Characterization and prognostic relevance of myocardial injury in patients with coronavirus disease-2019 (COVID-19): the "CardioCovid" study

Acronym: *CardioCovid*

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Firma

Background

Coronavirus disease-2019 (COVID-19) is a global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is resulting in substantial morbidity and mortality (1). Of interest, a significant proportion of patients presenting with COVID-19 infection and requiring hospitalization demonstrate biomarker evidence of myocardial injury (defined as elevation in circulating cardiac troponin levels), which has been shown to be associated with increased risk of in-hospital morbidity (i.e.: rate of non-invasive and invasive ventilation, access to intensive care unit, length of hospitalization, use of glucocorticoids or antibiotics) and mortality (2–6). The pathogenesis of myocardial injury in COVID-19 is still unclear, with proposed mechanisms that include cytokine-mediated damage, oxygen supply-demand imbalance, ischemic injury from microvascular thrombi formation and direct viral invasion of the myocardium (7–9). Notably, the clinical predictors of myocardial injury in COVID-19 infection are still unknown, and, therefore, there is lack of therapeutic opportunities to prevent or reduce myocardial injury and the related-unfavourable outcomes.

Moreover, the post-acute sequelae of COVID-19 could potentially involve the pulmonary and several extrapulmonary organs, including the cardiovascular system (10). A few studies to date have investigated cardiovascular outcomes in the post-acute phase of the COVID-19, and most with a short duration of follow-up and a narrow selection of cardiovascular outcomes (11–13). Therefore, a comprehensive assessment of post-acute COVID-19 sequelae on the cardiovascular system is still missing and, of interest, studies addressing the post-acute COVID-19 sequelae in patients who developed myocardial injury during COVID-19

infection are lacking (14).

Given these shortcomings in this evolving area of clinical research, a comprehensive characterization of myocardial injury in patients with COVID-19 infection and the identification of clinical predictors for its occurrence could allow the development of predictive models, thus helping clinicians in the disease phenotyping and the early assessment of the risk of unfavourable outcome and improving a fast determination of most appropriate treatments and clinical paths, efficient planning and use of clinical resources in terms of treatment type and units (such as intensive care or coronary intensive care). In addition, the identification of clinical predictors and/or protective factors for myocardial injury in COVID-19 infection may pave the way for the development of specific therapeutic strategies aiming to reduce the impact of myocardial injury on COVID-19-related morbidity and mortality. Finally, assessing the long-term cardiovascular impact of myocardial injury in COVID-19 infection could help clinicians in the prognostic stratification and the choice of therapeutic strategies in the post-acute COVID-19 phases, possibly identifying those patients that may need a more aggressive therapy and a closer follow-up.

A comprehensive characterization of myocardial injury in COVID-19 infection is still lacking, and no clinical predictors of myocardial injury has been identified yet. Moreover, the long-term cardiovascular outcome of myocardial injury in the post-acute COVID-19 phase is largely unknown. We thus hypothesize that:

- that clinical predictors and/or protective factors (including vaccination status) for myocardial injury in COVID-19 infection could be identified, thus allowing the development of predictive models that could help clinicians in the disease phenotyping,

the early assessment of the risk of unfavourable outcome and improving a fast determination of most appropriate management;

- that myocardial injury in COVID-19 patients could be associated with a worse clinical course characterized by higher incidence of in-hospital complications and need for escalation of therapies;
- that myocardial injury in COVID-19 patients could be associated with a worse angina status and quality of life as well as with a higher rate of adverse cardiovascular events in the post-acute COVID-19 phase, thus helping in the prognostic stratification of COVID-19 patients and identifying those that may need a more aggressive therapy and a closer follow-up.

OBJECTIVES

Primary objective

To identify clinical predictors of myocardial injury in patients hospitalized for COVID-19 infection since the introduction of vaccines (i.e., March 1, 2021).

Secondary objectives

1. To evaluate if the presence of myocardial injury during the index hospitalization for COVID-19 is associated with a worse in-hospital clinical course in terms of in-hospital complications and need for aggressive therapies.
2. To evaluate if the presence of myocardial injury during the index hospitalization for COVID-19 are associated with a worse angina status and quality of life (evaluated using the Seattle Angina Questionnaire [SAQ] summary score (15)) at 12-months follow-up.
3. To evaluate if the presence of myocardial injury during the index hospitalization for COVID-19 predicts a worse clinical outcome in terms of major adverse cardiovascular events (MACE) (defined as the composite of cardiovascular death, ischemic heart disease [acute or chronic coronary syndromes], stroke/transient ischemic attack [TIA] and hospitalization for heart failure), dysrhythmias (defined as the composite of new-onset atrial fibrillation and/or ventricular arrhythmias), inflammatory heart disease (pericarditis and/or myocarditis) or thrombotic disorders (pulmonary embolism, deep vein or superficial vein thrombosis) at 12-months follow-up.

