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Longitudinal correlation of biomarkers of cardiac injury, inflammation, and coagulation to outcome in hospitalized COVID-19 patients

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ABSTRACT

Background: Cardiac injury, as measured by troponin elevation, has been reported among hospitalized coronavirus disease 2019 (COVID-19) patients and portends a poor prognosis. However, how the dynamics of troponin elevation interplay with inflammation and coagulation biomarkers over time is unknown. We assessed longitudinal follow-up of cardiac injury, inflammation and coagulation markers in relation to disease severity and outcome.

Methods: We retrospectively assessed 2068 patients with laboratory-confirmed COVID-19 between January 29 and April 1, 2020 at Tongji Hospital in Wuhan, China. We defined cardiac injury as an increase in high sensitivity cardiac troponin-I (hs-cTnI) above the 99th of the upper reference limit. We explored the dynamics of elevation in hs-cTnI and the relationship with inflammation (interleukin [IL]-6, IL-8, IL-10, IL-2 receptor, tumor necrosis factor-α, C-reactive protein) and coagulation (d-dimer, fibrinogen, international normalized ratio) markers in non-critically ill versus critically ill patients longitudinally and further correlated these markers to survivors and non-survivors.

Results: Median age was 63 years (first to third quartile 51–70 years), 51.4% of whom were women. When compared to non-critically ill patients (N = 1592, 77.0%), critically ill (defined as requiring mechanical ventilation, in shock or multiorgan failure) patients (N = 476, 23.0%), had more frequent cardiac injury on admission (30.3% vs. 2.3%, $p < 0.001$), with increased mortality during hospitalization (38.4% vs. 0%, $p < 0.001$). Among critically ill patients, non-survivors (N = 183) had a continuous increase in hs-cTnI levels during hospitalization, while survivors (N = 293) showed a decrease in hs-cTnI level between day 4 and 7 after admission. Specifically, cardiac injury is an independent marker of mortality among critically ill patients at admission, day 4–7 and 8–14. Consistent positive correlations between hs-cTnI and interleukin (IL)-6 on admission (r = 0.59), day 4–7 (r = 0.66) and day 8–14 (r = 0.61; all $p < 0.001$) and d-dimer (at the same timepoints r = 0.54; 0.65; 0.61, all $p < 0.001$) were observed. A similar behavior was observed between hs-cTnI and most of other biomarkers of inflammation and coagulation.

Conclusions: Cardiac injury commonly occurs in critically ill COVID-19 patients, with increased levels of hs-cTnI beyond day 3 since admission portending a poor prognosis. A consistent positive correlation of hs-cTnI with IL-6 and d-dimer at several timepoints along hospitalization could suggest nonspecific cytokine-mediated cardiotoxicity.

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Subject terms

Cardiac injury
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Nonstandard Abbreviations and Acronyms:

CK-MB	creatine kinase-myocardial band
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
ECG	electrocardiogram
FiO_2	fraction of inspired oxygen
hs-cTnI	high-sensitivity cardiac troponin I
ICU	intensive care unit
IL	interleukin
IL-2R	IL-2 receptor
INR	international normalized ratio
LVEF	left ventricular ejection fraction
MB	myoglobin
NT-proBNP	N-terminal pro-brain natriuretic peptide
PaO_2	arterial partial pressure of oxygen
Q1-Q3	interquartile range
SaO_2	oxygen saturation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TNF-α	tumor necrosis factor-α
URL	upper reference limit

