Prevalence and prognostic value of cardiac troponin in elderly patients hospitalized for COVID-19

Vincenzo De Marzo

Cardiovascular Diseases Unit, IRCCS Ospedale Policlinico San Martino – IRCCS Italian Cardiology Network, Genova, Italy <https://orcid.org/0000-0002-8031-9761>

Antonio Di Biagio

Infectious Diseases Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Roberta Della Bona

Cardiovascular Diseases Unit, IRCCS Ospedale Policlinico San Martino – IRCCS Italian Cardiology Network, Genova, Italy

Antonio Vena

Infectious Diseases Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Eleonora Arboscello

Emergency Department, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Harusha Emirjona

Emergency Department, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Sara Mora

Department of Informatics, Bioengineering, Robotics and System Engineering, University of Genova, Genova, Italy

Mauro Giacomini

Department of Informatics, Bioengineering, Robotics and System Engineering, University of Genova, Genova, Italy

Giorgio Da Rin

Laboratory Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Paolo Pelosi

Anesthesia and Intensive Care Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Matteo Bassetti

Infectious Diseases Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Pietro Ameri (✉ pietroameri@unige.it)

Cardiovascular Diseases Unit, IRCCS Ospedale Policlinico San Martino – IRCCS Italian Cardiology Network, Genova, Italy

Italo Porto

Cardiovascular Diseases Unit, IRCCS Ospedale Policlinico San Martino – IRCCS Italian Cardiology Network, Genova, Italy

Research Article

Keywords: COVID-19, troponin, biomarker, mortality, heart

Posted Date: October 23rd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-96524/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Increases in cardiac troponin (cTn) in coronavirus disease 2019 (COVID-19) have been associated with worse prognosis. Nonetheless, data about the significance of cTn in elderly subjects with COVID-19 are lacking.

Methods: From a registry of consecutive patients with COVID-19 admitted to a hub hospital in Italy from 25/02/2020 to 03/07/2020, we selected those ≥ 60 year-old and with cTnI measured within 3 days from the molecular diagnosis of SARS-CoV-2 infection. When available, a second cTnI value within 48 hours was also extracted. The relationship between increased cTnI and all-cause in-hospital mortality was evaluated by a Cox regression model and restricted cubic spline functions with three knots.

Results: Of 343 included patients (median age 75.0 (68.0-83.0) years, 34.7% men), 88 (25.7%) had cTnI above the upper-reference limit (0.046 $\mu\text{g/L}$). Patients with increased cTnI had more comorbidities, greater impaired respiratory exchange and higher inflammatory markers on admission than those with normal cTnI. Furthermore, they died more (73.9% vs. 37.3%, $p < 0.001$) over 15 (6-25) days of hospitalization. The association of elevated cTnI with mortality was confirmed by the adjusted Cox regression model (HR: 1.61, 95%CI: 1.06-2.52, $p = 0.039$) and was linear until 0.3 $\mu\text{g/L}$, with a subsequent plateau. Of 191 (55.7%) patients with a second cTnI measurement, 49 (25.7%) had an increasing trend, which was not associated with mortality (univariate HR 1.39, 95%CI 0.87-2.22, $p = 0.265$).

Conclusions: In elderly COVID-19 patients, an initial increase in cTn is common and predicts a higher risk of death. Serial cTn testing may not confer additional prognostic information.

Introduction

Coronavirus disease 2019 (COVID-19) is the clinical manifestation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The most common symptoms are fever, dry cough, fatigue, myalgia, anosmia, and dysgeusia [1]. About 80% of patients with COVID-19 have mild pneumonia, whilst around 15% suffer from acute respiratory failure, and about 5% are critically ill with rapid progression towards acute respiratory distress syndrome (ARDS), cytokine storm, and multisystem failure [1, 2].

Within this clinical picture, cardiovascular (CV) alterations are common and have been associated with worse prognosis [3-6]. The spectrum includes elevation of biomarkers of cardiac injury, arterial and venous thromboembolism, and arrhythmias. In severe cases, cardiogenic shock and fatal cardiac arrest may occur [4, 7].

Among these CV abnormalities, particular emphasis has been given to an increase in cardiac troponin (cTn) concentrations. During COVID-19, cardiac stress and damage may arise because of a variety of mechanisms, including type 2 ischemia, hypoxia, sepsis and systemic inflammation, pulmonary thrombosis and embolism, cardiac adrenergic hyperstimulation during cytokine storm syndrome, and

myocarditis [2, 8]. A rise in cTn may be also due to pre-existing cardiac disease and concomitant comorbidities [9].