METHODS

Study design

Retrospective and prospective observational study.

Population

All consecutive patients hospitalized at Policlinico Universitario A. Gemelli IRCSS since March 1, 2021, with a diagnosis of SARS-CoV-2 infection (≥1 positive nasopharyngeal swab) and at least one value of high-sensitivity cardiac troponin I (hs-cTnI) measured during the index hospitalization will be enrolled. Given that the patients are unable to physically sign the informed consent form due to epidemiological reasons (contamination of papers by SARS-CoV-2), each patient will verbally declare the consent to "Consenso al trattamento dei dati personali e dei campioni biologici a scopo di ricerca – no profit", "modulo di dichiarazione della volontà espresso ai fini del consenso informato generale alle cure" and "modulo dossier sanitario – richiesta di oscuramento/deoscuramento di eventi/episodi" at the presence of at least two witnesses.

Inclusion criteria

- Age ≥18 years;
- Overt COVID-19 infection (molecular nasopharyngeal swab positive for SARS-CoV-2 ≥1);
- Patient with at least a high sensitivity Troponin I measured during hospitalization course.
- Available data on vaccination.
- Verbal informed consent

Exclusion criteria

- Age <18 years;
- Patient in whom at least one high sensitivity Troponin I value measured during the course of hospitalization is not available.
- No data available on vaccination status.

Variables and procedures

This study will make use of Data Mart COVID-19 developed within Generator Real World Data Unit. The Data Mart COVID-19 belongs to the family of the diagnostic and prognostic mini-bots developed within the Generator Real World Data Unit project in which artificial intelligence solutions (such as text mining) are adopted to automatically extract both structured and unstructured data from hospital databases of patients infected from SARS-CoV-2. Feature selection and machine learning algorithms can be applied to develop diagnostic and prognostic support systems for clinicians.

The specific data that which will be exploited are:

- Demographics data;
- Patient comorbidities, vital signs and symptoms at the time of admission;
- Laboratory analysis;
- In-hospital complications (e.g.: need for non-invasive or invasive ventilation, access to intensive care unit, length of hospitalization, use of glucocorticoids or antibiotics, death);

- Blood gas exchange information;
- Radiological reports;
- Medications at the time of admission, during hospitalization and at the time of discharge;
- Vaccination status.

Clinical follow-up

All patients will undergo a clinical follow-up by telephonic interview and/or clinical visit at 12 months from hospital discharge, during which the incidence of MACE, dysrhythmias, inflammatory heart disease and/or thrombotic disorders (both as incidence of the composite and as incidence of each individual components) in the past months will be investigated, the SAQ will be administered and the SAQ summary score will be collected.

ENDPOINTS

Primary endpoint

To assess for the presence of clinical predictors for the occurrence of myocardial injury, defined as at least one value of hs-cTnI >99th percentile upper reference limit (16), in patients hospitalized for COVID-19 infection.

Secondary endpoints

1. The occurrence of myocardial injury during the index hospitalization for COVID-19 infection will be correlated with in-hospital complications (defined as the composite of the need for non-invasive or invasive ventilation, access to intensive care unit, length of hospitalization, use of glucocorticoids or antibiotics, and death).
2. The occurrence of myocardial injury in patients during the index hospitalization for COVID-19 infection will be included in a prediction model and correlated with future cardiovascular events (MACE), dysrhythmias, inflammatory heart disease and/or thrombotic disorders at 12-months follow-up.
3. The occurrence of myocardial injury during the index hospitalization for COVID-19 infection will be correlated with angina status and quality of life, evaluated using the SAQ summary score, at 12-months follow-up.

STATISTICAL ANALYSIS PLAN

Sample size calculation

A comprehensive characterization of myocardial injury in COVID-19 infection is still lacking, and no clinical predictors of myocardial injury has been identified yet. Moreover, the long-term cardiovascular outcome of myocardial injury in the post-acute COVID-19 phase is largely unknown. Thus, this configures as a pilot study on large-scale cohort. As such no formal sample size calculation is needed. However, based on the COVID-19 datamart of our clinical institution and on inclusion criteria, we expect to include in the study around 2000 patients hospitalized with COVID-19. Such a sample size is largely consistentwith common rules of thumb for pilot studies. In addition, the estimated sample size is largely consistent with the van Smeden metamodels related to the new statistical approaches for the development of clinical prediction models (17). The square root of the mean squared prediction error (rMPSE) and mean absolute prediction error (MAPE) may be approximated via the results of these. Lower values for rMSPE and MAPE indicate better performance. For instance, at a sample size of N=400, with P=8 candidate predictors and an expected event fraction of ¼, the predicted out-of-sample rMPSE would be 0.065 when ML model (without variable selection) is applied, and 0.053 for Ridge regression; MAPE would instead be 0.045 for the ML model and 0.038 for the Ridge regression.

