Received: 16 November 2021 | Accepted: 4 February 2022

DOI: 10.1111/eci.13760

ORIGINAL ARTICLE

WILEY

Effects of multimorbidity on incident COVID-19 events and its interplay with COVID-19 event status on subsequent incident myocardial infarction (MI)

Gregory Y. H. Lip[1] | **Ash Genaidy**[2] | **George Tran**[3] | **Patricia Marroquin**[2] | **Cara Estes**[2] | **Sue Sloop**[2]

[1]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK

[2]Anthem Inc, Indianapolis, Indiana, USA

[3]IngenioRX, Indianapolis, Indiana, USA

Correspondence
Gregory Y.H. Lip, Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool L7 8TX, UK.
Email: gregory.lip@liverpool.ac.uk

Ash Genaidy, 11884 quarterhorse court, Cincinnati, Ohio 45249, USA.
Email: ashgenaidy@gmail.com

Abstract

Background: With the spread of COVID-19 pandemic, there have been reports on its impact on incident myocardial infarction (MI) emanating from studies with small to modest sample sizes. We therefore examined the incidence of MI in a very large population health cohort with COVID-19 using a methodology which integrates the dynamicity of prior comorbid history. We used two approaches, i.e. main effect modelling and a machine learning (ML) methodology, accounting for the complex dynamic relationships among comorbidity and other variables.

Methods: We studied a very large prospective 18–90-year US population, including 4,289,481 patients from medical databases in a 12-month investigation of those with/without newly incident COVID-19 cases together with a 2-year comorbid profile in the baseline period. Incident MI outcomes were examined in relationship to diverse multimorbid conditions, COVID-19 status and demographic variables—with ML accounting for the dynamic nature of changing multimorbidity risk factors.

Results: Multimorbidity, defined as a composite of cardiometabolic/noncardiometabolic comorbid profile, significantly contributed to the onset of confirmed COVID-19 cases. Furthermore, a main effect model (C-index value 0.932; 95%CI 0.930–0.934) had medium to large effect sizes with incident MI outcomes in a COVID-19 cohort for the classic multimorbid conditions in medical history profile which includes prior coronary artery disease (OR 4.61 95%CI 4.49–4.73); hypertension (OR 3.55 95%CI 3.55–3.83); congestive heart failure (2.31 95%CI 2.24–2.37); valvular disease (1.43 95%CI 1.39–1.47); stroke (1.30 95%CI 1.26–1.34); and diabetes (1.26 95%CI 1.23–1.34). COVID-19 status (1.86 95%CI 1.79–1.93) contributed an independent large size risk effect for incident MI. The ML algorithm demonstrated better discriminatory validity than the main effect model (training: C-index 0.949, 95%CI 0.948–0.95; validation: C-index 0.949, 95%CI 0.948–0.95). Calibration of the ML-based formulation was satisfactory and better than the main effect model. Decision curve analysis demonstrated that the ML clinical

utility was better than the 'treat all' strategy and the main effect model. The ML logistic regression model was better than the neural network algorithm.

Conclusion: The very large investigation conducted herein confirmed the importance of cardiometabolic and noncardiometabolic multimorbidity in increasing vulnerabilities to a higher risk of COVID-19 infections. Furthermore, the presence of COVID-19 infections increased incident MI complications both in terms of independent effects and interactions with the multimorbid profile and age.

KEYWORDS

cardiovascular/noncardiovascular multimorbidity, COVID-19, machine learning, main effect analysis, myocardial infarction

1 | INTRODUCTION

Although the COVID-19 pandemic is a primary story of public health crisis impacting the global populations, its effects have triggered severe downturns in all industries which almost paralysed the world's economy and brought it down into its knees. Therefore, it is paramount to learn as much as possible from this crisis, with an eye to extract the maximum opportunities of knowledge learning so as to improve the health and wealth of people everywhere. In this report, an examination of the cardiovascular complications of COVID-19 has been undertaken.

With the spread of COVID-19 pandemic, there have been reports on its impact on incident myocardial infarction (MI) and MI-related morbidity and mortality using mostly small samples. Some researchers reported significant reduction in MI hospitalizations during the COVID-19 pandemic.[1,2] Others such as Modin et al[3] and Bangalore et al[4] found evidence of increased incidence of MI in small COVID-19 cohorts. Wilson et al[5] suggested that these discrepancies may be attributed in part due to behaviour change leading to delayed worsened MI conditions and based on our experience perhaps due to potential biases with respect to healthcare services providing priorities for COVID-19 care treatment.

We maintain herein that the uncertainties surrounding the impact of COVID-19 on cardiovascular complications particularly incident MI (the subject of this investigation) are attributed in part to the smaller size of reported cohorts in the published literature as well as potential biases to offering healthcare services primarily to COVID-19 patients with reference to other care needed by other patients.

The specific aim of this study is to examine the incidence of MI in a very large population health cohort with COVID-19 in reference to a non-COVID-19 cohort using an approach which integrates the dynamicity of prior comorbid history. The use of a very large population in this instance is paramount in order to better understand the dynamic interplay between incident COVID-19 status and multimorbid profile.