Irrespective of the underlying causes, evidence of cardiac injury at the time of admission for COVID-19 has been associated with a more severe clinical course and higher mortality [2, 6, 8, 10]. Limited data also indicate that a rising trend of cTn levels during the hospitalization identifies a subset of COVID-19 patients with worse outcome [10, 11].

Nonetheless, the specific impact of cTn measurement has not been investigated yet in the elderly. This lack of evidence has potential practical implications, since COVID-19 patients older than 60 years of age need hospitalization more often than younger ones [12-14] and, thereby, are more likely to be tested for cTn.

Aims of this study were to evaluate the relationship between cardiac injury, as demonstrated by cTn elevation either at baseline or on a second measurement within 48 hours, and all-cause in-hospital mortality in ≥ 60 year-old patients hospitalized for COVID-19.

Methods

Study population

This is a retrospective analysis of a prospective registry enrolling all consecutive patients diagnosed with COVID-19 in a hub hospital in Genova, Italy, from February 25th to July 3rd, 2020. Genova is the main city of an Italian region with an overall old population (around 1,500,000 inhabitants, with 35.6% being ≥ 60 -year-old).

The registry was developed by modifying an established registry of patients with infectious diseases [15, 16], was approved by the local Ethics Committee (study number 163/2020) and contained anonymized data; all capable subjects gave written informed consent to the use of such data for research purposes. SARS-CoV-2 infection was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) of pharyngeal swabs or bronchoalveolar aspirates. Laboratory exams and diagnostic procedures were performed as per standard clinical practice.

The study sample consisted of patients aged ≥ 60 years with cTnI measured within 3 days from the molecular confirmation of SARS-CoV-2 infection. A second cTnI measurement within 48 hours from the first one was available for a subset. The 60-year age cut-off was chosen according to the general agreement that ≥ 60 year-old COVID-19 patients represent a distinctive population with specific features [12-14].

The patients and the public were not involved in the design, conduct, reporting, or dissemination plans of the research.

Demographic and clinical data

For every patient the following information was retrieved: age, gender, Charlson comorbidities index (CCI), prior myocardial infarction (MI), history of chronic heart failure (CHF), and presence of hypertension, atrial fibrillation (AF), neurological disorder, chronic obstructive pulmonary disease (COPD), diabetes, cancer or chronic kidney disease (CKD), need of non-invasive or invasive ventilation, and admission to the intensive care unit (ICU), as reported in the medical records.

We also assessed the clinical features on admission, including laboratory exams.

Plasma cTnI concentration was measured using a sandwich chemiluminescent immunoassay based on LOCI® technology on Dimension Vista® 1500 System. The limit of quantitation (functional sensitivity), which corresponds to the cTnI concentration at which the coefficient of variation is 10%, was $<0.04 \mu\text{g/L}$ [17]. The upper-reference limit (URL), as defined at the 99th percentile of the reference interval, was $0.046 \mu\text{g/L}$.

Study outcome

All-cause in-hospital mortality was ascertained by review of the medical records.

Statistical analysis

Categorical variables are presented as frequencies and percentages and were compared by chi-square test or Fisher's exact test. Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range according to their distribution. Normally distributed variables were compared by means of unpaired Student's t test and non-normally distributed ones with the U Mann-Whitney non-parametric test.

For those patients for whom a second cTnI determination was available, the trend between the second and the first measurement was categorized as increase or non-increase, depending on whether the difference between the two values was >0 or ≤ 0 .

Time to all-cause in-hospital death was graphically depicted using the Kaplan-Meier method and compared by log-rank test. Patients were right-censored if they were discharged from the hospital alive or were still hospitalized at the time of data extraction (July 3, 2020).

A Cox regression model was used to estimate the hazard ratios (HRs) with 95% confidence interval (CI) of all-cause in-hospital mortality according to cTnI values below or above the URL. The model was adjusted for clinically meaningful covariates that were different between dead and alive patients with $p < 0.05$.

A potentially non-linear relationship between admission cTnI and all-cause in-hospital mortality was tested by using restricted cubic spline functions with three knots; data were then displayed graphically. As a sensitivity analysis, fitting a proportional sub-distribution hazards regression to the same variables included in the Cox regression model, we performed a competing risk analysis in which discharge from the hospital was treated as a competing risk for all-cause in-hospital mortality.