Statistical analysis

All demographic, clinical and laboratory characteristics will be summarized by descriptive statistics techniques. In depth, qualitative variables will be expressed by absolute and relative percentage frequencies. Quantitative variables, indeed, will be reported either as mean and standard deviation (SD) or median and interquartile range (IQR), respectively in the case they were normally or not normally distributed. Their distribution will be previously assessed by the Shapiro Wilk test. Between groups differences in the demographic, clinical, laboratory and pathologic features will be assessed by the Chi Square or the Fisher's exact test as for qualitative variables, with Yates correction, as appropriate, whilst quantitative variables will be evaluated either by the Student's t test or the Mann-Whitney U test, according to their distribution. Univariable and multivariable logistic regression models will be performed to evaluate the presence of clinical predictors for the occurrence of myocardial injury in COVID-19 infection. Results will be expressed as odds ratio (OR) with 95% confidence interval (CI). Model calibration performances will be evaluated via the Hosmer-Lemeshow goodness of fit test with 10 groups. Model performance will be assessed through receiver-operator characteristic (ROC) curve analysis by reporting the area under the curve, sensitivity, specificity and +/− likelihood ratio (LR). Univariable and multivariable logistic regression analysis will be performed also to assess the association of myocardial injury in COVID-19 infection with in-hospital complications and need for aggressive therapies.

Univariable and multivariable multiple linear regression will be instead used to assess

whether SAQ summary score at 12-months follow-up is affected by myocardial injury in patients with COVID-19 infection.

Finally, to assess whether the presence of myocardial injury during COVID-19 predicts a worse outcome, in term of both MACEs at 12 months and single components, uni- and multivariable interaction proportional hazard Cox regression models will be computed. We will consider, as for MACEs, time to first event, and for each component, time to each event. To evaluate combined effects between each clinical/laboratory predictor and presence/absence of Myocardial Injury (MI), multivariable interaction Cox models will be fitted, and the interaction hazard ratios (IHR) evaluated. In particular, for each predictor, one interaction Cox model will be fitted. In this framework, IHR = 1 indicates no synergy between predictor and MI, IHR <1 expresses a reduction of hazard due to the synergy, while IHR >1 an increased hazard. The interaction parameters (IHR) will be interpreted as difference (in HR terms) of the predictor and MI (absence of MI as reference category). Proportionality of the hazard functions will be assessed by visual inspection of hazard plots and Schoenfeld residuals. When proportionality was doubtful, weighted Cox regression models would be fitted.

A two-tailed analysis will be performed and a p value <0.05 will be considered as statistically significant. Statistical analyses will be performed using R software version 4.2.1 (CRAN ®, R Core 2021) (and its packages *survival*, *survminer*, *coxphw* and *Hmisc*) (18).

Data privacy and data protection

Privacy issues related to this project have been analyzed with Policlinico Gemelli Data Protection Officer (D.P.O.). As a GENERATOR RWD study, this project will be compliant with GDPR Italian and European directives and regulation (EU Directive 2016/679 and under Italian Laws: Decreto Legislativo 196/2003, Decreto Legislativo 101 2018, Autorizzazione Generale Garante 9/2016)

The guidelines for data privacy are covered by two main documents prepared with the D.P.O.:

- Generator main document "Linee Guida Utilizzo Real World Data" which prescribes the governance mechanisms for Generator through two main bodies (Comitato di Supervisione and Comitato Operativo) where representatives appointed from IRCSS and other key Units of Policlinico participate and have mandate to decide;
- "Orizzonte Normativo Real World Data" prepared by the D.P.O., which provides the directives for the execution of any Generator study to assure its compliance with European and Italian GDPR directives.

All RWD studies have research purposes and therefore consent-related procedures are consistent with European Directive 2016/679. The data architecture which supports RWD studies has been defined to provide the highest degree of protection, in accordance with all GDPR and security requirements. In this respect, RWD provides "protection by design" in each step of the process.

Significance and innovation

This study will provide a detailed characterization of myocardial injury in patients with COVID-19 and its role in determining the different clinical courses of SARS-CoV-2 infection. Moreover, the aim of study is to identify, for the first time, the clinical predictors of the occurrence of myocardial injury in patients with COVID-19 infection that could allow the development of predictive models as well as help clinicians in the early assessment of the risk of myocardial injury and the prevention of the associated unfavourable outcomes. Furthermore, this study will characterize the cardiovascular outcomes in the post-acute COVID-19 phase, and it will evaluate for the first time the long-term clinical outcomes of patients who experienced myocardial injury, possibly paving the way for the implementation of specific therapies aiming to reduce the cardiovascular risk and the long-term sequelae of COVID-19.

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