We used an integrated statistical-machine learning approach so as to better understand the effects induced by COVID-19 infections within the context of prior comorbid history. This was formulated using two approaches, i.e. (a) main effect modelling for better understanding of the independent effects of COVID-19 infections as well as the comorbid profile and (b) a machine learning (ML) approach, accounting for the complex dynamic relationships among comorbidity and other variables.

2 | METHODS

2.1 | Cohort detailed definition and data sources

We examined a very large prospective US population over a 12-month period starting April 1, 2020, to determine their effects on potential new COVID-19 cases and, subsequently, the incidence of new onset MI. The comorbid profile for the study population at baseline was gathered from 1 April 2018 to 31 March 2020 to ensure there was no prior history of MI and COVID-19 in this time period.

The study population consisted of three health plans, namely, Commercial, Medicare and Medicaid with a diverse group of socioeconomic status and age groups spanning from 18 to 90 years. The Commercial health plan was financed by private insurance, while the Medicare and Medicaid plans were covered by the federal and state governments.

The comorbid history was gathered for a two-year period prior to the start of the study and consisted of common cardiovascular and noncardiovascular multimorbidities. Only subjects without a history of MI and COVID-19 prior to April 1 2020 were included in the study.

Based on the aforementioned, the study cohort was gathered from medical claims databases during the 1 April 2018–31 March 2021 time window (2 years for comorbid history and 1 yr for the study period for COVID-19 incidence and subsequent MI incidence) based on primary and secondary ICD10 codes. Each participant had to contribute at least 36 months of medical and pharmacy coverage during the study and records in the medical database (i.e. 12 months for the prospective cohort investigation and 24 months of prior medical history for nonincidence MI/COVID-19 conditions).

IRB approval was not required for the extraction of data from the claims databases; however, compliance with US privacy laws and company governance is strictly required and enforced by Anthem Inc for use of data by all of its employees.

2.2 | Parameter identification and definition

At baseline (Day 0, upon entry into the study on 1 April 2020), subjects *without* any history of COVID-19 and MI conditions were enrolled for prior two years to gather the comorbid profile and were followed up over a 12-month period with two prospective cohorts defined as follows: (a) cohort 1—incident (new) COVID-19 cases and followed up for incidence of MI (at least one day after occurrence of a COVID-19 case); (b) cohort 2—non-COVID-19 cases with or without developing incident MI cases (i.e. without subsequent COVID-19 cases in later days or simultaneous COVID-19 cases on the same day).

The comorbid history was identified on the basis of ICD10 codes (Table S1 for ICD 10 codes), including congestive heart failure, hypertension, diabetes mellitus, stroke (i.e. ischemic stroke, transient ischemic attack, thromboembolic events), atrial fibrillation, peripheral artery disease, valvular disease, coronary artery disease, sleep apnoea, chronic kidney disease, chronic obstructive pulmonary disease/bronchiectasis, major bleeding, cognitive impairment, lipid disorders, liver disease, anaemia, depression, spondylosis/intervertebral discs, osteoarthritis, hyperthyroidism, metabolic syndrome and asthma.

An incident COVID-19 case was determined as the first case upon entry into the prospective follow-up using the US CDC code of 'U071'. Confirmed cases of COVID-19 infections via the use of the ICD-10 code "U071" were recommended by the US Centers for Disease Control as of 1 April 2020. In this respect, a confirmed diagnosis of COVID-19 was issued as documented by the provider, documentation of a positive COVID-19 test result, or a presumptive positive COVID-19 test result. Furthermore, "confirmation" does not require documentation of the type of test performed; the provider's documentation that the individual has COVID-19 is sufficient.

An incident MI outcome was defined as occurring by at least 1 day after the development of a COVID-19 condition or upon entry into the study in the absence of any developed COVID-19 case. It was defined in terms of ICD 10 codes as reported in Table S1.

The study population should not have had any prior history of MI or COVID-19 during the 2-year baseline period as defined in terms of ICD10 codes (see Table S1). Two demographic variables were utilized in this investigation, namely, gender and age. Age was defined as either a continuous variable or in 5 categories (18–45, 45–55, 55–65, 65–75, 75–90 years). Furthermore, the health plan factor was introduced as a macro socioeconomic factor (Commercial or 0, Medicare or 1, Medicaid or 2).

2.3 | Analytic computations

The analytic computations included descriptive statistics and model prediction using inferential statistics and machine learning algorithms. The descriptive and inferential analyses were performed using the Statistical Analysis Software (SAS) Enterprise, and the ML computations were conducted using the SAS Enterprise Miner.

The descriptive analyses included identification of member counts (percent) for demographic parameters, comorbid history and incident COVID-19 and AF conditions (with the exception of mean (SD) for age and enrolment period as continuous variables). The outcome (i.e. COVID-19 or MI) and input (i.e. comorbid history, gender) variables had binary representations. Age groups and health plan were the only nominal variables (i.e. categorical variable with 3/more levels).

