypic overlap with multiorgan injury which occurs in a sizable minority of hospitalized patients. ACovCS encompasses cardiac manifestations and myocardial injury for both cardiac predominate and mixed disease. Non-cardiopulmonary predominate disease represents a variety of other presentations such as altered mental status (neurological), isolated deep vein thrombosis (hypercoagulable), diarrhea (gastrointestinal), and rash (dermatologic).

Abbreviations: ACS, acute coronary syndrome; ACovCS, acute COVID-19 cardiovascular syndrome; AMI, acute myocardial injury; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; COVID-19, Coronavirus Disease 2019; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PE, pulmonary embolism; STEMI, ST-elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

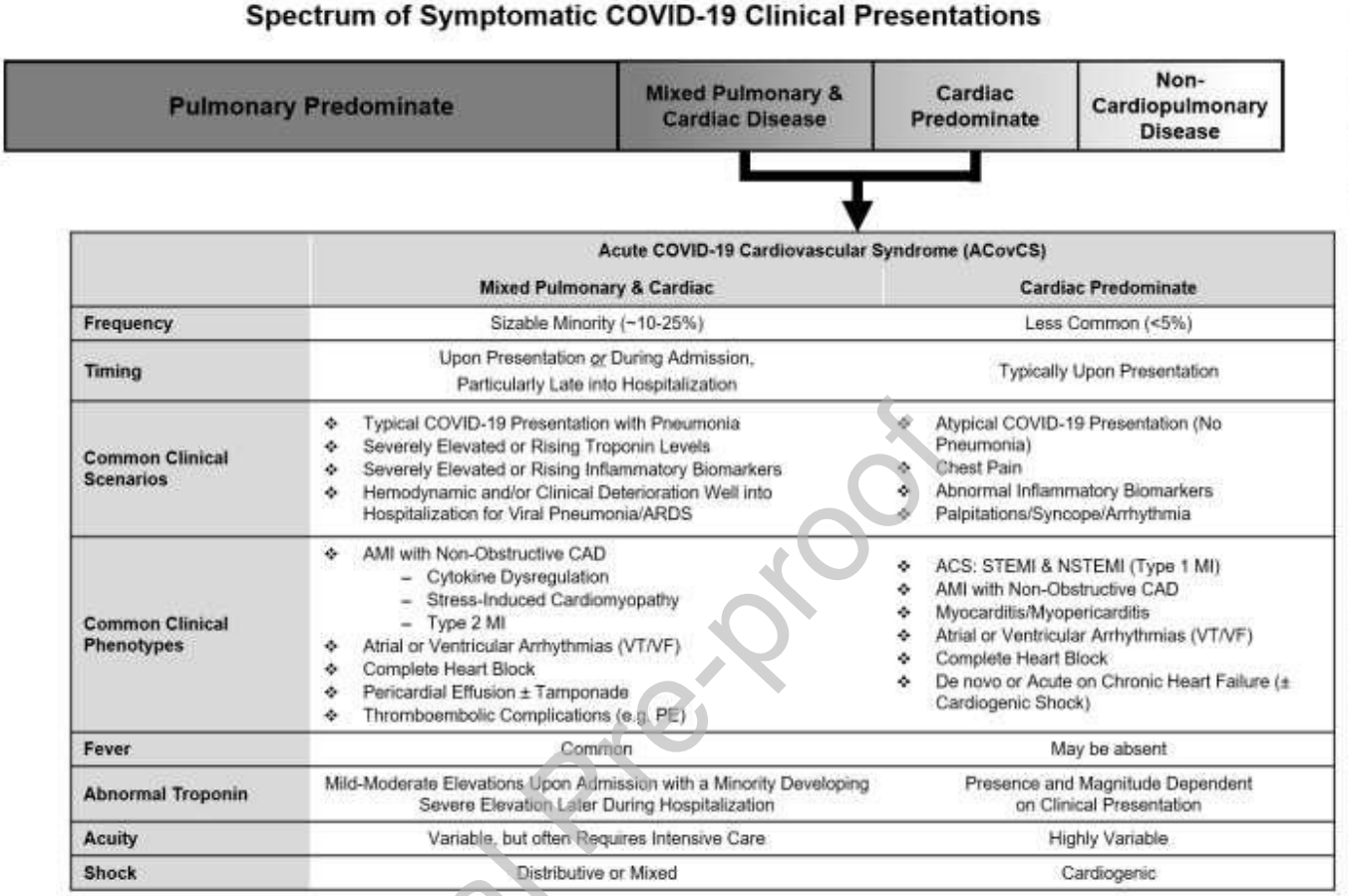
Figure 2.