All analyses were performed with R environment 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and packages finalfit, survival, ggplot2, survminer, rms, and cmprsk.

Results

A total of 1275 consecutive patients admitted during the study period were included in the registry. Of them, 468 had cTnI measured within 3 days from the RT-PCR for SARS-CoV-2. One-hundred twenty-five subjects were excluded from the analysis because they had <60 years of age, leaving a final sample of 343 patients. Their baseline characteristics are shown in **Table 1**. Median age was 75.0 (68.0-83.0) years and 119 (34.7%) were men. One-hundred ninety-eight (58.1%) patients had hypertension and 17.6% diabetes. Based on medical history, the prevalence of cardiovascular comorbidities was around 10%. Most patients presented with fever and around half had dyspnoea (**Table 1**). Median oxygen saturation (SpO₂) and arterial oxygen partial pressure (pO₂) were 94.0 (90.0-97.0) % and 67.1 (55.0-84.3) mmHg, respectively. Inflammatory biomarkers were elevated (**Table 1**).

Median cTnI was 0.02 (0.02-0.05) µg/L; 88 (25.7%) patients had a cTnI value above the URL. These latter were older and had more often AF, CKD and a neurological disorders than the subjects with normal cTnI (**Table 1**). Although the frequency of dyspnoea was not different between the two groups, patients with cTnI above the URL presented with lower SpO₂ and arterial pO₂. Concentrations of creatinine, AST, bilirubin, inflammatory parameters, D-dimer, creatine phosphokinase (CPK), and international normalized ratio (INR) were higher in subjects with baseline cTnI above the URL, whilst haemoglobin levels were lower (**Table 1**).

Overall, 28.7% and 17.6% patients received non-invasive and mechanical ventilation, respectively; 18.8% were admitted to the ICU. The frequencies of non-invasive and invasive ventilation support, as well as of ICU admission, were non-significantly lower in the group with elevated cTnI (**Table 1**).

During a median hospital stay of 15 (6-25) days, 160 (46.6%) patients died (**Additional table 1**). All-cause mortality was higher in patients with increased admission cTnI (65 deaths/88 patients, 73.9% vs. 95 deaths/255 patients, 37.3%, $p<0.001$).

Kaplan-Meyer curve showed that patients with increased cTnI survived less throughout the hospitalization than those with normal cTnI (**Figure 1**). The association between baseline cTnI and all-cause in-hospital mortality was confirmed by the adjusted Cox regression model (HR: 1.61, 95%CI: 1.06-2.52, $p=0.039$) (**Table 2**). The sensitivity competing risk analysis yielded results consistent with the Cox regression model (HR for admission cTnI: 1.46, 95%CI: 1.11-2.93, $p=0.043$) (**Additional table 2**).

As shown in **Figure 2**, the association of admission cTnI with all-cause in-hospital mortality began with concentrations within the range of normality as per manufacturer's indications and was linear until the threshold of 0.3 µg/L, after which a plateau was observed with no further increase in mortality.

A second cTnI measurement within 48 hours was available for 191 (55.7%) patients, the median value being 0.02 (0.02-0.05) µg/L; an increasing trend was found in 49 (25.7%) of them.

The concentrations of cTnI were higher at both the first (0.03 (0.02-0.06) µg/L vs. 0.02 (0.02-0.02) µg/L, $p<0.001$) and the second determination (0.05 (0.02-0.08) µg/L vs. 0.02 (0.02-0.03) µg/L, $p<0.001$) in patients who died than in those who did not (**Figure 3**). However, an increase in cTnI within 48 hours was not associated with higher all-cause in-hospital mortality (univariate HR: 1.39, 95%CI: 0.87-2.22, $p=0.265$).

Discussion

In this study, the first evaluating the prognostic significance of cTn elevation in elderly patients with COVID-19, we show that an initially increased cTn value portends a higher risk of in-hospital mortality in subjects older than 60 years with COVID-19. In the population examined, an increased cTnI concentration within 3 days from the molecular diagnosis of SARS-CoV-2 infection conferred a 60% higher risk of all-cause in-hospital death. By contrast, a further elevation in cTn over the following 48 hours did not provide additional prognostic information.

CV involvement is common in COVID-19 and has been pointed out as one of the factors contributing to the dismal prognosis that many patients face [1].