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, in late 2019 and is now causing a pandemic [1–5]. On initial presentation or during hospitalization, a significant proportion of coronavirus disease 2019 (COVID-19) patients require admission to the intensive care unit (ICU) due to severe respiratory insufficiency, shock or multiorgan failure, being classified as critically ill patients. Mortality is high (ranging from 26.0 to 61.5%) among critically ill patients [6–9]. Better predictors of prognosis are needed at the time of admission and during hospitalization for critically ill COVID-19 patients [7]. Beyond hypoxemia, biomarkers of cardiac injury, inflammation (e.g. interleukin [IL]-6, and C-reactive protein [CRP]) and coagulation (e.g. d-dimer) have emerged as useful in the identification of patients at increased risk of mortality [5,10–14]. Relevance of cardiac involvement has been confirmed in two cohorts including 603 COVID-19 patients. The reported rate of cardiac injury ranged between 19.7% and 27.8% of cases on admission [10,11], with an associated mortality rate between 23.0% and 51.2%. Importantly, the mechanisms of cardiac injury are unclear. While there have been case reports of myocarditis in the setting of SARS-CoV-2 infection [15,16], the majority of cases of myocardial injury are not due to classic myocarditis [17,18]. An alternative explanation is that cardiac injury occurs due to an intense cytokine response which further results in inflammatory injury and activates the coagulative cascade resulting in myocardial and vascular damage [8,12,19–22]. Using a large cohort of hospitalized COVID-19 patients with biomarkers measured at time of admission and throughout hospitalization, we explored the rate of cardiac injury in relation to clinical condition comparing survivors and non-survivors among critically ill patients in a large single-center population of COVID-19 patients. We followed trends of high-sensitivity cardiac troponin I (hs-cTnI) during hospitalization correlating these to clinical outcome. Finally, we analyzed the temporal relationships between troponin elevation and markers of inflammation and coagulation in the attempt to describe their interplay and provide insights into mechanisms of myocardial injury during hospitalization.

2. Methods

2.1. Study design and oversight

This study was a retrospective analysis involving hospitalized patients with a diagnosis of COVID-19 between January 29, 2020 and April 1, 2020 in Tongji Hospital, a tertiary teaching institute in Wuhan, China. It was approved by the institutional review board of Tongji Hospital (TJ-IRB20200229). The requirement for written informed consent was waived by the Ethics committee because of the retrospective and anonymous nature of the data, collected during an emerging infectious disease as reported in other hospitals in Wuhan [5]. The clinical follow-up was terminated on April 1, 2020.

2.2. Data collection

Health care data regarding clinical characteristics, coexisting comorbidities, laboratory results, in-hospital therapies, incident cardiovascular events and overall outcome were collected by data coordinators through the electronic medical records. Presence of coexisting disease was based on the clinical evaluation of the attending physician or self-reported by the patient at the time of admission. Laboratory results included markers of cardiac injury, inflammation and coagulation reported at admission (day 0), between day 1 and day 3 after admission (defined as day 1–3), between day 4 and day 7 (day 4–7), between day 8 and day 14 (day 8–14) and finally beyond day 14 to discharge, last follow up or death (day > 14). If more than one laboratory result was available, we selected the highest value for each day or for each specified time interval following admission. Hs-cTnI was used to identify patients with cardiac injury, defined as serum levels above the 99th percentile of the upper reference limit (URL, 34.2 pg/mL) in accordance with the definition used in previous studies [10,11].

2.3. Study population

Patients were eligible for inclusion in this study if they had a diagnosis of COVID-19 requiring hospitalization based on symptoms in association with a positive real-time polymerase chain reaction (PCR) for SARS-CoV-2 either on nasopharyngeal swab (2058/2068, 99.5%) or anal swab (10/2068, 0.5%) and positive chest-computed tomography. SARS-CoV-2-specific antibodies were tested by a Chinese investigational kit since February 26th, 2020. The levels of SARS-CoV-2-Specific immunoglobulin (Ig) G antibodies on admission were available in 344 non-critically ill patients, 36 critically ill survivors, and only 1 critically ill non-survivor; the levels of SARS-CoV-2-Specific IgM antibodies on admission were available in 345 non-critically ill patients, 36 critically ill survivors, and only 1 critically ill non-survivor (Table 1). Bilateral pneumonia was observed in 1862/2068, 90%; while patchy infiltrates in 1586/2068, 76.7% and/or ground glass opacities in 1060/2068 (51.3%), and/or consolidations in 392/2068 (19.0%) [23]. Based on the Guidelines on the Diagnosis and Treatment of COVID-19 used in Wuhan [24], COVID-19 patients were categorized into four classes:1) mild: defined as presenting with mild symptoms without pneumonia; 2) moderate: defined as presenting with fever or other respiratory track symptoms accompanied by pneumonia; 3) severe: defined as presenting with shortness of breath (respiratory rate ≥ 30 cpm), oxygen saturation (SaO_2) < 93% at rest or the ratio between arterial partial pressure of oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) ≤300 mmHg; 4) critically ill: defined as requiring mechanical ventilation, in shock or multiorgan failure. The used definition of critically ill patient was also in agreement with previous reports, that defined critically ill patients as those requiring admission to ICU [7,13]. Tongji Hospital, as a tertiary teaching hospital admitted only moderate, severe or critically ill patients, while mild cases were hospitalized in so called cabin hospitals in the early period of pandemic, or other low-grade hospitals in the later period. Thus, all patients had radiological findings of pneumonia.

