Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Cardiology 338 (2021) 278–285

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Prevalence and characteristics of myocardial injury during COVID-19 pandemic: A new role for high-sensitive troponin

Alessandro Maino [a,*,1], Enrico Di Stasio [b,c,1], Maria Chiara Grimaldi [a], Luigi Cappannoli [a], Erica Rocco [a], Rocco Vergallo [a], Federico Biscetti [d,e], Silvia Baroni [b,c], Andrea Urbani [b,c], Raffaele Landolfi [d,f], Luigi Marzio Biasucci [a,g]

[a] Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[b] Dipartimento di Scienze biotecnologiche di base, cliniche intensivologiche e perioperatorie, Università Cattolica del Sacro Cuore, Roma, Italy
[c] Dipartimento di scienze laboratoristiche ed infettivologiche, UOC Chimica, Biochimica e Biologia Molecolare Clinica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy
[d] U.O.C. Clinica Medica e Malattie Vascolari, Catholic University School of Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[e] Laboratory of Vascular Biology and Genetics, Università Cattolica del Sacro Cuore, Rome, Italy
[f] Division of Internal Medicine, Università Cattolica del Sacro Cuore, Rome, Italy
[g] Department of Cardiovascular and Pulmonary Sciences, Università Cattolica Sacro Cuore, Rome, Italy

ARTICLE INFO

Article history:
Received 26 April 2021
Received in revised form 31 May 2021
Accepted 15 June 2021
Available online 19 June 2021

Keywords:
Myocardial injury
Troponin
Heart failure
Coronavirus
COVID-19
SARS-CoV-2

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a pandemic disease that is causing a public health emergency. Characteristics and clinical significance of myocardial injury remain unclear.
Methods: This retrospective single-center study analyzed 189 patients who received a COVID-19 diagnosis out of all 758 subjects with a high sensitive troponin I (Hs-TnI) measurement within the first 24 h of admission at the Policlinico A.Gemelli (Rome, Italy) between February 20th 2020 to April 09th 2020.
Results: The prevalence of myocardial injury in our COVID-19 population is of 16%. The patients with cardiac injury were older, had a greater number of cardiovascular comorbidities and higher values of acute phase and inflammatory markers and leucocytes. They required more frequently hospitalization in Intensive Care Unit (10 [32.3%] vs 18 [11.4%]; $p = .003$) and the mortality rate was significantly higher (17 [54.8%] vs. 15 [9.5%], $p < .001$). Among patients in ICU, the subjects with myocardial injury showed an increase need of endotracheal intubation (8 out of 9 [88%] vs 7 out of 19[37%], $p = .042$). Multivariate analyses showed that hs-TnI can significantly predict the degree of COVID-19 disease, the intubation need and in-hospital mortality.
Conclusions: In this study we demonstrate that hs-Tn can significantly predict disease severity, intubation need and in-hospital death. Therefore, it may be reasonable to use Hs-Tn as a clinical tool in COVID-19 patients in order to triage them into different risk groups and can play a pivotal role in the detection of subjects at high risk of cardiac impairment during both the early and recovery stage.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic disease that is causing a public health emergency due to its high rapid spread, to the high mortality rate, and the high percentage of patients requiring hospitalization and intensive care.

These epidemiological characteristics are prominent in countries north of the equator known to have low seasonal air temperatures and low humidity is supposed to favor the transmission and survival of SARS-COV-2 [1,2]. In a notable recent report was described a significant decrease of the severity of COVID-19 between March and May and the seasonality of COVID-19 was assumed as the most likely explanation [3]. The mode of infection of COVID-19 is thought to be direct entry of the SARS-CoV-2 virus into cells via the human angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed predominantly in the lungs but also throughout the cardiovascular system. Thus, while the most virulent manifestation of COVID-19 is acute respiratory distress syndrome (ARDS), reports worldwide have also

Abbreviations: CE, angiotensin-converting enzyme; ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; ARDS, acute respiratory distress syndrome; CMR, cardiovascular magnetic resonance; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CVD, cardiovascular disease; Hs-Tn, high sensitive troponin; ICU, intensive care unit; MOF, multiorgan failure; MRA, antimineralocorticoid; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WBC, white blood cells.

* Corresponding author at: Largo Agostino Gemelli, 8, 00168 Rome, Italy.
E-mail address: alessandro.maino01@icatt.it (A. Maino).

[1] These authors equally contributed to the present manuscript.

https://doi.org/10.1016/j.ijcard.2021.06.028
0167-5273/

demonstrated cardiac injury associated with elevated troponin concentrations in infected patients [4].

The clinical spectrum of SARS-CoV-2 infection is wide, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and death [5–7].

However, accumulating evidences points to myocardial injury as a COVID-19-related complication with an incidence ranging from 7.2% to 36% [5,7–10].

According to limited information on cardiac complication of COVID-19, characteristics and clinical significance of myocardial injury remain unclear. In this study, we determined the pattern of high sensitivity troponin elevation in patients affected by SARS-CoV-2 and the prevalence of myocardial injury in this population; furthermore, we investigated the predictive value of Hs-Tn on disease severity and mortality. Finally, we sought to explore the potential causes of myocardial injury in cases of COVID-19 in our hospital.

2. Methods

2.1. Study design and participants

This single-center, retrospective, observational study was performed at "Policlinico Universitario Agostino Gemelli – Università Cattolica del Sacro Cuore", Rome (Italy). We retrospectively analyzed patients with a troponin measurement within the first 24 h of admission who received a COVID-19 diagnosis, according to the interim guidance of the World Health Organization [11], between February 20th 2020 to April 09th 2020. Patients whose clinical documentation was not available at the time of the study or under 18 years of age were excluded from the report. This study complied with the edicts of the 1975 Declaration of Helsinki [12] and was approved by the institutional ethics board of Catholic University of Sacred Heart. Consent was obtained from patients or patients' next of kin.