Title: Potential Factors Influencing the Variability of COVID-19 Disease

Caption: Factors influencing SARS-CoV-2 infection penetrance and disease course remain unclear. Several factors are hypothesized to influence the clinical phenotype and illness severity of COVID-19 including the presence of a co-infection, environmental factors, host factors, host genetics and viral factors among others.

Abbreviations: ACE2, Angiotensin-Converting Enzyme 2; ADAM17, ADAM metallopeptidase domain 17; COVID-19, Coronavirus Disease 2019; CV, cardiovascular; SARS-CoV-2, ICU, Intensive Care Unit; Severe Acute Respiratory Syndrome Coronavirus-2; TMPRSS2, Transmembrane Serine Protease 2.

Figure 1.



	Acute COVID-19 Cardiovascular Syndrome (ACovCS)	
	Mixed Pulmonary & Cardiac	**Cardiac Predominate**
Frequency	Sizable Minority (~10-25%)	Less Common (<5%)
Timing	Upon Presentation or During Admission, Particularly Late into Hospitalization	Typically Upon Presentation
Common Clinical Scenarios	❖ Typical COVID-19 Presentation with Pneumonia ❖ Severely Elevated or Rising Troponin Levels ❖ Severely Elevated or Rising Inflammatory Biomarkers ❖ Hemodynamic and/or Clinical Deterioration Well into Hospitalization for Viral Pneumonia/ARDS	❖ Atypical COVID-19 Presentation (No Pneumonia) ❖ Chest Pain ❖ Abnormal Inflammatory Biomarkers ❖ Palpitations/Syncope/Arrhythmia
Common Clinical Phenotypes	❖ AMI with Non-Obstructive CAD – Cytokine Dysregulation – Stress-Induced Cardiomyopathy – Type 2 MI ❖ Atrial or Ventricular Arrhythmias (VT/VF) ❖ Complete Heart Block ❖ Pericardial Effusion ± Tamponade ❖ Thromboembolic Complications (e.g. PE)	❖ ACS: STEMI & NSTEMI (Type 1 MI) ❖ AMI with Non-Obstructive CAD ❖ Myocarditis/Myopericarditis ❖ Atrial or Ventricular Arrhythmias (VT/VF) ❖ Complete Heart Block ❖ De novo or Acute on Chronic Heart Failure (± Cardiogenic Shock)
Fever	Common	May be absent
Abnormal Troponin	Mild-Moderate Elevations Upon Admission with a Minority Developing Severe Elevation Later During Hospitalization	Presence and Magnitude Dependent on Clinical Presentation
Acuity	Variable, but often Requires Intensive Care	Highly Variable
Shock	Distributive or Mixed	Cardiogenic

Figure 2.