Table 1
Clinical characteristics of the study patients.

	Total (n = 2068)	Non-critically ill (n = 1592)	Critically ill (n = 476)	p	Critically ill		
					Survivors (n = 293)	Non-survivors (n = 183)	p
Age (years)	63 [51, 70]	61 [49, 68]	69 [60, 78]	< 0.001	68 [59, 77]	71 [62, 79]	0.012
Male n.(%)	1005 (48.6)	723 (45.4)	282 (59.2)	< 0.001	161 (54.9)	121 (66.1)	0.016
BMI (kg/m^2)	23.5 [21.5, 25.6]	23.5 [21.5, 25.6]	23.6 [20.5, 25.6]	0.378	23.7 [20.3, 25.4]	23.1 [20.9, 26.6]	0.959
Time from onset to admission (days)	15 [9, 26]	16 [10, 29]	13 [8, 19]	< 0.001	14 [9, 21]	11 [7, 17]	0.005
Time from admission to becoming critically ill (days)			0 [0,2]		0 [0, 2]	0 [0, 2]	0.661
Length of hospital stay (days)	19 [11, 28]	18 [11, 27]	20 [9, 31]	0.319	28 [19, 39]	9 [5, 16]	< 0.001
Co-existing conditions							
Presence of 1 or more comorbidity n.(%)	976 (47.2)	657 (41.3)	319 (67.0)	< 0.001	196 (66.9)	123 (67.2)	0.943
History of hypertension n.(%)	722 (34.9)	489 (30.7)	233 (48.9)	< 0.001	150 (51.2)	83 (45.4)	0.215
History of diabetes mellitus n.(%)	292 (14.1)	202 (12.7)	90 (18.9)	0.001	59 (20.1)	31 (16.9)	0.386
History of coronary heart disease n.(%)	182 (8.8)	114 (7.2)	68 (14.3)	< 0.001	40 (13.7)	28 (15.3)	0.617
History of heart failure n.(%)	14 (0.7)	6 (0.4)	8 (1.7)	0.002	8 (2.7)	0 (0.0)	0.024
History of arrhythmias n.(%)	24 (1.2)	14 (0.9)	10 (2.1)	0.029	6 (2.0)	4 (2.2)	0.919
History of cancer n.(%)	75 (3.6)	46 (2.9)	29 (6.1)	0.001	12 (4.1)	17 (9.3)	0.021
History of stroke n.(%)	61 (2.9)	31 (1.9)	30 (6.3)	< 0.001	23 (7.8)	7 (3.8)	0.079
History of COPD n.(%)	32 (1.5)	16 (1.0)	16 (3.4)	< 0.001	11 (3.8)	5 (2.7)	0.547
History of renal disease n.(%)	31 (1.5)	13 (0.8)	18 (3.8)	< 0.001	12 (4.1)	6 (3.3)	0.649
Signs and symptoms on admission							
Heart rate (beats/min)	90 [80, 102]	89 [80, 100]	94 [81, 107]	< 0.001	93 [80, 104]	95 [82, 110]	0.161
Respiratory rate (counts/min)	20 [20,22]	20 [19, 22]	21 [20, 25]	< 0.001	20 [20, 25]	22 [20,30]	< 0.001
Oxygen saturation ≤ 93% n.(%)	331 (16.2)	159 (10.0)	172 (37.2)	< 0.001	89 (30.8)	83 (48.0)	< 0.001
Median (Q1-Q3)	97 [95, 98]	97 [96, 98]	96 [89, 98]	< 0.001	96 [92, 99]	94 [82, 98]	< 0.001
Fever n.(%)	1257 (60.8)	936 (58.8)	321 (67.4)	0.001	189 (64.5)	132 (72.1)	0.084
Cough n.(%)	1018 (49.2)	756 (47.5)	262 (55.0)	0.004	161 (54.9)	101 (55.2)	0.959
Dyspnea n.(%)	654 (31.6)	442 (27.8)	212 (44.5)	< 0.001	130 (44.4)	82 (44.8)	0.925
Diarrhea n.(%)	371 (17.9)	282 (17.7)	89 (18.7)	0.624	53 (18.1)	36 (19.7)	0.666
Fatigue n.(%)	289 (14.0)	208 (13.1)	81 (17.0)	0.029	46 (15.7)	35 (19.1)	0.333