Statistical analyses were conducted using main effects with COVID-19 or MI as an outcome, with logistic regression modelling using the SAS Enterprise software. Prediction modelling was pursued using the Enterprise SAS Miner software for complex relationships between MI as a binary outcome and comorbid history/COVID-19 status/demographic variables/health plan type. All ML-based modelling accounted for *dynamic changes* in risk including newly acquired risk factors, hence consisting of complex interactions among the comorbid condition history as well as incident conditions such as COVID-19 conditions.

The ML algorithms consisted of two parametric methods. The first is the logistic regression algorithm which included main effects, interaction terms and polynomial effects, with the model selection based on the stepwise procedures. Several polynomial terms were also included. Neural network utilized a multilayer perceptron architecture with direct connection for a feedforward multilayer

network architecture composed of several layers of neurons including input, output and hidden layers.

Model validation was based on calibration, discrimination and clinical utility. Each model was trained on 67% of the data, with the remaining 33% data used for external validation. In this respect, the development and validation samples were extracted at random. Discriminant validity was assessed using C-indices (area under the curve) for both the development and validation samples, separately. In addition, clinical utility was assessed using decision curve analysis (DCA).

3 | RESULTS

3.1 | Characteristics of cohort included in the study

The COVID-19 and non-COVID-19 cohorts included 110957 and 4178524 individuals, respectively (Table 1) (please see Figure S1 for derivation of study cohorts). The age 18–44-year group dominated the presence in each cohort with a percentage close to 55% of all individuals in each cohort. The age 65–74- and 75–89-year groups had the lowest percentages in each cohort.

There was a diverse multimorbid history with hypertension, lipid disorders, spondylosis/intervertebral disc having the highest prevalence rates, >40% and >20%, respectively, for the COVID and non-COVID cohorts (Table 1), with prevalence rates always higher for the COVID cohort.

The incidence of MI in the new COVID-19 cases was 3.7% compared to 0.8% in the non-COVID-19 cases. The crude incidence frequency ratio for incident MI cases was 4.3 in COVID-19 cases.

TABLE 1 Baseline characteristics for total cohort. Values are numbers (%) unless stated otherwise

Baseline characteristic	COVID cohort	Non-COVID cohort
Age group (years)		
18–45	59997 (54.1)	2303792 (55.1)
45–55	15141 (13.6)	710579 (17.0)
55–65	14766 (13.3)	757203 (18.1)
65–75	9345 (8.4)	196998 (4.7)
75–90	11708 (10.6)	209952 (5.0)
Age (years), mean (SD)	45.4 (19.9)	43.2 (17.5)
Gender		
Males	37418 (33.7)	1767680 (42.7)
Females	73539 (66.3)	2410844 (57.7)
Total	110957 (100.0)	4178524 (100.0)
Comorbid history		
Congestive heart failure	7849 (7.1)	95137 (2.3)
Hypertension	48850 (44.0)	1062086 (25.4)
Diabetes mellitus	18317 (16.5)	271501 (6.5)
Stroke	5298 (4.8)	89069 (2.1)
Atrial fibrillation	6735 (6.1)	81786 (2.0)
Peripheral artery disease	8570 (7.7)	103912 (2.5)
Valvular disease	10348 (9.3)	158198 (3.8)
Coronary artery disease	10252 (9.2)	150580 (3.6)
Chronic sleep apnoea	8894 (8.0)	120691 (2.9)
Chronic kidney disease	4439 (4.0)	67574 (1.6)
Chronic pulmonary obstructive disease/ bronchiectasis	20862 (18.8)	359570 (8.6)
Major bleeding	12924 (11.6)	213049 (5.1)
Cognitive impairment	3238 (2.9)	37183 (0.9)
Liver disease	18402 (16.6)	295963 (7.1)
Anaemia	30195 (27.2)	468299 (11.2)
Depression	27780 (25.0)	592393 (14.2)
Lipid disorders	46055 (41.5)	988026 (23.6)
Spondylosis and intervertebral discs	56263 (50.7)	1190581 (28.5)
Osteoarthritis	24541 (22.1)	428524 (10.3)
Hyperthyroidism	2267 (2.0)	40222 (1.0)
Metabolic syndrome	1507 (1.4)	26765 (0.6)
Asthma	21519 (19.4)	419186 (10.0)
Enrolment period (months), mean (SD)	51.9 (8.5)	52.0 (11.0)

3.2 | Main effect modelling

With COVID-19 as an outcome variable, the strongest associations ($p<0.0001$) were found for hypertension, diabetes, peripheral artery disease, cognitive impairment, liver disease, anaemia, lipid disorders, spondylosis/intervertebral discs, osteoarthritis and asthma (Table 2). The highest odds ratios were obtained for spondylosis/intervertebral discs (OR 1.69 95%CI 1.66–1.71) and anaemia (1.62 95%CI 1.60–1.65), both noncardiovascular morbidities.