The elevation of markers of myocardial injury, especially cTn, has drawn much attention, since it can be readily assessed and is clinically relevant [2, 4, 7, 8]. Several authors have reported that an increase in cTn concentrations portends a higher risk of in-hospital death [3-6, 10, 11, 18-20]. This evidence has been gathered by analysing various cohorts with important differences, for instance in the severity of COVID-19 and, thus, the intensity of treatments, in ethnicity and in the burden of comorbidities [9]. Therefore, it is assumed that the results of these studies can be generalized to all patients hospitalized for COVID-19 [8]. However, data about the value of cTn specifically in elderly subjects admitted for COVID-19 are scarce. This lack of information is remarkable, considering the epidemiology of the SARS-CoV-2 pandemic, in which old individuals are the most affected and often need hospitalization [13, 21, 22].

Our results confirm that cTnI elevation is an independent predictor of in-hospital mortality in elderly patients hospitalized for COVID-19, like it is in younger ones.

The cohort we investigated was particularly old. In fact, the median age was 75 years, whilst the mean or median age in the other investigations of cTn in COVID-19 was ≤ 70 years, with the exception of 2 studies with a mean age of 71 years (**Additional table 3**). Furthermore, almost 1 in 2 patients died during the hospitalization. A similar proportion of deaths has been described for critically ill COVID-19 Italian patients with a median age of 63 (56-69) years [23]. We believe that the comparable mortality of our patients, who were admitted to the ICU only in about 20% of cases, is explained by the substantially older age. It is notable that, even within this vulnerable population, an initial increase in cTn identified a frailer group with worse prognosis.

The mechanisms leading to cTn elevation during COVID-19 are manifold and likely often concomitant [24]. Autopsy studies indicate that myocardial ischemia due to plaque rupture, coronary artery spasm or direct injury, or microthrombi are rare in COVID-19 [25], and the pathogenesis of cardiac damage has been primarily ascribed to other events [4, 9, 10, 19]. First, the heart may suffer from severe hypoxia in the context of acute respiratory insufficiency. Second, hyperinflammation and sepsis with cytokine storm may directly affect cardiomyocytes, up to causing stress cardiomyopathy or myocarditis. Third, cardiac injury may develop following pulmonary thromboembolism. Finally, SARS-CoV-2 can localize to the myocardium, although an ensuing inflammatory infiltrate has not been demonstrated [18]. The elderly may be more prone to all these events because of the reduced resistance of the aging heart to stressors and of concomitant asymptomatic or overt cardiac disease. Other authors found a continuous relationship between cTn concentrations and mortality [6]. Moreover, in subjects admitted for COVID-19 younger than those evaluated by us, the trend between two measurements of cTn obtained at the beginning of the hospitalization may help better stratifying the risk of death [21]. By contrast, in our cohort, the troponin-mortality risk curve plateaued after a relatively low level and the changes in cTn did not refine prognostication. Thus, our analysis suggests that the presence, but not the entity of cardiac injury corresponds to worse outcomes in elderly patients hospitalized for COVID-19, and that multiple determinations of cTn may be of value only if clinically motivated.

The retrospective design is the main limitation of this work. However, most of the literature about the CV complications in COVID-19 is based on data collected retrospectively. Moreover, in Italy the most intense phase of the SARS-CoV-2 epidemic, when the majority of patients was hospitalized, had a relatively brief course, making the conduct of prospective studies very challenging. The possibility of a selection bias must be also acknowledged, since only part of the subjects included in the registry we analysed had cTnI measured.

Conclusions

An initial elevation in cTnI is associated with all-cause in-hospital mortality in elderly patients admitted for COVID-19. Beyond the relatively low threshold of 0.3 µg/L, additional increases in the cTnI concentrations do not confer a higher risk of mortality, indicating that the rise in cTnI in itself, rather than its entity, is marker of worse outcome. An increasing trend in cTnI levels on a second assessment does not give further information about prognosis.

Abbreviations

AF: atrial fibrillation

ALT: alanine transaminase

ARDS: acute respiratory distress syndrome

AST: aspartate transaminase

CCI: Charlson comorbidities index

CHF: chronic heart failure

CKD: chronic kidney disease

COPD: chronic obstructive pulmonary disease

COVID-19: coronavirus disease 2019

CPK: creatine-phosphokinase

CRP: C-reactive protein

cTnl: cardiac troponin I

HR: hazard ratio

ICU: intensive care unit

IL-6: interleukin-6

INR: international normalized ratio

MI: myocardial infarction

MV: mechanical ventilation

NIV: non-invasive ventilation

pO₂: partial oxygen pressure

RT-PCR: reverse transcriptase-polymerase chain reaction

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SD: standard deviation

SpO₂: oxygen saturation

URL: upper-reference limit

Declarations

Ethics approval and consent to participate

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Liguria Region (registry number 163/2020). All capable subjects gave written

informed consent to the use of their anonymised data for research purposes.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used for the current study is not available because other analyses are being run. Nonetheless, it can be made available on reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors declare that they received no funding for this study.