2.2. Data collection

Clinical information was collected on admission and during hospitalization by attending physicians. Each patient was identified with a numerical code to guarantee respect for privacy and anonymity. The data were collected from the medical and nursing diary, monitoring and administration form of drug therapy, and consisted of:

- personal data (gender, age, admission diagnosis);
- epidemiological-clinical data (comorbidities such as history of ischemic heart disease, atrial fibrillation, chronic heart failure, significant valvular heart disease, supraventricular or ventricular arrhythmia and cardiomyopathy; cardiovascular risk factors such as history of hypertension, smoking habits, dislipidemia, diabetes, chronic renal failure and malignant tumor; previous pharmacologic therapy such as use of loop diuretics, ACEi, ARBs, Betablockers, Calcium Blocker, Antimineralocorticoid (MRA), Statin and Cardioaspirin);
- clinical data (disease severity, complications i.e. ARDS, sepsis, AKI, MOF, polmonary embolism, ICU need and death);
- laboratory data (blood count, creatinine, NT-proBNP, inflammation indexes with PCR and PCT)

The hs-TnI values were analyzed through TNIH Advia Centaur high-sensitivity troponin kit (Siemens Healthineers, USA): CLIA method, antisera consisting of two bound biotinylated capture monoclonal antibodies and 1 recombinant monoclonal antibody of detection obtained in sheep against cTnI human conjugated with acridinium ester. LOD 1.6 ng / L and LOQ of 2.5 ng / L with CV at 20% and gender specific URL at the 99th percentile of 57 ng / L in male and 37 ng/L in female. The assays are performed on Siemens Advia Centaur XPT analyzer (Siemens Healthineers, USA);

Patients were categorized according to the presence or absence of myocardial injury. Cardiac injury was defined as blood levels of cardiac biomarkers (hs-TnI) above the gender specific 99th-percentile upper reference limit, regardless of new abnormalities in electrocardiography and echocardiography.

Covid-19 was diagnosed on the basis of the WHO interim guidance [11]. A confirmed case of Covid-19 was defined as a positive result on highthroughput sequencing or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens [5]. Only laboratory-confirmed cases were included in the analysis.

We defined the degree of severity of Covid-19 (mild, severe and critical) using the Chinese CDC report [13].

The authors of the Chinese CDC report divided the clinical manifestations of the disease by their severity:

- Mild disease: non-pneumonia and mild pneumonia;
- Severe disease: dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio or P/F [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)] < 300, and/or lung infiltrates >50% within 24 to 48 h;
- Critical disease: respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF).

Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition [14]. Acute kidney injury was diagnosed according to the KDIGO clinical practice guidelines [15]. Furthermore, Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock [16].

2.3. Statistical analysis

The statistical analysis of the data was carried out using the "Statistical Package for Social Science (SPSS)" program. Continuous variables were expressed as mean ± D.S. or median and range, as appropriate, and categorical variables represented as frequencies. Normal data distribution was verified using the Kolmogorov-Smirnov test. We log-transformed hs-Tn levels in order to reduce the positive skew of their distribution. The appropriate statistical, parametric and non-parametric test (Student *t*-test, Mann-Whytney *U* test, X2-test, as detailed in tables) was used in the analysis of the results. Correlations between variables was calculated using Pearson or Spearman coefficient, as appropriate. Multiple linear regression with backward-stepwise method, with the *p*-value for a feature to leave the model set at 0.05, was also performed to study the relationship between COVID gravity and clinical / laboratory parameters. Finally, a multivariate binary logistic analysis was performed to evaluate the relationship between death during hospitalization and clinical/laboratory findings. Effect modification by each previously described covariate was evaluated by testing whether including the interaction term in the multivariate logistic model significantly changed the log likelihood of the model applying stepwise logistic regression. The coefficients obtained from the logistic regression were expressed in terms of odds ratio with 95% confidence intervals. All of the tests were two-sided and statistical significance was set at $p < .05$.

3. Results

3.1. Characteristics of the general population and Troponin levels on admission

The sample was composed of 189 out of 758 patients in whom hs-TnI was determined at the Policlinico A.Gemelli (Rome, Italy) from February 20th to April 09th, 2020. We excluded 560 patients that were not

confirmed by SARS-CoV-2 RNA detection and nine inpatients without available key information in their medical records.

Thirty-two patients died during hospitalization and one hundred fifty-seven were discharged. The median age of the 189 patients was 66 years old (SD 12), ranging from 18 years old to 95 years old; 128 patients were male (Table 1) and 61 were female.

History of cardiovascular disease was found in nearly 26.8% of patients, with Ischemic heart disease (11.6%) being the most common comorbidity, followed by atrial fibrillation (5.3%), chronic heart failure(5.3%), significant valvular heart disease (1.6%), supraventricular or ventricular arrhythmia (1.6%) and cardiomyopathy (0.05%) (Table 1).

Cardiovascular risk factors were present in 55.3%: the most common of them was hypertension (42.3%), followed by dyslipidemia (17.5%), diabetes (14.8%), chronic renal disease (9.5%), smoking (7.9%) and cancer (2.1%).

Table 1
Demographics and clinical characteristics of patients With COVID-19.

