American Journal of Preventive Cardiology 7 (2021) 100197

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/the-american-journal-of-preventive-cardiology

COVID-19 associated risks of myocardial infarction in persons with familial hypercholesterolemia with or without ASCVD

Kelly D. Myers[a,b,*], Katherine Wilemon[a], Mary P. McGowan[a,c], William Howard[b], David Staszak[b], Daniel J. Rader[a,d]

[a] The FH Foundation, 110 Chelton Circle, Winter Park, FL, 32789, United States
[b] Atomo, Inc. 108 Wild Basin, Suite 250, West Lake Hills, TX, 78746, United States
[c] Division of Cardiology, Department of Medicine Dartmouth Hitchcock Medical Center, NH, Lebanon
[d] Department of Genetics, Perelman School of Medicine at the University of Pennsylvania, 11-125 Smilow Center for Translational Research, 3400 Civic Center Blvd, Philadelphia, PA, 19104-5158, United States

Cardiovascular disease (CVD), hypertension, and heart failure are associated with higher rates of coronavirus disease 2019 (COVID-19) related morbidity and mortality [1,2]. However, studies have documented fewer individuals presenting to hospitals with acute myocardial infarction (AMI) during the pandemic [3,4]. To better understand the impact of COVID-19 on AMI rates in individuals with pre-existing atherosclerotic cardiovascular disease (ASCVD), familial hypercholesterolemia (FH), or both, the FH Foundation performed an analysis in a large longitudinal national database.

Data secured from Symphony Health (Blue Bell, PA) consisted of laboratory data and diagnostic, procedural, and prescription claims covering May 1, 2012 through June 30, 2020 (n = 301,628,074 individuals). This dataset includes all available healthcare encounter data on individuals who are being evaluated or treated for CVD. While the dataset spans 8 years, coverage for each unique individual does not necessarily span the full window. All data were anonymized thus neither informed consent nor IRB approval was necessary. Patients in the study were limited to those ≥18 years old, with valid demographic data (age/sex), and with at least one record within both the 'covariates window' and the 'exposure window' ('covariates window': dates prior to the COVID-19 'exposure window', March 1 – June 30). Individuals who qualified (n = 55,441,462) were further divided into six study groups by combinations of the presence or lack of comorbidities within the covariates window: diagnosed ASCVD, diagnosed FH, probable FH (identified by the FIND FH® machine learning model [5] since 90% of Americans with FH have yet to be diagnosed [6]), or none of the above (**Table 1**). Each individual is included in only one of the six groups.

We analyzed rates of AMI in all six groups by history of COVID-19 status. Individuals with COVID-19 were identified by the U07.1 ICD-10 code within the exposure window. For individuals with a COVID-19 diagnosis, days of risk in the study started counting 14 days prior to first date of U07.1 coding, reflecting CDC guidance on the average time between exposure and diagnosis. For individuals without a COVID-19 diagnosis, days of risk in the study started counting on March 1, 2020.

Within each group, we accounted for baseline differences between those individuals who did and did not contract COVID-19 in the exposure window by using propensity scoring (PS)-matching. Variables considered in PS-matching included demographic data (age, sex, household income, education level, and ethnicity), documented history of cardiac conditions (acute ischemic heart disease, cardiac arrest, coronary artery bypass graft, MI, and percutaneous coronary intervention), comorbidities (diabetes mellitus, hypertension, and ischemic stroke), cholesterol-lowering prescriptions (statin, ezetimibe, and PCSK9i claims), and selected laboratory test results (total cholesterol, low-density lipoprotein cholesterol, and lipoprotein (a)). We performed case-controlled matching without replacement using the MatchIt library [7] within the R statistical language (version 3.5.2) and balanced groups on both the number of patients with a given condition in the covariates window and the length of time the condition persisted in the patient's record. All individuals were followed through the data until they reached the end of the study period, experienced an AMI, or were lost to follow-up. Identification of AMI in the data was judged by an algorithm previously published [8], whereby incidents of acute MI are distinguished from follow-up coding from a prior MI.

We found that AMI rates and Annualized Incidence Density Rates (AIDRs) were significantly increased in those diagnosed with COVID-19 as compared with matched individuals who did not contract COVID-19 in all six groups, including the largest group with no ASCVD and no FH (**Table 1**). Across the study groups with a COVID-19 diagnosis, we found that rates of AMI were higher in the presence of diagnosed FH, probable FH, and ASCVD. Additionally, patients with a history of ASCVD and diagnosed with COVID-19 had a significantly higher rate of AMI when compared to the population with COVID-19 but without ASCVD or FH (AMI rate +1.05%, Cl 95%; 0.99–1.11, p-value <0.0002). Importantly, the addition of probable FH to pre-existing ASCVD represented a critical additive risk factor over ASCVD-alone, +0.70% (Cl 95%; 0.25–1.16, p-value: <0.0002), leading to the highest AMI rates in COVID-19 vs matched non-COVID-19 individuals.

* Corresponding author.
E-mail address: km@thefhfoundation.org (K.D. Myers).

https://doi.org/10.1016/j.ajpc.2021.100197
Received 21 March 2021; Received in revised form 13 May 2021; Accepted 15 May 2021

Table 1
AMI rates (March 1 – June 30, 2020) and AIDR are shown for both unmatched and 1:1 or 5:1 PS-matched cohorts. 5:1 matching was used in lower statistics groups. (FH – Familial Hypercholesterolemia, AMI – Acute Myocardial Infarction, ASCVD – Atherosclerotic Cardiovascular Disease, AIDR - Annualized Incidence Density Rates.).