Authors' contributions

VDM planned the research project, performed the statistical analysis and wrote the manuscript draft; RDB, EA, HE, SM, MG contributed to collection of data and reporting of results; ADB and AV were responsible of the collection of data, contributed to reporting of results and revised the manuscript draft; GDR was responsible for the laboratory evaluations and contributed to their interpretation; MB was responsible of the collection of data and provided critical input; PP and IP provided critical input and revised the manuscript draft; PA planned the research project, wrote the manuscript draft and is responsible for the overall content as guarantor. All authors approved the final version of manuscript.

Acknowledgements

GECOVID-19 Study group: Anna Alessandrini; Marco Camera; Emanuele Delfino; Andrea De Maria; Chiara Dentone; Antonio Di Biagio; Ferdinando Dodi; Antonio Ferrazin; Giovanni Mazzarello; Malgorzata Mikulska; Laura Nicolini; Federica Toscanini; Daniele Roberto Giacobbe; Antonio Vena; Lucia Taramasso; Elisa Balletto; Federica Portunato; Eva Schenone; Nirmala Rosseti; Federico Baldi; Marco Berruti; Federica Briano; Silvia Dettori; Laura Labate; Laura Magnasco; Michele Mirabella; Rachele Pincino; Chiara Russo; Giovanni Sarteschi; Chiara sepulcri; Stefania Tutino (**Clinica di Malattie Infettive**); Roberto Pontremoli; Valentina Beccati; Salvatore Casciaro; Massimo Casu; Francesco Gavaudan; Maria Ghinatti; Elisa Gualco; Giovanna Leoncini ; Paola Pitto; Kassem salam (**Clinica di Medicina interna 2**); Angelo Gratarola; Mattia Bixio; Annalisa Amelia; Andrea Balestra; Paola Ballarino; Nicholas Bardi; Roberto Boccafogli; Francesca Caserza; Elisa Calzolari; Marta Castelli; Elisabetta Cenni; Paolo Cortese; Giuseppe Cuttone; Sara Feltrin; Stefano Giovinnazzo; Patrizia Giuntini; Letizia Natale; Davide Orsi; Matteo Pastorino; Tommaso Perazzo; Fabio Pescetelli; Federico Schenone; Maria Grazia Serra; Marco Sottano (**Anestesia e Rianimazione; Emergenza Covid padiglione 64**); Iole Brunetti; Maurizio Loconte; Lorenzo Ball; Denise Battaglini; Chiara

Robba; Nicolò Patroniti (**Anestesiologia e Terapia Intensiva**); Roberto Tallone; Massimo Amelotti; Marie Jeanne Majabò; Massimo Merlini; Federica Perazzo (**Cure Intermedie**); Nidal Ahamd; Paolo Barbera; Marta Bovio; Paola Campodonico; Andrea Collidà; Ombretta Cutuli; Agnese Lomeo; Francesca Fezza; Nicola Gentilucci; Nadia Hussein; Emanuele Malvezzi; Laura Massobrio; Giulia Motta; Laura Pastorino; Nicoletta Pollicardo; Stefano Sartini; Paola Vacca; Valentina Virga (**Dipartimento di Emergenza ed Accettazione**); Italo Porto; Gian Paolo Bezante; Roberta Della Bona; Giovanni La Malfa; Alberto Valbusa; Vered Gil Ad (**Clinica Malattie Cardiovascolari**); Emanuela Barisione; Michele Bellotti; Aloe' Teresita; Alessandro Blanco; Marco Grosso; Maria Grazia Piroddi (**Pneumologia ad Indirizzo Interventistico**); Paolo Moscatelli; Paola Ballarino; Matteo Caiti; Elisabetta Cenni; Patrizia Giuntini; Ottavia Magnani (**Medicine d'Urgenza**); Samir Sukkar; Ludovica Cogorno; Raffaella Gradaschi; Erica Guiddo; Eleonora Martino; Livia Pisciotta (**Dietetica e Nutrizione clinica**); Bruno Cavagliere; Rossi Cristina; Farina Francesca (**Direzione delle Professioni Sanitarie**); Giacomo Garibotto; Pasquale Esposito (**Clinica nefrologica, Dialisi e Trapianto**); Giovanni Passalacqua; Diego Bagnasco; Fulvio Braidò; Annamaria Riccio; Elena Tagliabue (**Clinica Malattie Respiratorie ed Allergologia**); Claudio Gustavino; Antonella Ferraiolo (**Ostetricia e Ginecologia**); Salvatore Giuffrida; Nicola Rosso (**Direzione Amministrativa**); Alessandra Morando; Riccardo Papalia; Donata Passerini; Gabriella Tiberio (**Direzione di Presidio**); Giovanni Orengo; Alberto Battaglini (**Gestione del Rischio Clinico**); Silvano Ruffoni; Sergio Cagliaris.