	All patients ($n = 189$)	Patients with myocardial injury ($n = 31$)	Patients without myocardial injury ($n = 158$)	p value
Age (years)	66 (14)	77 (10)	64 (14)	**<0.001***
Female	61(32.3%)	16 (51.6%)	45 (28.5%)	**0.012§**
Comorbidities, *n* (%)				
History of all CVD	51 (26.8%)	10 (32.3%)	41(25.8%)	0.457§
Ischemic heart disease	22 (11.6%)	7 (22.6%)	15 (9.5%)	**0.038§**
History of myocardial infarction	8 (4.2%)	2(6.5%)	6 (3.8%)	0.620§
Atrial fibrillation	10 (5.3%)	3 (9.7%)	7 (4.4%)	0.213§
Chronic heart failure	10 (5.3%)	4 (12.9%)	6 (3.8%)	0.061§
Cardiomyopathy	1 (0.05%)	0	1 (0.06%)	1.000§
Significant valvular heart disease	3 (1.6%)	2 (6.5%)	1 (0.6%)	0.070§
Supraventricular or ventricular arrhytmias	3 (1.6%)	0	3 (1.9%)	1.000§
Risk factors, *n* (%)				
History of CVD risk factors	105 (55.3%)	25 (80.6%)	80 (50.3%)	**0.002§**
Hypertension	80 (42.3%)	20 (64.5%)	60 (38%)	**0.006§**
Diabetes	28 (14.8%)	6 (19.4%)	22 (13.9%)	0.436§
Former Smoking	15 (7.9%)	1 (3.2%)	14 (8.9%)	0.472§
Dyslipidemia	33 (17.5%)	7 (22.6%)	26 (16.5%)	0.411§
Chronic renal disease (eGFR <60 mL/min)	18 (9.5%)	10 (32.3%)	8 (5.1%)	**<0.001§**
History of Malignant neoplasms	4 (2.1%)	1 (3.2%)	3 (1.9%)	0.515§
Previous farmacological therapy, *n* (%)				
Use of Loop Diuretics	170 (10.1%)	10 (32.3%)	9 (5.7%)	**<0.001§**
Use of ACEi	16 (9.41%)	4 (12.9%)	12 (7.7%)	0.310§
Use of ARBs	27 (14.3%)	7 (22.6%)	20 (12.7%)	0.149§
Use of Betablockers	34 (18%)	12 (38.7%)	22 (13.9%)	**0.001§**
Use of Calcium Blocker	17 (9.0%)	3 (9.7%)	14 (8.9%)	1.000§
Antimineralocorticoid(MRA)	4 (2.1%)	2 (6.5%)	2 (1.3%)	0.126§
Use of Statin	24 (12.7%)	8 (25.8%)	16 (10.1%)	**0.017§**
Use of Cardioaspirin	32 (17.0%)	10 (32.3%)	22 (14.0%)	**0.014§**
Complications during hospitalitation, *n* (%)				
ARDS	89 (47.1%)	27 (87.1%)	62 (39.2%)	**<0.001§**
Sepsis	15 (7.9%)	6 (19.4%)	9 (5.7%)	**0.010§**
AKI	9 (4.8%)	5 (16.1%)	4 (2.5%)	**0.007§**
MOF	12 (6.3%)	5 (16.1%)	7 (4.4%)	**0.029§**
Polmonary embolism	6 (3.2%)	0	6 (3.8%)	0.592§
Clinical outcomes				
ICU need	28 (14.8%)	10 (32.3%)	18 (11.4%)	**0.003§**
Death	32 (16.9%)	17 (54.8%)	15 (9.5%)	**<0.001§**
Laboratory findings				
White blood cell (x10^9/L)	7.2 (3.6)	10.0 (5.1)	6.6 (3.0)	**<0.001***
	6.3 [1.7–27.7]	8.9 [3.2–27.7]	6.1 [1.7–26.8]	
Lymphocytes (%)	19.8 (12.6)	16.1 (15.1)	20.5 (11.9)	**0.003***
	16.5 [2.5–87.8]	13.0(3.3–76.7)	18.1 (2.5–87.8)	
Neutrophils (%)	71.7 (16.8)	78.2 (16.6)	70.4 (16.6)	**0.001***
	75.4 (1.5–95.2)	83.7 (12.7–94.7)	72.9 (1.5–95.2)	
Hemoglobin (g/dL)	12.9 (2.0)	12.5 (2.1)	12.9 (2.0)	0.347*
	13.0 (7.1–17.1)	12.6 (7.1–17.0)	13.1 (7.3–17.1)	
C Reactive Protein (mg/L)	98 (87)	144 (82)	89 (86)	**0.001#**
	87 (0–420)	148 (6–310)	62 (0–420)	
Procalcitonin (ng/mL)	1.2. (5.8)	2.4 (6.3)	1.0 (5.7)	**<0.001#**
	0.1 (0.0–59.9)	0.2 (0.0–27.0)	0.1 (0.0–59.0)	
D-dimers (mcg/mL)	2192 (403)	8763 (11699)	2192 (4034)	**<0.001#**
	1218 (6–35,200)	3974 (413–35,200)	10,278 (6–35,200)	
NTproBNP (pg/mL)	3195 (4827)	5428 (5501)	1067 (3036)	**<0.001#**
	852 (32–20,863)	4286 (337–20,863)	302 (32–13,426)	
Creatinine (mg/mL)	1.2 (1.2)	1.2 (0.6)	1.1 (0.9)	0.564*
	0.8 (0.4–7.6)	1.0 (0.5–2.4)	0.8 (0.4–4.8)	

Statistical tests used to assess difference between subgroups: * = Student's t-test, # = Mann-Whitney U test; § = X^2-test. Normal data distribution was verified using the Kolmogorov-Smirnov test and all of the tests were two-sided with statistical significance set at $p < .05$
Bold is emphasized the p value <.05.

The most frequent cardiovascular pharmacologic therapy was use of beta-blockers (34 [18%]), followed by cardioaspirin (32 [17.0%]), ARBs (32 [17.0%]), Statin (24 [12.7%]), Loop Diuretic (17 [10.1%]), ACEi (16 [9.41%]), Calcium blockers(17 [9.0%]) and MRAs (4 [2.1%]).

High sensitivity troponin-I concentrations detected on admission are presented in Fig. 1. In our study, the population affected by SARS-CoV-2 ($n = 189$) showed a significant association between disease severity and troponin levels (median [range] = 4.0 ng/L [<2.4–227.0 ng/L], 13.0 ng/L [<2.4–545.0 ng/L] and 34.0 ng/L [<2.4–9619.0 ng/L], $p < .001$, for mild, severe and critical state, respectively; see Fig. 2). Moreover, 31 subjects out of 189 (16%) showed high sensitivity troponin values higher than the 99 percentile upper reference limit stratified among previously defined severity classes as follows $n = 3$ (9.7%), $n = 9$ (29.0%) and $n = 19$ (61.3%), respectively. The distribution of hs-Tn values among survivor and non-survivor patients are described in Fig. 3. In our report, a significant correlation between hs-Tn levels and mortality was established (median [range] = survivors 9.0 ng/L [3–2231 ng/L] and non-survivors 46.0 ng/L [12–5184 ng/L], $p < .001$).

Univariate linear regression analyses using hs-TnI as a continuous variable demonstrated that age ($p < .001$), history of cardiovascular disease (overall [$p = .004$], ischemic heart disease [$p = .001$] and atrial fibrillation [$p = .007$]), presence of cardiac risk factors (overall [0.001], arterial hypertension [p0.004] and dyslipidemia [$p = .007$]), several previous drug use (loop diuretics [<0.001], ARBs[0.001], B-blockers [0.001], statin[<0.001], cardioaspirin [<0.001]) and laboratory findings (in particular WBC [<0.001], lymphocites count[<0.001], neutrophil count[0.001]) correlated positively with the concentration of hs-TnI (and inverse correlation with chronic kidney disease).