With (new onset) MI as an outcome variable, main effect modelling demonstrated that the strongest associations ($p<0.0001$) with incident MI outcomes were for the classic cardiometabolic conditions of prior coronary artery disease (OR 4.61 95%CI 4.49–4.73); hypertension (OR 3.55 95%CI 3.55–3.83); congestive heart failure (2.31 95%CI 2.24–2.37); valvular disease (1.43 95%CI 1.39–1.47); stroke (1.30 95%CI 1.26–1.34); and diabetes (1.26 95%CI 1.23–1.34). Of noncardiometabolic conditions, COVID-19 status (1.86 95%CI 1.79–1.93) was an independent risk for incident MI, as was liver disease (1.69 95%CI

TABLE 2 Effects of baseline characteristics and demographic variables on COVID-19 outcomes using main effect model

Effect	Levels	Point estimate	95% confidence interval		Pr > ChiSq
			Lower limit	Upper limit	
Congestive heart failure	(1 vs 0)	1.08	1.05	1.11	<.0001
Hypertension	(1 vs 0)	1.42	1.40	1.45	<.0001
Diabetes mellitus	(1 vs 0)	1.34	1.31	1.36	<.0001
Stroke	(1 vs 0)	1.12	1.08	1.15	<.0001
Atrial fibrillation	(1 vs 0)	1.10	1.06	1.14	<.0001
Peripheral artery disease	(1 vs 0)	1.26	1.23	1.30	<.0001
Valvular disease	(1 vs 0)	1.10	1.07	1.13	<.0001
Coronary artery disease	(1 vs 0)	1.10	1.07	1.12	<.0001
Sleep apnoea	(1 vs 0)	1.10	1.07	1.14	<.0001
Chronic kidney disease	(1 vs 0)	1.16	1.13	1.19	<.0001
Chronic pulmonary obstructive disease/bronchiectasis	(1 vs 0)	1.18	1.16	1.20	<.0001
Major bleeding	(1 vs 0)	1.21	1.18	1.23	<.0001
Cognitive impairment	(1 vs 0)	1.48	1.42	1.53	<.0001
Liver disease	(1 vs 0)	1.28	1.25	1.30	<.0001
Anaemia	(1 vs 0)	1.62	1.60	1.65	<.0001
Depression	(1 vs 0)	1.13	1.12	1.15	<.0001
Lipid disorders	(1 vs 0)	1.52	1.49	1.54	<.0001
Spondylosis and intervertebral discs	(1 vs 0)	1.69	1.66	1.71	<.0001
Osteoarthritis	(1 vs 0)	1.27	1.25	1.29	<.0001
Hyperthyroidism	(1 vs 0)	1.19	1.14	1.24	<.0001
Metabolic syndrome	(1 vs 0)	1.13	1.07	1.19	<.0001
Asthma	(1 vs 0)	1.32	1.30	1.34	<.0001
Gender	Female vs male	1.30	1.28	1.32	<.0001
Age	years	0.98	0.98	0.98	<.0001

Note: 1 - presence of condition or female.

0 - absence of condition or male.

Age - in years.

C index =0.716.

1.65–1.74), chronic obstructive pulmonary disease/bronchiectasis (1.47 95%CI 1.43–1.50), depression (1.38 95%CI 1.34–1.41) and chronic kidney disease (1.23 95%CI 1.20–1.37). Females had lower risk relative to males for incident MI (OR 0.75 95%CI 0.73–0.76), and age was a risk factor (Table 3).

3.3 | Machine learning algorithms

For the training dataset, the discriminant validity for the ML logistic regression algorithm was 0.949 (95%CI 0.948–0.950) and was higher than that obtained for the ML-based neural network formulation (C-index 0.903 95%CI 0.903–0.903). Similar results were obtained for the external validation cohort (logistic regression: 0.949 95%CI 0.948–0.950; neural network: 0.901 95%CI 0.899–0.903) (Figure 1).

Figure 2 further shows the ML logistic regression demonstrating better results than the neural network model in terms of the cumulative lift. Targeting 5% of the high risk population reaches 68.6% and 65.8% of this group in terms of true positives using the logistic regression and neural network models, respectively. For 10% and 15% of the target populations, these percentages increased, respectively, for the logistic regression (82.5%, 89.6%) and neural network formulations (i.e. 78.5%, 83.3%). Table S2 depicts the complex relationships between the incident MI outcome and model features in terms of main effect, interactions and polynomial effects.