References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC: **Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review.** *JAMA* 2020.
2. Imazio M, Klingel K, Kindermann I, Brucato A, De Rosa FG, Adler Y, De Ferrari GM: **COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis?** *Heart* 2020, **106**(15):1127-1131.
3. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, Chen Y, Han Y: **Cardiovascular manifestations and treatment considerations in COVID-19.** *Heart* 2020, **106**(15):1132-1141.
4. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O: **Potential Effects of Coronaviruses on the Cardiovascular System: A Review.** *JAMA Cardiol* 2020.
5. Ruan Q, Yang K, Wang W, Jiang L, 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, **46**(5):846-848.
6. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q *et al*: **Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China.** *JAMA Cardiol* 2020.
7. Long B, Brady WJ, Koyfman A, Gottlieb M: **Cardiovascular complications in COVID-19.** *Am J Emerg Med* 2020, **38**(7):1504-1507.
8. Gaze DC: **Clinical utility of cardiac troponin measurement in COVID-19 infection.** *Ann Clin Biochem* 2020, **57**(3):202-205.
9. Sandoval Y, Januzzi JL, Jr., Jaffe AS: **Cardiac Troponin for the Diagnosis and Risk-Stratification of Myocardial Injury in COVID-19: JACC Review Topic of the Week.** *J Am Coll Cardiol* 2020.

10. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A *et al*: **Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection.** *J Am Coll Cardiol* 2020, **76**(5):533-546.
11. Li C, Jiang J, Wang F, Zhou N, Veronese G, Moslehi JJ, Ammirati E, Wang DW: **Longitudinal correlation of biomarkers of cardiac injury, inflammation, and coagulation to outcome in hospitalized COVID-19 patients.** *J Mol Cell Cardiol* 2020.
12. Mueller AL, McNamara MS, Sinclair DA: **Why does COVID-19 disproportionately affect older people?** *Aging (Albany NY)* 2020, **12**(10):9959-9981.
13. Nanda A, Vura N, Gravenstein S: **COVID-19 in older adults.** *Aging Clin Exp Res* 2020, **32**(7):1199-1202.
14. Shahid Z, Kalayanamitra R, McClafferty B, Kepko D, Ramgobin D, Patel R, Aggarwal CS, Vunnam R, Sahu N, Bhatt D *et al*: **COVID-19 and Older Adults: What We Know.** *J Am Geriatr Soc* 2020, **68**(5):926-929.
15. Giannini B, Riccardi N, Cenderello G, Di Biagio A, Dentone C, Giacomini M: **From Liguria HIV Web to Liguria Infectious Diseases Network: How a Digital Platform Improved Doctors' Work and Patients' Care.** *AIDS research and human retroviruses* 2018, **34**(3):239-240.
16. Vena A, Giacobbe DR, Di Biagio A, Mikulska M, Taramasso L, De Maria A, Ball L, Brunetti I, Loconte M, Patroniti NA *et al*: **Clinical characteristics, management and in-hospital mortality of patients with COVID-19 In Genoa, Italy.** *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2020.
17. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J, Bio-Markers ITFoCAoC: **Cardiac Troponin Assays: Guide to Understanding Analytical Characteristics and Their Impact on Clinical Care.** *Clin Chem* 2017, **63**(1):73-81.
18. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z: **Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19).** *JAMA Cardiol* 2020.
19. Lippi G, Lavie CJ, Sanchis-Gomar F: **Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis.** *Prog Cardiovasc Dis* 2020, **63**(3):390-391.
20. Lombardi CM, Carubelli V, Iorio A, Inciardi RM, Bellasi A, Canale C, Camporotondo R, Catagnano F, Dalla Vecchia LA, Giovino S *et al*: **Association of Troponin Levels With Mortality in Italian Patients Hospitalized With Coronavirus Disease 2019: Results of a Multicenter Study.** *JAMA Cardiol* 2020.
21. Lithander FE, Neumann S, Tenison E, Lloyd K, Welsh TJ, Rodrigues JCL, Higgins JPT, Scourfield L, Christensen H, Haunton VJ *et al*: **COVID-19 in older people: a rapid clinical review.** *Age Ageing* 2020, **49**(4):501-515.
22. Nikolich-Zugich J, Knox KS, Rios CT, Natt B, Bhattacharya D, Fain MJ: **SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes.** *Geroscience* 2020, **42**(2):505-514.
23. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G *et al*: **Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive**