3.2. Comparison of clinical characteristics between the groups with and without myocardial injury

Compared with patients with normal hs-TnI levels (Table 1), those with elevated hs-TnI levels were older (mean [SD] age, 77.26 [10.35] vs 63.82 [14.05]) and had a higher proportion of female (16 [51.6%]vs 45 [28.5%]). Patients with elevated Hs-TnI levels had significantly higher rate of history of ischemic heart disease (7 (22.6%] vs 15 [9.5%]); the rates of other comorbidities, such as atrial fibrillation (3 [9.7%] vs. 7 [4.4%]) and chronic heart failure(4 [12.9%] vs. 6 [3.8%]) cardiomyopathy (8 [15.4%] vs 0), did not differ between those with normal and elevated Hs-TnI levels.

The group with myocardial injury presented significantly higher rates of all risk factors together (25 [80.6%] vs. 80 [50.3%]), hypertension (20 [64.5%] vs. 60 [38%]) and chronic kidney disease (10 [32.3%] vs 8 [5.1%]). Rates of diabetes (6 [19.4%] vs. 22 [13.9%]), smoking (1 [3.2%] vs. 14 [8.9%]), dyslipidemia (7 [22.6%] vs. 26 [16.5%]) and malignant neoplasms(1 [3.2%] vs. 3 [1.9%]) did not differ significantly between those with elevated and normal Hs-TnI levels.

The group of patients with myocardial injury was significantly associated with previous use of beta-blockers (12 [38.7%] vs. 22 [13.9%]), Cardioaspirin (10 [32.3%]vs. 22 [14.0%]), Statin (8 [25.8%] vs. 22 [14.0%]) and loop diuretics(10 [32.3%] vs. 9 [5.7%]). There were not a significant difference between the groups with and without myocardial injury according to the pharmacological therapy of ARBs (7 [22.6%] vs. 20 [12.7%]), ACEi (4 [12.9%] vs. 12 [7.7%]), MRA (2 [6.5%] vs. 14 [8.9%]) and calcium blockers (3 [9.7%] vs. 14 [8.9%]).

3.3. Laboratory findings on admission

On admission, most patients affected by SARS-CoV-2 presented abnormal laboratory results, such as D-Dimer, C-reactive protein and NT-proBNP (Table 1).

Patients with elevated Hs-TnI levels were characterized with significantly higher white blood cell count (median [SD] 10.0 [5.10] vs 6.6 [3.00]/μL [to convert to ×10^9 per liter, multiply by 0.001]) and neutrophil count (median [SD], 78.2 [16.6] vs 70.4 [16.6] expressed in percentage of total WBC ($p < .001$ for both) and lower lymphocyte count (median [SD], 16.1 (15.1) vs 20.5 (11.9) expressed in percentage of total WBC; $p = .003$) than those with normal Hs-TnI levels (Table 2). The levels of acute phase and inflammatory markers were higher among patients with troponin elevations above the 99th percentile cut-off as well: D-dimer (median [SD], 8763 microg/mL [11,699.0] vs. 2192 [4034.0]), C-reactive protein (median [SD], 144.0 mg/L [82.0] vs. 88.6 [85.6]) and procalcitonin (median [SD], 2.4 ng/mL [6.3] vs. 1.00 [5.7]) (Table 1).

In addition, NT-proBNP was significantly higher in the group with myocardial injury (median [SD], 5428 ng/L [5501] vs 1067 [3036]).

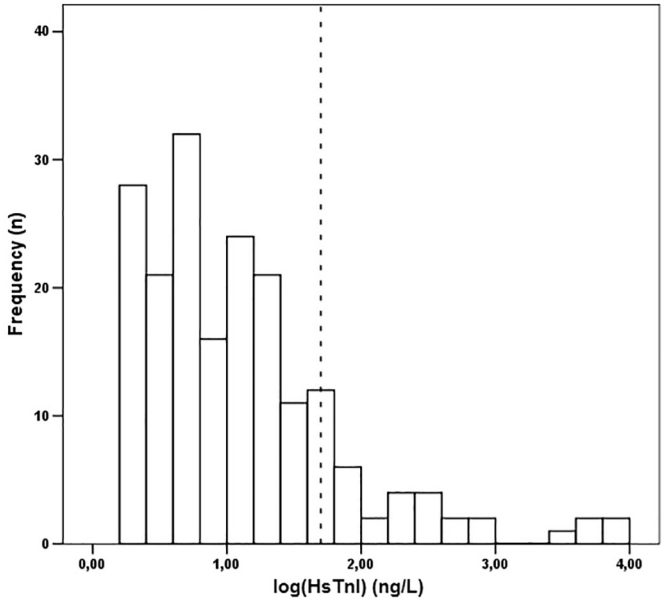

Fig. 1. Frequency of log10 HsTnI concentrations in the population under study. Dotted line represent the mean cut-off level (1.7 ng/L) for male (1.8 ng/L) and female (1.6 ng/L) subjects for myocardial injury.

3.4. Complications during hospitalization and clinical outcome

During hospital admission, 89 patients (47.1%) had ARDS, and 15 patients (7.9%) has fulfilled the criteria for diagnosis of sepsis and 12 patients (6.3%) of MOF (multiorgan failure); other common complications during hospitalization included acute kidney injury (9 patients [4.8%]) and pulmonary embolism (6 [3.2%]).

Most of the complications were more common among patients with cardiac injury than those without cardiac injury; these included ARDS (27 [87.1%] vs 62 [39.2%]; $p < .001$), acute kidney injury (5 [16.1%] vs 4 [2.5%]; $p = .007$), sepsis (6 [19.4%] vs. 9 [5.7%]; $p = .010$) and MOF (5 [16.1%] vs. 7 [4.4%]; $p = .029$). There was not significant difference between the two group for the pulmonary embolism.

During the stay, a total of 28 patients (14.8%) needed admission in ICU and 32 patients (13.7%) died.

Compared with those without cardiac injury, patients with cardiac injury required more frequently hospitalization in Intensive Care Unit (10 [32.3%] vs 18 [32.3%]; $p = .003$) (Table 1). Among patients in ICU, 15 out of 28 (54%) needed endotracheal intubation: the subjects with myocardial injury showed an increase odds of intubation (8 out of 9 [88%] vs 7 out of 19[37%], $p = .042$; OR 10.0 [1.0–100.5]). Furthermore, the mortality rate was significantly higher in patients with hs-TnI above the 99th percentile cut-off (17 [54.8%] vs. 15 [9.5%], $p < .001$).