TABLE 3 Results of main effect model for incident myocardial infarction outcome using baseline characteristics and COVID status

Effect	Levels	Point estimate	95% confidence interval		Pr > ChiSq
			Lower limit	Upper limit	
COVID−19 status	(1 vs 0)	1.86	1.79	1.93	<.0001
Congestive heart failure	(1 vs 0)	2.31	2.24	2.37	<.0001
Hypertension	(1 vs 0)	3.69	3.55	3.83	<.0001
Diabetes mellitus	(1 vs 0)	1.26	1.23	1.30	<.0001
Stroke	(1 vs 0)	1.30	1.26	1.34	<.0001
Atrial fibrillation	(1 vs 0)	1.05	1.02	1.09	0.0015
Peripheral artery disease	(1 vs 0)	1.06	1.03	1.09	0.0001
Valvular disease	(1 vs 0)	1.43	1.39	1.47	<.0001
Coronary artery disease	(1 vs 0)	4.61	4.49	4.73	<.0001
Sleep apnoea	(1 vs 0)	0.85	0.82	0.89	<.0001
Chronic kidney disease	(1 vs 0)	1.23	1.20	1.27	<.0001
Chronic pulmonary obstructive disease/bronchiectasis	(1 vs 0)	1.47	1.43	1.50	<.0001
Major bleeding	(1 vs 0)	1.16	1.13	1.19	<.0001
Cognitive impairment	(1 vs 0)	0.91	0.87	0.95	<.0001
Liver disease	(1 vs 0)	1.69	1.65	1.74	<.0001
Anaemia	(1 vs 0)	1.21	1.18	1.24	<.0001
Depression	(1 vs 0)	1.38	1.34	1.41	<.0001
Lipid disorders	(1 vs 0)	1.23	1.19	1.27	<.0001
Spondylosis and intervertebral discs	(1 vs 0)	1.36	1.33	1.40	<.0001
Osteoarthritis	(1 vs 0)	1.07	1.05	1.10	<.0001
Hyperthyroidism	(1 vs 0)	0.95	0.88	1.01	0.1159
Metabolic syndrome	(1 vs 0)	0.82	0.74	0.90	<.0001
Asthma	(1 vs 0)	1.08	1.05	1.11	<.0001
Gender	Female vs male	0.75	0.73	0.76	<.0001
Age	years	1.02	1.02	1.02	<.0001

Note: 1 - presence of condition or female.

0 - absence of condition or male.

Age - in years.

C index =0.932.

In Figure 3, the clinical utility of main effect model and ML-based logistic regression algorithm had better net benefit than the two treatment strategies (i.e. treat all or none). In this respect, the "treat all" or "treat none" (i.e. provide no therapy) interventions are two default strategies where patients are managed without the use of a model.

As evident from Figure 3, the developed models provide better net benefit values than the "treat all" strategy. Above the probability threshold of 0.5%, the ML formulation provided better clinical utility than the main effect model and the differences increased with an increase in the probability threshold. At a probability threshold of 0.5%, the differences were minimal with the net true positives equal to 0.87 and 0.85 events per 100 patients, respectively, for the ML and main effect models.

3.4 | Model calibration

From calibration standpoint, the main effect model and machine learning algorithm (Figure S2) were well calibrated in the lower segment of predicted probability (0–20%). Beyond this probability range, the main effect model did not seem well calibrated perhaps due to the absence of adequate number of parameters (in other words, misspecification error in the 5% to 100% probability range) resulting in risk over-estimation. The ML-based algorithm overestimated the risk beyond 20% (beyond the range of operation) but had better calibration than that obtained for the main effect model. It should be noted that the probability threshold as pointed out is in the range of 0.5% which provides excellent calibration for the validation sample.