Palpation n.(%)	45 (2.2)	34 (2.1)	11 (2.3)	0.818	10 (3.4)	1 (0.5)	0.043
Chest pain n.(%)	65 (3.1)	54 (3.4)	11 (2.3)	0.236	5 (1.7)	6 (3.3)	0.267
Chest distress n.(%)	296 (14.3)	231 (14.5)	65 (13.7)	0.640	38 (13.0)	27 (14.8)	0.581
Laboratory values on admission							
White blood cells							
< 3.5*10^9/L	167 (8.2)	138 (8.7)	29 (6.2)	0.086	18 (6.3)	11 (6.2)	0.980
Median (Q1-Q3)	5.9 [4.7, 7.7]	5.6 [4.5, 7.1]	7.8 [5.5, 11.8]	< 0.001	7.2 [5.3, 10.6]	9.2 [6.0, 13.3]	0.001
Neutrophil							
< 1.8*10^9/L	128 (6.3)	111 (7.0)	17 (3.7)	0.009	10 (3.5)	7 (4.0)	0.793
Median (Q1-Q3)	3.8 [2.7, 5.5]	3.5 [2.6, 4.8]	6.4 [4.2, 10.3]	< 0.001	5.8 [4.0, 8.6]	8.1 [4.7, 12.1]	< 0.001
Lymphocytes							
< 1.1*10^9/L	903 (44.2)	536 (33.9)	367 (79.1)	< 0.001	212 (73.9)	155 (87.6)	< 0.001
Median (Q1-Q3)	1.2 [0.8, 1.7]	1.3 [1.0, 1.8]	0.7 [0.5, 1.0]	< 0.001	0.8 [0.6, 1.1]	0.6 [0.4, 0.8]	< 0.001
Monocyte							
< 0.1*10^9/L	23 (1.1)	10 (0.6)	13 (2.8)	< 0.001	7 (2.4)	6 (3.4)	0.547
Median (Q1-Q3)	0.5 [0.4, 0.6]	0.5 [0.4, 0.6]	0.5 [0.3, 0.7]	0.007	0.5 [0.3, 0.7]	0.4 [0.2, 0.6]	0.010
SARS-CoV-2-Specific IgG antibodies[a]							
> 10 AU/mL	339 (89.0)	312 (90.7)	27 (73.0)	0.001	27 (75.0)	0 (0.0)	–
Median (Q1-Q3)	167.8 [90.1, 208.9]	171.7 [96.7, 211.4]	96.7 [9.3, 165.2]	0.001	102.1 [18.7, 168.7]	1.91 [1.91, 1.91]	–
SARS-CoV-2-Specific IgM antibodies[a]							
> 10 AU/mL	262 (68.6)	245 (71.0)	17 (45.9)	0.002	17 (47.2)	0 (0.0)	–
Median (Q1-Q3)	27.9 [5.8, 78.0]	30.8 [6.9, 79.9]	5.8 [1.2, 28.8]	< 0.001	7.4 [1.3, 31.4]	0.8 [0.8, 0.8]	–
Estimated GFR							
Rate of < 90 mL/min/1.73 m^2 (%)	889 (43.6)	588 (37.5)	301 (63.9)	< 0.001	165 (57.1)	136 (74.7)	< 0.001
Median (Q1-Q3) (mL/min/1.73 m^2])	92.7 [77.4, 103.1]	94.4 [82.3, 104.2]	80.7 [55.2, 96.3]	< 0.001	86.6 [63.5, 97.8]	72.2 [47.5, 90.3]	< 0.001
Elevation of markers of cardiac injury on admission							
hs-cTnI n.(%)	181 (8.8)	37 (2.3)	144 (30.3)	< 0.001	61 (20.8)	83 (45.4)	< 0.001
Mb n.(%)	174 (11.2)	52 (4.2)	122 (39.2)	< 0.001	65 (31.4)	57 (54.8)	< 0.001
CK-MB n.(%)	40 (2.6)	6 (0.5)	34 (11.1)	< 0.001	15 (7.4)	19 (18.8)	0.003
NT-proBNP n.(%)	1194 (64.3)	786 (55.2)	408 (93.8)	< 0.001	247 (91.5)	161 (97.6)	0.011
Elevation of markers of inflammation on admission							
IL-6 n. (%)	433 (43.8)	232 (30.1)	201 (91.8)	< 0.001	124 (87.9)	77 (98.7)	0.005
IL-8 n. (%)	58 (6.0)	23 (3.1)	35 (16.7)	< 0.001	17 (12.8)	18 (23.4)	0.047
IL10 n.(%)	134 (13.9)	50 (6.6)	84 (40.0)	< 0.001	40 (30.1)	44 (57.1)	< 0.001
IL2R n.(%)	281 (29.4)	138 (18.4)	143 (68.8)	< 0.001	87 (65.4)	56 (74.7)	0.167
TNF-α n.(%)	472 (49.7)	320 (43.3)	152 (72.4)	< 0.001	93 (69.9)	59 (76.6)	0.295