A multiple regression analysis was carried out to investigate whether hs-TnI could significantly predict the degree of COVID-19

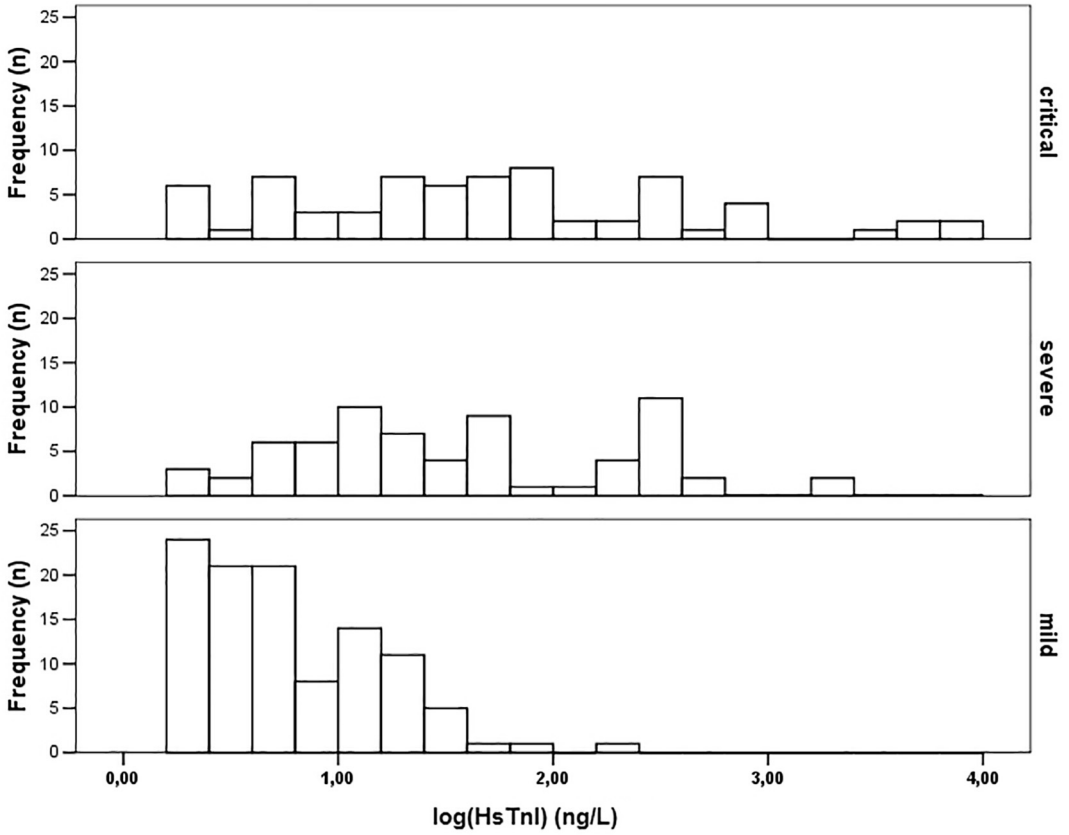

Fig. 2. Frequency of log10 HsTnI concentrations in the population under study for different clinical severity pictures.

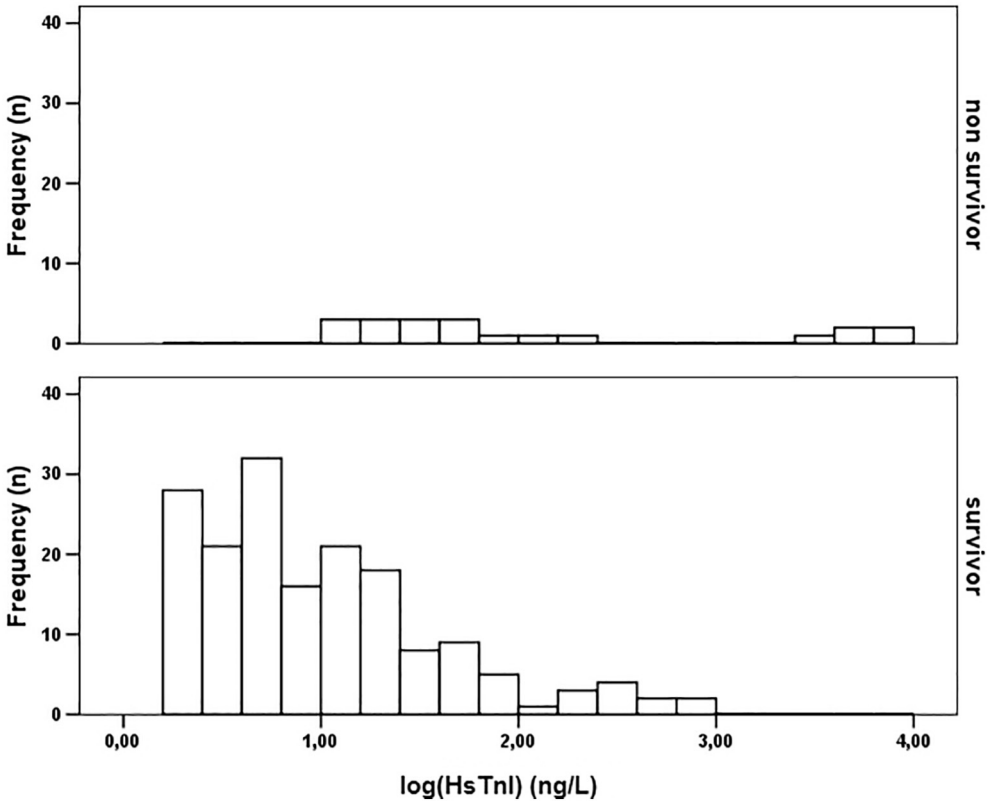

Fig. 3. Frequency of log10 HsTnI concentrations in the population under study for clinical outcome of death.

Table 2
Multiple linear regression. Dependent variable: COVID Gravity. Covariates: clinical and laboratoristic parameters. Adjusted $R^2 = 0.27$.

Covariate	Correlation coefficients	Standard Error	*p*
Log[hsTnI] (ng/L)	0.440	0.087	**<0.001**
Gender (female/male)	−0.048	0.117	0.681
Age (years)	0.004	0.005	0.404
History of Cardiovascula Diseases	0.118	0.130	0.365
Presence of Risk Factors	0.058	0.120	0.629
CRP (mg/L)	0.001	0.001	0.163
White Blood Cells (count/L)	0.026	0.017	0.111
Reduced Model of the regression obtained with a backward-stepwise method. Adjusted $R^2 = 0.27$			
Covariate	**Correlation coefficients**	**Standard Error**	***p***
Log[hsTnI] (ng/L)	0.525	0.077	**<0.001**
CRP (mg/L)	0.001	0.001	**0.020**

Bold is emphasized the *p* value <.05.

disease (Table 2). Hs-TnI and CRP contributed significantly to the model (B = . 0.525, $p < .001$; B = 0.001, $p = .020$, respectively)

We included 189 patients with complete data for all variables (32 non-survivors and 157 survivors) in the multivariable logistic regression model. We found that hs-Tn at admission, older age and CRP levels were associated with increased odds of death (Table 3).