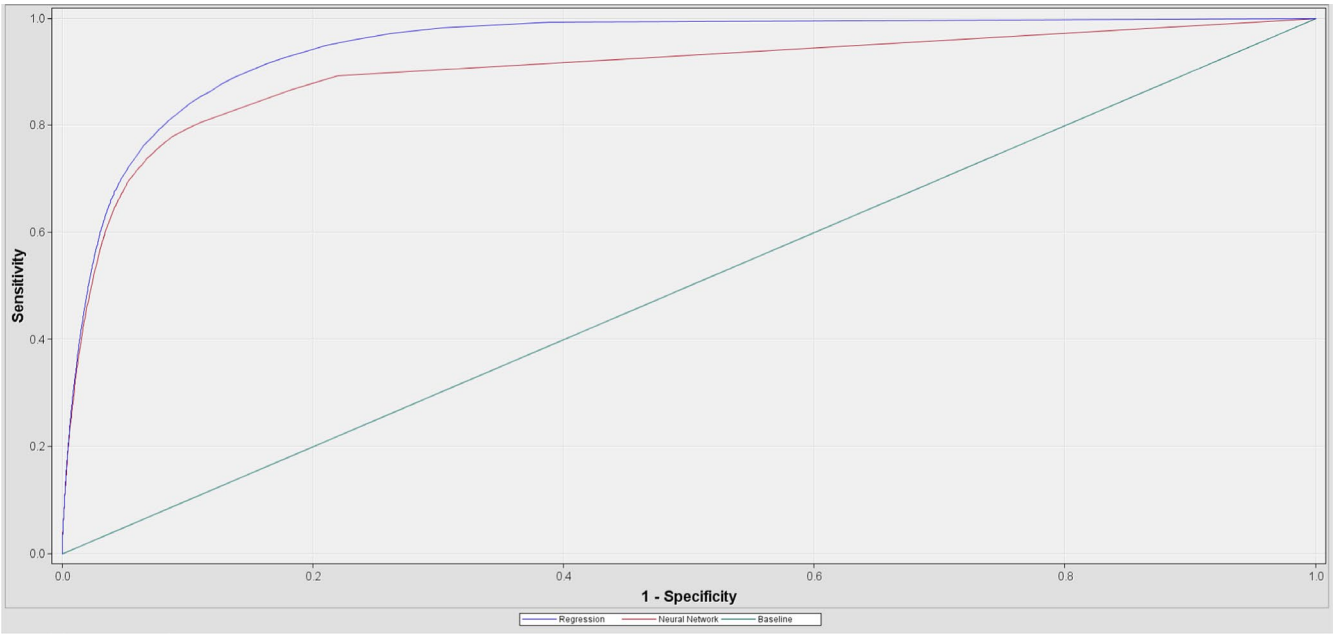

FIGURE 1 Discriminant validity for ML logistic regression (C index 0.949 95%CI 0.948–0.950) and neural network (C index 0.901 95%CI 0.899–0.903) algorithms

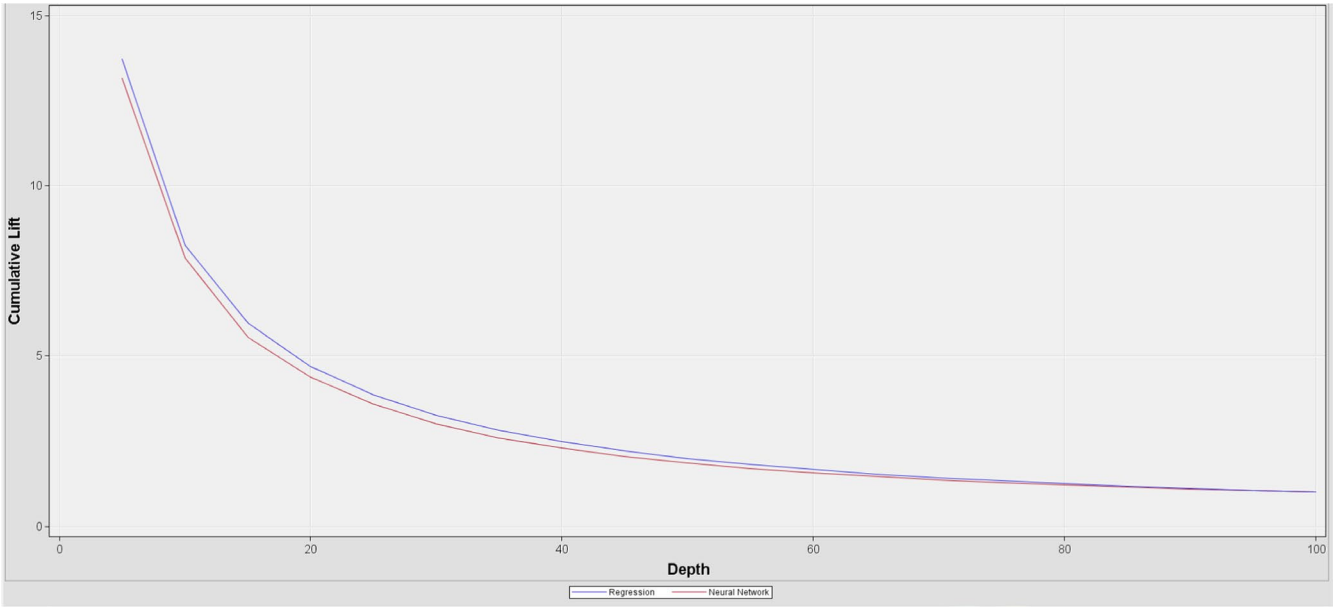

FIGURE 2 Cumulative lift indices for externally validated ML logistic regression and neural network algorithms

4 | DISCUSSION

In this very large analysis of patients aged 18 to 90 years who are free of MI and COVID-19 (for at least 2 years prior to the prospective follow-up) at baseline, but followed up for new COVID-19 cases in the form of MI events, we analysed the independent influencers of incident COVID-19 infection events with the comorbid/demographic/health plan factors as well the main influencers and complex interplay of the same factors with incident MI events in COVID-19 patients.