	Unmatched Cohorts				1:1 or 5:1 Matched Cohorts						
Cohort	Num. Patients (COVID / No-COVID)	AMI Incidence (COVID)	AMI Incidence (No COVID)	p-value	Num. Matched (COVID / No-COVID)	AMI Incidence (COVID)	AMI Incidence (No COVID)	p-value	AIDR (COVID)	AIDR (No-COVID)	p-value
National Database - No ASCVD and No FH (Probable or Diagnosed FH)	447,192/41,956,785	0.34%	0.11%	<0.0002	204,962 / 204,962	0.33%	0.11%	<0.0002	3.1%	0.4%	<0.0002
Diagnosed FH	1216/121,396	0.41%	0.12%	0.003	1213/6006	0.41%	0.08%	0.005	3.2%	0.30%	<0.0002
Probable FH	3369/334,724	0.50%	0.12%	<0.0002	3366/16,806	0.51%	0.08%	<0.0002	4.3%	0.30%	<0.0002
ASCVD	176,946/12,051,757	1.40%	0.46%	<0.0002	169,923 / 169,923	1.38%	0.50%	<0.0002	10.7%	1.8%	<0.0002
Diagnosed FH and ASCVD	1399/89,396	1.57%	0.56%	<0.0002	1395/6916	1.58%	0.65%	0.0004	11.3%	2.3%	<0.0002
Probable FH and ASCVD	3833/253,449	2.09%	0.50%	<0.0002	3829/19,087	2.09%	0.59%	<0.0002	15.4%	2.1%	<0.0002

This analysis has several limitations and caveats. While the data contains records for a sizable fraction of Americans, we did not have access to a complete medical history. It is thus possible that history of ASCVD and/or FH was missed for some of the individuals, blurring the statistical differences between the groups. Similarly, the assignment of an individual into a COVID bucket is based solely on the presence of an ICD-10 diagnosis code and so may miss asymptomatic and untested individuals. Additionally, the process of PS-matching cannot account for unmeasured covariates (such as obesity, which is sparsely and poorly coded in the EHR) and so may introduce some bias related to unseen and unmeasured data. To account for this, we matched for an extensive range of lab tests, therapies, demographics, diagnosis, and procedural data, including nearly all major comorbidities directly relevant to population with cardiovascular related conditions. Finally, we were unable to answer a practical question, namely, did lipid lowering therapies (LLT) have a protective or deleterious effect on outcomes for those with FH in the COVID and No-COVID groups? Our analyses lacked statistical power for two main reasons. First, LLT rates were high in the matched groups that include diagnosed or probable FH patients (ranging from 63% to 83% of patients on one or more therapy). This was positive news for those patients but meant that a statistical comparison of event rates between individuals with and without LLT for the smallest groups in the analysis was difficult as the untreated population was small. Second, we found that patients with a history of LLT are generally also those patients with more recorded cardiac problems and comorbidities. To disentangle these competing effects of LLT therapy and higher severity individuals, we divided each of the main study groups into sub-groups containing those with a history of any LLT and those without LLT. We then PS-matched the sub-groups to directly measure the effect of LLT. Unfortunately, we found that the statistical comparisons between LLT and no-LLT was directional, but not significant.

Our analyses confirm that pre-existing ASCVD is associated with increased risk of AMI in the setting of COVID-19. Additionally, we establish that both diagnosed and probable FH are associated with increased risk for AMI in the setting of COVID-19. Critically, our data indicate that those with both ASCVD and FH are at very high risk of AMI if they contract COVID-19. Our results suggest that individuals with ASCVD and known FH should receive a COVID-19 vaccination when offered and demonstrate another reason for making greater efforts to identify and diagnose individuals with probable undiagnosed FH.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Kelly D Myers: Conceptualization, Methodology, Writing – original draft

Katherine Wilemon: Conceptualization, Writing – review & editing

Mary P McGowan: Conceptualization, Writing – review & editing

William Howard: Data curation, Software, Writing – review & editing

David Staszak: Formal analysis, Software, Methodology, Writing – original draft

Daniel J Rader: Methodology, Writing – review & editing

Author disclosures

KW, MPM, and DJR have no disclosures to report. KW and MPM are employees of the FH Foundation and DJR is an unpaid advisor. KDM, WH, and DS are paid consultants for the FH Foundation.

Funding

This analysis was funded by The FH Foundation.

References

[1] Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 Mar 27.

[2] Choudhary R, Mathur R, Sharma JB, Sanghvi S, Deora S, Kaushik A. Impact of Covid-19 outbreak on clinical presentation of patients admitted for acute heart failure in India. Am J Emerg Med 2020 Jan 1;39:162–3.

[3] Solomon MD, McNulty EJ, Rana JS, et al. The Covid-19 pandemic and the incidence of acute myocardial infarction. NEJM 2020 May 19.

[4] Bhatt AS, Moscone A, McElrath EE, et al. Fewer hospitalizations for acute cardiovascular conditions during the COVID-19 pandemic. J. Am Coll Cardiol 2020 Jul 21;76(3):280–8.

[5] Myers KD, Knowles JW, Staszak D, et al. Precision screening for familial hypercholesterolaemia: a machine learning study applied to electronic health encounter data. Lancet Digital Health 2019 Dec 1;1(8):e393–402.

[6] Wilemon KA, Patel J, Aguilar-Salinas C, et al. Reducing the clinical and public health burden of familial hypercholesterolemia: a global call to action. Jama Cardiol 2020 Feb 1;5(2):217–29.

[7] Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. J Stat Softw 2011 Jun 14;42(8):1–28.

[8] Myers KD, Farboodi N, Mwamburi M, et al. Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes. Circ Cardiovasc Qual Outcomes 2019;12 Aug.