In addition, a different multivariable logistic regression model was conducted to examine whether Hs-TnI could prognosticate the need of intubation in ICU patients. Table 4 describes that Hs-Tn at admission was associated with increased odds of intubation need.

On the basis of cut-off stratification, hs-troponin levels presented a sensibility of 30%, specificity of 97% and accuracy of 64% in predicting the degree of COVID-19. The predictive positive and negative values were 90.3% and 59.1%, respectively. On the other hand, hs-Tn showed a sensibility of 45.0%, specificity of 87.1% and accuracy of 82.6% in prognosticating mortality; in this case, the predictive positive and negative values were 29.0% and 93.1%.

4. Discussion

The SARS-CoV-2 is mainly a pulmonary disease, although there is multiple evidence of its multisystem involvement, in particular the cardiovascular one [17].

This study has highlighted a prevalence of myocardial injury of 16% in our COVID-19 population, in the absence of patients with acute coronary syndrome at the time of admission. This result is consistent with other published works with percentage between 7 and 36% [5,7–10].

The patients with myocardial injury were older, and had a greater number of cardiovascular comorbidities, in particular history of hypertension and ischemic heart disease, than those without cardiac injury. Furthermore, this group of patients was significantly associated with previous use of beta-blockers, Aspirin, Statin and loop diuretics. This finding could be a confounding phenomenon, because these drugs are commonly used in chronic therapy of cardiovascular disease, as reported in other studies [8,9,18,19]. In addition, there is no significant correlation between the use of ACEi/ARBs and myocardial injury. This is in keeping with recent studies demonstrating no increased risk associated with use of these drugs [20,21].

The patients with cardiac injury had higher values of acute phase and inflammatory markers and leucocytes, which were linear correlated with plasma hs-TnI levels. This difference suggests that myocardial injury may be closely related in his pathogenesis with sustained inflammatory response typical of COVID-19 infection. The release of inflammatory cytokines after infection can lead to mismatch of oxygen demand, destabilization of coronary plaque, microthrombogenesis, and apoptosis or necrosis of myocardial cells [5].

Our study demonstrated the correlation of hs-Tn concentration with disease severity. Each upper stage of COVID19 is characterized by a higher mean and median hs-Tn values and by a higher percentage of patients with myocardial injury. The multivariate analysis performed in function of disease severity (age, sex, CRP, WBC, CVD history, history of risk factors were the other variables) showed that hs-Tn was a significant independent variable, enlightening its positive predictive role.

The correlation between hs-Tn values and the outcome of death arose in our report, regardless of history of CVD or risk factors. The group of patients with myocardial injury showed a significantly higher event rate. Furthermore, multivariate analysis (age, sex, history of CVD and risk factors, CRP, WBC were the other variables) confirmed hs-Tn has an indipendent predictor of in-hospital death. This is in keeping with reports worldwide [8,9,18].

Our study suggests that hs-Tn can have a role also in SARS-CoV-2 as a marker with a high positive predictive value of serious illness and a high negative predictive value for death, already when measured at admission. It is therefore reasonable to hypothesize that the initial measurement of heart damage biomarkers immediately after hospitalization for COVID 19 infection, as well as longitudinal monitoring during hospitalization, may help to identify a subset of patients with possible heart damage and therefore predict the progress of SARS -CoV-2 toward a worse clinical picture.

In our cohort, among patients hospitalized in ICU emerged a significant increased probability of endotracheal intubation need in subjects with cardiac injury and the multivariate analysis validated Hs-Tn as a indipendent predictive marker. This data assume an important practical implication as troponin can play the role of an additional guiding tool for key clinical decisions in critically ill patients, supporting the identification of subjects who would benefit from prompt intubation and thus

Table 3
Logistic regression. Dependent variable: Death during Hospitalization. Covariates: clinical and laboratoristic parameters.

Variable	β ± S.E.	*p*	OR [95% CI]
Complete Model			
Log[hsTnI] (ng/L)	1.62 ± 0.40	**<0.001**	5.05 [2.29–11.13]
Gender (female/male)	0.06 ± 0.58	0.922	1.06 [0.34–3.32]
Age (years)	0.09 ± 0.03	**0.003**	1.09 [1.03–1.16]
History of Cardiovascular Diseases	0.18 ± 0.60	0.763	1.20 [0.37–3.88]
Presence of Risk Factors	−0.39 ± 0.65	0.545	0.68 [0.19–2.40]
CRP (mg/L)	0.008 ± 0.003	**0.007**	1.01 [1.00–1.02]
White Blood Cells (count/L)	0.056 ± 0.061	0.356	1.06 [0.94–1.19]
Reduced Model			
Log[hsTnI] (ng/L)	1.66 ± 0.40	**<0.001**	5.23 [2.41–11.36]
Age (years)	0.08 ± 0.03	**0.002**	1.09 [1.03–1.15]
CRP (mg/L)	0.009 ± 0.003	**0.001**	1.01 [1.00–1.02]

Bold is emphasized the *p* value <.05.

Table 4
Logistic regression. Dependent variable: Intubation during Hospitalization. Covariates: clinical and laboratoristic parameters.

Variable	β ± S.E.	*p*	OR [95% CI]
Complete Model			
Log[hsTnI] (ng/L)	3.70 ± 2.58	0.152	40.3 [0.3–6297]
Gender (female/male)	0.64 ± 2.13	0.765	1.9 [0−123]
Age (years)	0.08 ± 0.08	0.327	1.1 [0.9–1.3]
History of Cardiovascular Diseases	0.71 ± 1.45	0.621	2.0 [0.1–35]
Presence of Risk Factors	0.45 ± 1.43	0.751	1.6 [0.1–26]
CRP (mg/L)	−0.003 ± 0.008	0.683	1.0 [1.0–1.0]
White Blood Cells (count/L)	−0.24 ± 0.19	0.200	0.8 [0.5–1.1]
Reduced Model			
Log[hsTnI] (ng/L)	2.01 ± 0.96	**0.037**	7.4 [1.1–49.3]

Bold is emphasized the *p* value <.05.

avoiding the delay that often causes the irreversible worsening of clinical outcomes.