In the face of multiple comorbidities impacting the patient, there is truly a dire need to investigate these issues in very large health populations which can be derived mostly from national registries and major administrative databases. The present investigation is an example for such studies which may illuminate the body of knowledge about the influence of multimorbid profile in advancing

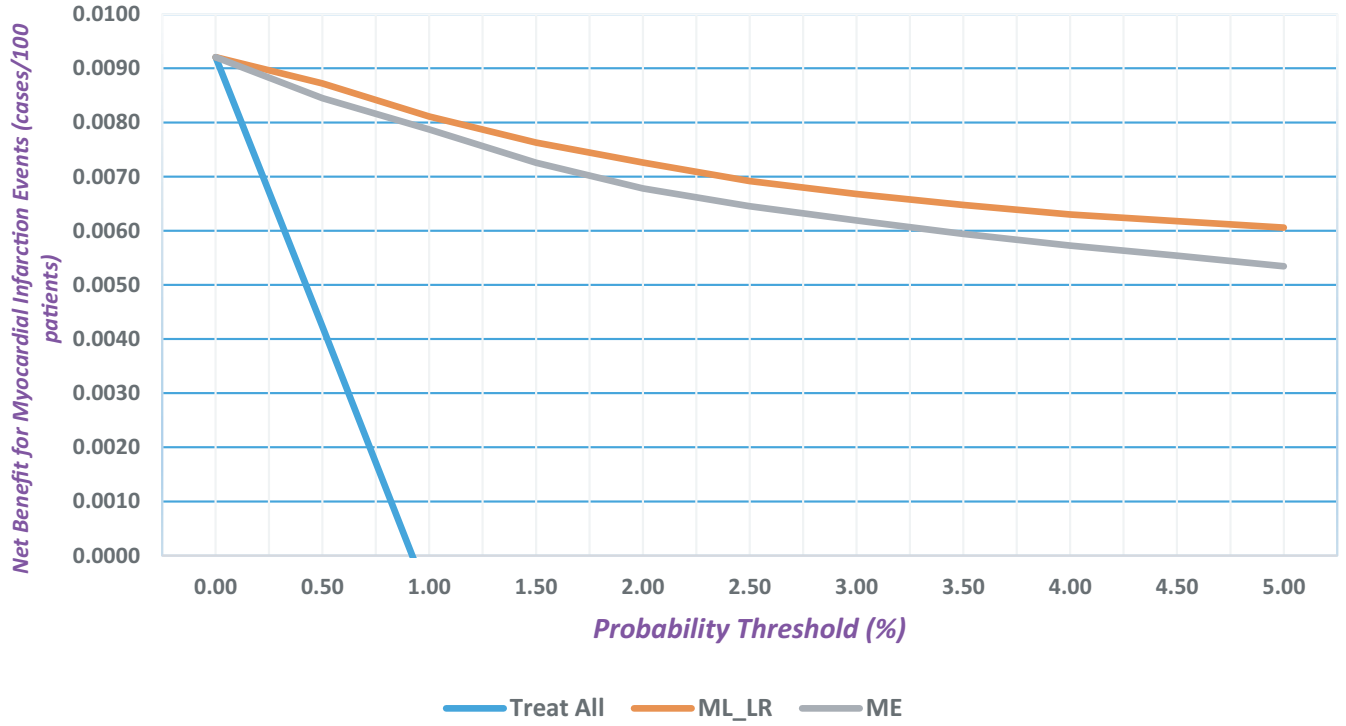

FIGURE 3 Decision curve analysis for main effect model (ME), machine learning-based logistic regression formulation (ML_LR) and treat all strategy

the associations with incident COVID-19 infections. Although there are, as expected, inherent biases in the use of individual data from administrative databases, there is a strength in numbers to enlighten the medical literature about the circumstances surrounding factors leading to COVID-19 infections and its complications.

In this investigation, the primary independent influencers of incident COVID-19 cases in terms of effect size (i.e. OR ≥1.5) are spondylosis/intervertebral discs (OR 1.69), anaemia (OR 1.62) and lipid disorders (OR 1.52). Moderate-size influencers (OR 1.25–1.49) included hypertension (OR 1.42), cognitive impairment (1.42), diabetes mellitus (OR 1.34), asthma (OR 1.32), liver disease (OR 1.28), osteoarthritis (OR 1.27) and peripheral artery disease (OR 1.26). Small size effects (OR 1.01–1.24) were derived from several cardiovascular (e.g. congestive heart failure, coronary artery disease, valvular disease, atrial fibrillation) and other comorbidities (e.g. kidney disease, COPD, metabolic disease).

It should be noted that the findings obtained for the largest effects are not typically reported in the literature, with the medium and smaller effects more commonly suggested in the published literature. Gasmi et al[6] and Gao et al[7] maintain that hypertension, diabetes mellitus, cardiovascular conditions, COPD and kidney disease provided the strongest and most consistent associations. They further indicate that asthma and cerebrovascular diseases have mixed results with COVID-19 infections.

Collectively, it can be inferred that both cardiometabolic and noncardiometabolic comorbidities may contribute to increased vulnerabilities due to risks of COVID-19 infections. At this time, one cannot elucidate the mechanisms precisely leading to COVID-19 outcomes. However, it can be stated that multimorbid conditions significantly contribute to the increased risks of COVID infections as the individual's resistance to any disease has been compromised and reduced. Consequently, a COVID-19 cohort may have serious complications such as MI incidence in reference to non-COVID-19 cohort.