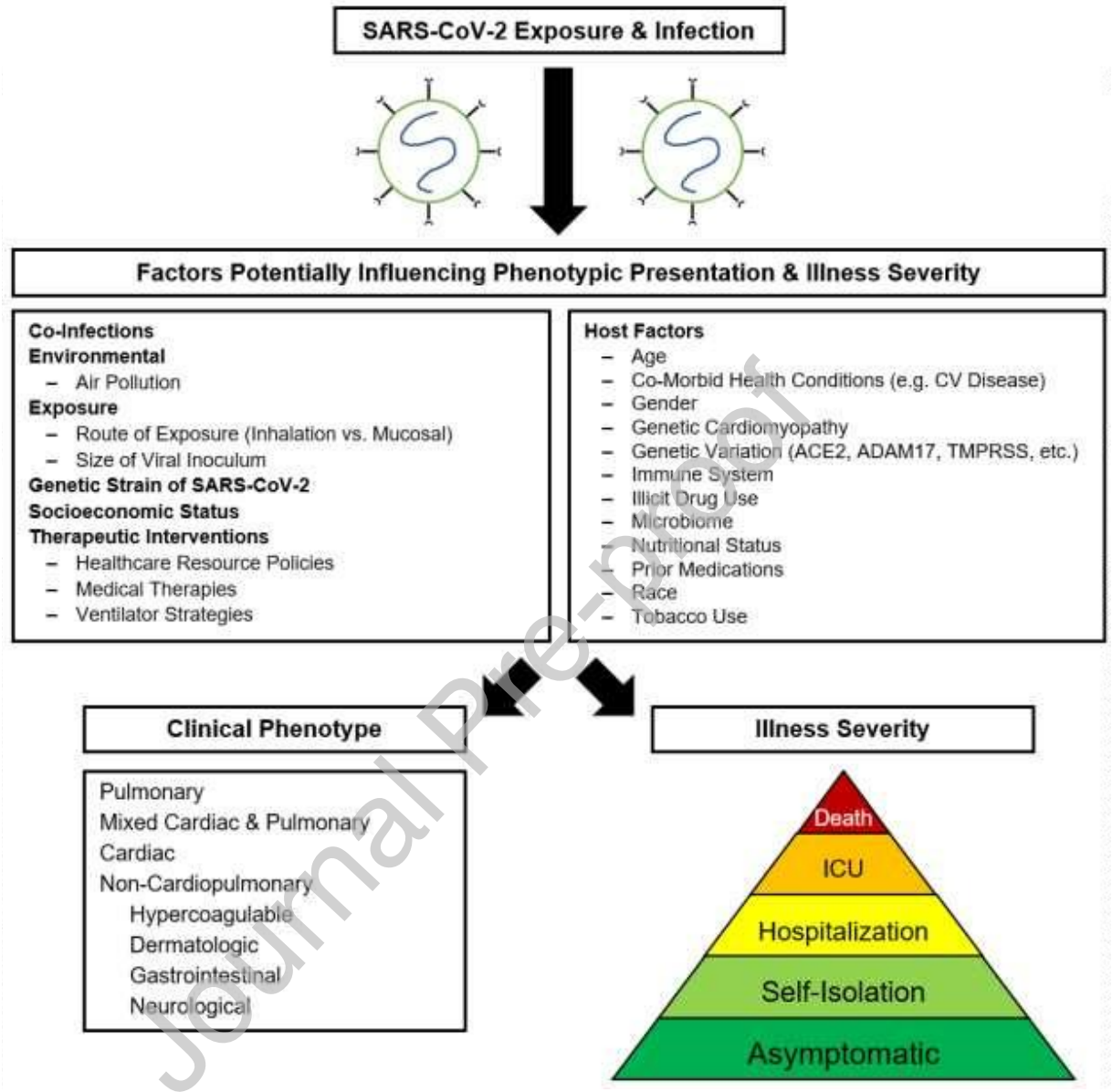


Table 1. Cardiac Predominate Presentations in COVID-19

Phenotype	Reference	Finding
Myocarditis	Inciardi et al, JAMA Cardiology, 2020.[12]	Case Report: 53-year-old with Acute Myopericarditis and Normal Chest X-ray.
Myocarditis	Fried et al, Circulation, 2020.[13]	Case Report: 64-year-old with Fulminant Myocarditis and Normal Chest X-ray.
Myocarditis	Paul et al, EHJ Cardiovascular Imaging, 2020.[14]	Case Report: 35-year-old with Acute Myocarditis and a Normal Chest CT scan.
STEMI	Bangalore et al, NEJM, 2020.[6]	Case Series: 17% of STEMI Cases (n=3) with Normal Chest X-ray.
STEMI	Stefanini et al, Circulation, 2020.[15]	Case Series: First Clinical Manifestation of COVID-19 was STEMI (n=24/28, 86%).
Stress Cardiomyopathy	Meyer et al, EHJ, 2020.[16]	Case Report: 83-year-old with Takotsubo Cardiomyopathy and Normal Chest X-ray.
Tamponade	Dabbagh et al, JACC CR, 2020.[17]	Case Report: 67-year-old with Tamponade and Chest X-ray without Infiltrate.
Tamponade	Hua et al, EHJ, 2020.[18]	Case Report: 47-year-old with Tamponade and Mild Pulmonary Congestion on Chest X-ray.
Abbreviations: CT, computed tomography; EHJ, European Heart Journal; JACC CR; Journal of the American College of Cardiology Case Reports; JAMA, Journal of the American Medical Association; NEJM, New England Journal of Medicine; STEMI, ST-elevation myocardial infarction.		