Care Units in Lombardy, Italy. *JAMA Intern Med* 2020.

24. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D: **Elevated Troponin in Patients With Coronavirus Disease 2019: Possible Mechanisms.** *J Card Fail* 2020, **26**(6):470-475.
25. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, Najafian B, Deutsch G, Lacy JM, Williams T *et al*: **Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series.** *Lancet* 2020, **396**(10247):320-332.

Tables

Table 1. Characteristics of the study patients according to baseline cardiac troponin I.

	Overall population (n=343)	cTnI ≤0.046 µg/L (n=255)	cTnI >0.046 µg/L (n=88)	p value
<i>Baseline and clinical characteristics</i>				
Age (years)	75.0 (68.0-83.0)	73.0 (66.0-81.0)	81.0 (74.0-89.3)	<0.001
Male sex	119 (34.7)	86 (33.7)	33 (37.5)	0.609
CCI	3.0 (2.0-4.0)	3.0 (2.0-4.0)	4.0 (3.0-4.0)	<0.001
Hypertension	198 (58.1)	145 (57.3)	53 (60.2)	0.725
Diabetes	60 (17.6)	46 (18.2)	14 (16.1)	0.781
Prior MI	41 (12.1)	26 (10.4)	15 (17.0)	0.143
CHF	26 (8.2)	17 (7.1)	9 (11.5)	0.308
AF	40 (11.9)	24 (9.6)	16 (18.6)	0.041
CKD	29 (8.6)	14 (5.6)	15 (17.2)	0.002
Neurological disorder	36 (10.7)	18 (7.1)	18 (20.9)	0.001
COPD	41 (12.2)	32 (12.8)	9 (10.3)	0.680
Cancer	38 (11.3)	24 (9.6)	14 (16.3)	0.136
<i>Symptoms and signs</i>				
Fever (°C)	37.7 (36.8-38.3)	37.7 (36.8-38.3)	37.8 (36.6-38.3)	0.721
Dyspnoea	179 (52.8)	131 (52.0)	48 (55.2)	0.697
Cough	138 (40.7)	109 (43.3)	29 (33.3)	0.134
Heart rate (per min)	88.0 (77.0-100.0)	87.0 (77.5-99.5)	90.0 (76.8-102.5)	0.142
Respiratory rate (per min)	20.0 (18.0-28.0)	20.0 (18.0-28.0)	22.0 (18.0-28.0)	0.481
Systolic BP (mmHg)	130.0 (120.0-150.0)	130.0 (120.0-150.0)	130.0 (116.5-145.0)	0.179
Diastolic BP (mmHg)	75.0 (70.0-85.0)	75.0 (70.0-85.0)	75.5 (67.3-80.0)	0.651
<i>Laboratory findings</i>				
SpO2 (%)	94.0 (90.0-97.0)	94.0 (91.0-97.0)	90.5 (85.0-96.0)	<0.001
Arterial pO2 (mmHg)	67.1 (55.0-84.3)	68.5 (58.5-86.0)	57.0 (48.0-73.0)	0.001
Creatinine (mg/dL)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	1.1 (0.9-1.8)	<0.001