In a COVID-19 cohort, the presence of COVID-19 infection was an independent contributor to incident MI events and produced a large effect size (OR 1.89) together with the classic cardiovascular comorbid factors such as coronary artery disease, congestive heart failure and hypertension. This effect was also much larger than well-established comorbidities for incident MI events such as COPD and diabetes mellitus.[8,9]

In addition to the above, the ML formulation uncovered the complex dynamic interrelationships among comorbid profile/demographic variables/health plan factor and incident MI. As expected, multimorbidity plays an important role in increasing the risk of COVID-19 infection.[10-12] There were significant and dynamic interactions between the presence of incident COVID-19 infections and coronary artery disease, liver disease, major bleeding as well as cognitive impairment. Demographic variables

continued to demonstrate their importance as well. There were interactive terms between age as a categorical variable and COVID-19 status with the incident MI.

Our findings are important given the worse prognosis among COVID-19 patients with MI, with a higher risk of morbidity when compared to MI patients without COVID-19 patients. Our ML prediction could be incorporated into telehealth approaches to monitor patients following their COVID-19 diagnosis, for the onset of incident MI. Given the increasing focus on integrated care management of patients with MI, novel ML approaches could facilitate structured management and follow-up, especially since risk profiles change in a dynamic manner over time. Such a structured approach to holistic MI care, including proactive risk evaluation, has been shown to be associated with improved clinical outcomes, especially with a reduction in hospitalizations and bleeding events.

4.1 | Limitations

Our study is limited by its observational design due to the possibility of residual confounding. Also, there may be a potential bias emerging due to healthcare services concentrating on the treatment of COVID-19 cases and possibly leading to the cancellation of routine services, such as office visits for established chronic conditions.

5 | CONCLUSIONS

The large investigation conducted herein confirmed the importance of cardiometabolic and noncardiometabolic multimorbidity in increasing vulnerabilities to a higher risk of COVID-19 infections. Furthermore, the presence of COVID-19 infections increased incident MI complications both in terms of independent effects and interactions with the multimorbid profile and age.

CONFLICT OF INTEREST

The authors report no conflict of interest in this work.

ORCID

Ash Genaidy https://orcid.org/0000-0002-5336-6941

REFERENCES

1. De Rosa S, Spaccarotella C, Basso C, et al. Società Italiana di Cardiologia and the CCU Academy investigators group. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *Eur Heart J*. 2020;41(22):2083-2088. doi:10.1093/eurheartj/ehaa409
2. Solomon MD, McNulty EJ, Rana JS, et al. The Covid-19 pandemic and the incidence of acute myocardial infarction. *N Engl J Med*. 2020;383(7):691-693. doi:10.1056/NEJMc2015630
3. Modin D, Claggett B, Sindet-Pedersen C, et al. Acute COVID-19 and the incidence of ischemic stroke and acute myocardial infarction. *Circulation*. 2020;142(21):2080-2082. doi:10.1161/CIRCULATIONAHA.120.050809
4. Bangalore S, Sharma A, Slotwiner A, et al. ST-segment elevation in patients with Covid-19 — A case series. *N Engl J Med*. 2020;382:2478-2480. doi:10.1056/NEJMc2009020
5. Wilson SJ, Connolly MJ, Elghamry Z, et al. Effect of the COVID-19 pandemic on ST-segment-elevation myocardial infarction presentations and in-hospital outcomes. *Circ Cardiovasc Interv*. 2020;13(7):e009438. doi:10.1161/CIRCINTERVENTIONS.120.009438
6. Gasmi A, Peana M, Pivina L, et al. Interrelations between COVID-19 and other disorders. *Clin Immunol*. 2021;224: doi:10.1016/j.clim.2020.108651
7. Gao Y-G, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: A review. *Allergy*. 2021;76(2):428-455. doi:10.1111/all.14657
8. Goedemans L, Bax JJ, Delgado V. COPD and acute myocardial infarction. *Eur Respir Rev*. 2020;29(156):190139.
9. Read SH, Fischbacher CM, Colhoun HM, et al. Trends in incidence and case fatality of acute myocardial infarction, angina and coronary revascularisation in people with and without type 2 diabetes in Scotland between 2006 and 2015. *Diabetologia*. 2019;62(3):418-425.
10. Mair FS, Foster HM, Nicholl BI. Multimorbidity and the COVID-19 pandemic - An urgent call to action. *J Comorb*. 2020;10:2235042X2096167.
11. Maddaloni E, D'Onofrio L, Alessandri F, et al. Cardiometabolic multimorbidity is associated with a worse Covid-19 prognosis than individual cardiometabolic risk factors: a multicentre retrospective study (CoViDiab II). *Cardiovasc Diabetol*. 2020;19(1):164.
12. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. *PLoS Medicine*. 2020;17(9):e1003321.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Lip GYH, Genaidy A, Tran G, Marroquin P, Estes C, Sloop S. Effects of multimorbidity on incident COVID-19 events and its interplay with COVID-19 event status on subsequent incident myocardial infarction (MI). *Eur J Clin Invest*. 2022;52:e13760. doi:10.1111/eci.13760