A valuable large meta-analysis reported that pre-existing cardiovascular comorbidities or risk factors were significant predictors of cardiovascular complications in COVID-19 patients, in addition to age and gender. In the same meta-analysis, involving 77,317 patients, pre-existing cardiovascular comorbidities or risk factors and the development of cardiovascular complications (among which cardiac injury) had a significant interaction with death at meta-regression analysis. These findings are relevant as they suggest that presence of cardiovascular comorbidities/risk factors is tied to a higher prevalence of cardiac injury, that is a proxy for death. This should inform vaccination strategies, suggesting a significant benefit from prioritization of cardiovascular patients [22].

The probable causes of heart suffering in the context of COVID 19 infection are a debated topic. The profound inflammatory response and hemodynamic changes associated with severe disease may confer risk for atherosclerotic plaque rupture in susceptible patients and may lead to type I myocardial infarction [23]. Coronary heart disease has also been found to be associated with acute cardiac events and poor outcomes in influenza and other respiratory viral infections [24–26].

Other mechanisms of myocardial damage could be involved, for example mismatch between oxygen supply and demand, increased ventricular strain, direct myocyte trauma and increased catecholamines.

A small number of autopsy cases suggest infiltration by interstitial mononuclear inflammatory cells [27], suggesting myocardial inflammation as a further possible mechanism, and some severe cases of myocarditis have been reported [28,29]. Tavazzi et al. described a case biopsy-proven myocardial localization of viral particles [30].

However, current key studies compared the myocardial involvement in intubated patients observed during COVID-19 infection to that observed during severe pneumonias of other origin.

Metkus et al. [31] documented that half of intubated patients with COVID-19 manifest myocardial injury, which is associated with a graded increase in overall mortality. Cardiac injury is actually less common in COVID-19 compared with conventional ARDS after adjusting for confounders of age, renal dysfunction, and degree of critical illness and the magnitude of mortality risk is attenuated after adjustment for degree of critical illness. A similar mortality pattern was found in the general ARDS population [32].

Likewise, Jirak et al. [33] demonstrated that myocardial damage prevalence is less frequent in SARS-CoV2 pneumonias than in pneumonia of other aetiologies (78.1 vs 96.4%, $p = .004$) with similar rate of left ventricular systolic dysfunction and in-hospital mortality (38.2 vs. 51.3%, $p = .142$). These data suggest that myocardial injury could be reflective of baseline risk, comorbidities and underlying multisystem organ dysfunction and reinforce the hypothesis that myocardial damage during SARS-CoV-2 infection is not a pathognomonic event triggered directly by the virus per se, but it depends on the severe systemic inflammatory state and the severity of the clinical condition.

Traditionally, cardiac imaging would feature prominently in the distinction between acute myocardial infarction and injury [34].

In a small study of recovered patients with ongoing cardiac symptoms, cardiovascular magnetic resonance (CMR) imaging during the acute phase revealed cardiac involvement in 58% of patients consisting of myocardial edema and scar by late gadolinium enhancement (LGE) [35].

In patients who have convalesced from COVID-19, studies have shown that myocardial damage and inflammation may be evident in a majority of patients when assessed with cardiac magnetic resonance imaging [34].

The study of Puntmann et al. enrolled 100 unselected patients recently recovered from COVID-19 illness and recorded a Cardiac Magnetic Risonance (CMR) two month after the acute phase of the disease. A total of 78 patients (78%) had cardiovascular involvement as detected by standardized CMR and this occured independently of the severity of original presentation and persists beyond the period of acute presentation. The most prevalent abnormality was myocardial inflammation (60%), followed by regional scar and pericardial enhancement. Most imaging findings pointed toward ongoing perimyocarditis after COVID-19 infection. In this report, high-sensitivity troponin was significantly correlated with CMR mapping, irrespective of comorbidities or treatment received during the COVID-19 illness [36].

Another study of Knight et al. used cardiovascular magnetic resonance (CMR) during early convalescence to assess the presence, type, and extent of myocardial injury in troponin-positive (during the hospitalitation) patients with COVID-19. In this cohort, abnormalities on CMR are common despite overall normal cardiac function. The CMR frequently revealed ischemic heart disease–related (17%), high rates of myocarditis-like Late Gadolinium Enhancement (38%), and sometimes dual pathology (ischemic and non-ischemic, 14%). The lack of edema in these patients suggests that the myocarditis-like scar may be permanent [37].

Furthermore, if the findings about cardiac involvement during [29,35,38,39] and months after [36,37] a COVID-19 diagnosis and high rate of risk are confirmed by larger cohorts, the pathologic basis for progressive left ventricular dysfunction is validated, and especially if longitudinal assessment reveals new-onset heart failure in the recovery phase of COVID-19, then the crisis of COVID-19 will not abate but will instead shift to a new de novo incidence of heart failure and other chronic cardiovascular complications [40]. In this clinical context, the detection of abnormal elevation of hs-Tn during the early acute phase may help to select patients at high risk, that need stricter cardiac monitoring, and during the convalescence phase the subjects with late myocardial impairment.

5. Limitations

Our study has several limitations. First, only 189 patients with confirmed COVID-19 were included, and a larger cohort study is needed to verify our conclusions. Second, this is a retrospective study and there is incomplete data concerning some other specific information of cardiovascular system and inflammation such as echocardiography and interleukin 6, owing to the conditions in the isolation ward. As a consequence, we were only able to define acute myocardial injury by troponin elevation without detailing myocardial tissue characteristics and haemodynamic function. Third, we assessed the hs-Tn value on admission and further data on the role of longitudinal assessment of troponin values are needed.

6. Conclusion

Myocardial injury is prevalent in patients affected by SARS-CoV-2 and the patients with hs-Tn value above the upper reference limit are older and had a greater number of cardiovascular comorbidities. In this study we demonstrate a high positive predictive value of hs-Tn for disease severity and a high negative predictive value for in-hospital death. Therefore, it may be reasonable to use high sensitivity troponin as a screening tool in COVID-19 patients in order to triage them into high and low general risk groups. In addition, our report indicates that hs-Tn is an indipendent predictor of intubation need among patients hospitalized in ICU, emerging as a guiding tool in critically ill patients, supporting the identification of subjects who would benefit from prompt intubation. Finally, recent studies enlighten cardiac involvement in the recovery phase of COVID-19 with evidence of active myocardial inflammation and regional scar; the prevalence is high in patient discharged with myocardial injury. In this constest, hs-Tn can play a pivotal role in the detection of subjects at high risk of cardiac impairment and heart failure during both the early and recovery stage.