Haemoglobin (g/L)	134.0 (120.0-147.0)	135.0 (123.5-148.0)	127.5 (114.0-143.0)	0.013
Platelets (x 10 ⁹ /L)	177.0 (134.0-240.5)	174.0 (135.5-234.5)	184.0 (130.8-268.5)	0.196
White blood cells (x 10 ⁹ /L)	6.4 (4.8-9.4)	6.2 (4.7-8.2)	8.1 (5.3-13.1)	<0.001
Lymphocytes (x 10 ⁹ /L)	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.8 (0.5-1.0)	0.163
ALT (IU/L)	30.0 (22.0-47.0)	30.0 (21.5-47.0)	30.0 (22.5-46.5)	0.803
AST (IU/L)	38.5 (26.3-58.0)	37.5 (26.0-54.0)	47.0 (29.8-78.3)	0.021
Total bilirubin (mg/dL)	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.6 (0.4-0.9)	0.034
INR	1.2 (1.1-1.3)	1.2 (1.1-1.3)	1.3 (1.2-1.4)	0.001
CRP (mg/L)	93.4 (43.1-136.0)	87.0 (42.3-134.0)	106.0 (52.2-160.0)	0.076
IL-6 (pg/mL)	50.7 (23.1-95.9)	46.0 (21.1-82.3)	75.6 (37.4-146.3)	<0.001
Fibrinogen (mg/dL)	5.7 (4.5-7.1)	5.7 (4.6-7.3)	5.3 (4.1-7.0)	0.128
D-dimer (ng/mL)	1081.0 (677.0-1704.3)	970.0 (622.1-1459.0)	1627.5 (1070.2-4333.3)	<0.001
CPK (µg/L)	126.5 (70.8-293.3)	114.0 (69.0-203.0)	186.00 (93.0-516.5)	<0.001
<i>Critically ill</i>				
No ventilation support	183 (53.7)	128 (50.6)	55 (62.5)	0.152
NIV	98 (28.7)	77 (30.4)	21 (23.9)	
MV	60 (17.6)	48 (19.0)	12 (13.6)	
MV duration (days)	10.0 (5.5-18.0)	12.0 (5.0-19.0)	8.0 (6.0-10.5)	0.329
Admitted to ICU	64 (18.8)	51 (20.2)	13 (14.8)	0.339

AF: atrial fibrillation; ALT: alanine-transaminase; AST: aspartate transaminase; BP: blood pressure; CHF: chronic heart failure; CKD: chronic kidney disease; COPD: chronic

obstructive pulmonary disease; CPK: creatine-phosphokinase; CRP: C-reactive protein; ICU: intensive care unit; INR: international normalized ratio; IL-6: interleuchin-6; MI: myocardial infarction; MV: mechanical ventilation; NIV: non-invasive ventilation; pO2: partial oxygen pressure; SpO2: oxygen saturation.

Table 2. Univariate and multivariate Cox regression models for all-cause in-hospital mortality with baseline cardiac troponin I.

Predictor	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.06	1.04-1.08	<0.001	1.07	1.04-1.09	<0.001
Increased baseline troponin	2.73	1.99-3.74	<0.001	1.61	1.06-2.52	0.039
CKD	2.66	1.71-4.15	<0.001	1.01	0.45-1.93	0.854
CHF	1.86	1.16-2.99	0.010	1.00	0.47-2.29	0.928
AF	1.83	1.20-2.79	0.005	1.55	0.86-2.77	0.143
Dyspnoea	1.74	1.26-2.41	0.001	2.29	1.48-3.54	<0.001
Systolic BP	0.99	0.98-1.00	0.094	1.00	0.99-1.01	0.475
SpO2	0.96	0.94-0.97	<0.001	0.98	0.95-1.01	0.202
Haemoglobin	0.99	0.99-1.00	0.111	1.00	0.99-1.01	0.870
White blood cells	1.02	1.00-1.05	0.051	0.96	0.91-1.02	0.215
Creatinine	1.30	1.17-1.45	<0.001	1.25	1.00-1.58	0.052
D-dimer	1.01	1.01-1.02	0.003	1.00	1.00-1.00	0.183
CRP	1.01	1.00-1.01	<0.001	1.00	1.00-1.01	0.001

AF: atrial fibrillation; BP: blood pressure; CHF: chronic heart failure; CKD: chronic kidney disease; CRP: C-reactive protein; SpO2: oxygen saturation.

Figures

Figure 1

Kaplan-Meier curves for all-cause in-hospital mortality according to baseline cardiac troponin I above or below the limit of quantification. cTnI: cardiac troponin I.

Figure 2

Spline curve for the hazard ratios of all-cause mortality according to baseline cardiac troponin I. cTnI: cardiac troponin I.

Figure 3

Baseline and subsequent cardiac troponin I levels according to all-cause in-hospital mortality. AF: atrial fibrillation; BP: blood pressure; CHF: chronic heart failure; CKD: chronic kidney disease; CRP: C-reactive protein; SpO2: oxygen saturation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [DeMarzocTnIHSMSupplementaldata.docx](#)