Statement of authorship

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Disclosures

None

Acknowledgement

None

References

[1] K.A. Adedokun, A.O. Olarinmoye, J.O. Mustapha, R.T. Kamorudeen, A close look at the biology of SARS-CoV-2, and the potential influence of weather conditions and seasons on COVID-19 case spread, Infect. Dis. Poverty 9 (77) (2020).
[2] S.K. Raina, et al., Does temperature and humidity influence the spread of Covid-19?: a preliminary report, J. Fam. Med. Prim. Care 9 (2020) 1811–1814.
[3] D. Kifer, et al., Effects of environmental factors on severity and mortality of COVID-19, Front. Med. 7 (2020) 607786.
[4] M. Cascella, M. Rajnik, A. Cuomo, S.C. Dulebohn, R. Di Napoli, Features, Evaluation and Treatment Coronavirus (COVID-19). in, 2020.
[5] C. Huang, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet (London, England) 395 (2020) 497–506.
[6] N. Chen, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet (London, England) 395 (2020) 507–513.
[7] D. Wang, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA 323 (2020) 1061–1069.
[8] A. Lala, et al., Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection, J. Am. Coll. Cardiol. (2020), https://doi.org/10.1016/j.jacc.2020.06.007.
[9] T. Guo, et al., Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol. 5 (2020) 1–8.
[10] S. Shi, et al., Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019, 2020 1–10, https://doi.org/10.1093/eurheartj/ehaa408.
[11] W. Who, Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. 2019, 2020 1–19.
[12] World Medical Association, Declaration of Helsinki: ethical principles for medical research involving human subjects, JAMA 310 (2013) 2191–2194.
[13] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, JAMA (2020), https://doi.org/10.1001/jama.2020.2648.
[14] V.M. Ranieri, et al., Acute respiratory distress syndrome: the Berlin definition, JAMA 307 (2012) 2526–2533.
[15] A. Khwaja, KDIGO clinical practice guidelines for acute kidney injury, Nephron. Clin. Pract. 120 (2012) c179–c184.
[16] M. Singer, et al., The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (2016) 801–810.
[17] J.A. Fried, et al., The variety of cardiovascular presentations of COVID-19, Circulation 141 (2020) 1930–1936.
[18] S. Shi, et al., Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China, JAMA Cardiol. 5 (2020) 802–810.
[19] J.-F. Wei, et al., Acute Myocardial Injury is Common in Patients with Covid-19 and Impairs Their Prognosis, 2020 1–6, https://doi.org/10.1136/heartjnl-2020-317007.
[20] H.R. Reynolds, et al., Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19, N. Engl. J. Med. 382 (2020) 2441–2448.
[21] G. Mancia, F. Rea, M. Ludergnani, G. Apolone, G. Corrao, Renin-angiotensin-aldosterone system blockers and the risk of Covid-19, N. Engl. J. Med. 382 (2020) 2431–2440.
[22] J. Sabatino, S. De Rosa, G. Di Salvo, C. Indolfi, Impact of cardiovascular risk profile on COVID-19 outcome. A meta-analysis, PLoS One 15 (2020), e0237131, .
[23] F. Zhou, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet (London, England) 395 (2020) 1054–1062.
[24] V.F. Corrales-Medina, D.M. Musher, S. Shachkina, J.A. Chirinos, Acute pneumonia and the cardiovascular system, Lancet (London, England) 381 (2013) 496–505.
[25] J.A. Udell, et al., Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis, JAMA 310 (2013) 1711–1720.
[26] R. Blackburn, H. Zhao, R. Pebody, A. Hayward, C. Warren-Gash, Laboratory-confirmed respiratory infections as predictors of hospital admission for myocardial infarction and stroke: time-series analysis of English data for 2004-2015, Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 67 (2018) 8–17.
[27] D. Lindner, et al., Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases, JAMA Cardiol. (2020), https://doi.org/10.1001/jamacardio.2020.3551.
[28] X. Wei, Y. Fang, H. Hu, Glucocorticoid and immunoglobulin to treat viral fulminant myocarditis, Eur. Heart J. 41 (2020) 2122.
[29] R.M. Inciardi, et al., Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19), JAMA Cardiol. 5 (2020) 819–824.
[30] G. Tavazzi, et al., Myocardial Localization of Coronavirus in COVID- 1 9 Cardiogenic Shock Case Description, 2020 1–5, https://doi.org/10.1002/ejhf.1828.
[31] T.S. Metkus, et al., Myocardial injury in severe COVID-19 compared with non-COVID-19 acute respiratory distress syndrome, Circulation 143 (2021) 553–565.
[32] T.S. Metkus, et al., Prevalence and prognostic association of circulating troponin in the acute respiratory distress syndrome, Crit. Care Med. 45 (2017) 1709–1717.
[33] P. Jirak, et al., Myocardial injury in severe COVID-19 is similar to pneumonias of other origin: results from a multicentre study, ESC Hear. Fail. 8 (2021) 37–46.
[34] P.C. Cremer, SARS-CoV-2 and myocardial injury: few answers, many questions, Cleve. Clin. J. Med. 87 (2020) 521 LP – 525.
[35] L. Huang, et al., Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging, JACC Cardiovasc. Imaging (2020), https://doi.org/10.1016/j.jcmg.2020.05.004.
[36] V.O. Puntmann, et al., Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19), JAMA Cardiol. (2020), https://doi.org/10.1001/jamacardio.2020.3557.
[37] D.S. Knight, et al., COVID-19: myocardial injury in survivors, Circulation 142 (2020) 1120–1122.
[38] J.A. Luetkens, et al., Diffuse myocardial inflammation in COVID-19 associated myocarditis detected by multiparametric cardiac magnetic resonance imaging, Circ. Cardiovasc. Imaging 13 (2020), e010897.
[39] P. Gravinay, N. Issa, D. Girard, F. Camou, H. Cochet, CMR and serology to diagnose COVID-19 infection with primary cardiac involvement, Eur. Heart J. Cardiovasc. Imaging (2020), https://doi.org/10.1093/ehjci/jeaa169.
[40] C.W. Yancy, G.C. Fonarow, Coronavirus Disease 2019 (COVID-19) and the Heart — Is Heart Failure the Next Chapter ? 2019, 2019–2020, 2020.