(*continued on next page*)

Table 1 (*continued*)

	Total (n = 2068)	Non-critically ill (n = 1592)	Critically ill (n = 476)	p	Critically ill		
					Survivors (n = 293)	Non-survivors (n = 183)	p
CRP n. (%)	1018 (51.2)	604 (39.3)	414 (91.6)	< 0.001	248 (88.9)	166 (96.0)	0.009
Elevation of markers of coagulation on admission							
D-Dimer n. (%)	1154 (58.6)	745 (48.9)	409 (91.7)	< 0.001	249 (90.5)	160 (93.6)	0.261
Fibrinogen n.(%)	1079 (58.0)	781 (53.8)	298 (72.9)	< 0.001	196 (75.1)	102 (68.9)	0.177
INR n.(%)	218 (10.9)	62 (4.0)	156 (33.9)	< 0.001	77 (27.3)	79 (44.4)	< 0.001
Pharmacological therapy during hospitalization							
Cardiovascular drugs							
Beta-blocker n.(%)	234 (11.3)	149 (9.4)	85 (17.9)	< 0.001	63 (21.5)	22 (12.0)	0.009
Diuretic n.(%)	346 (16.7)	122 (7.7)	224 (47.1)	< 0.001	119 (40.6)	105 (57.4)	< 0.001
Vasoactive agent n.(%)	306 (14.8)	79 (5.0)	227 (47.7)	< 0.001	83 (28.3)	144 (78.7)	< 0.001
Digitalis n.(%)	74 (3.6)	5 (0.3)	69 (14.5)	< 0.001	31 (10.6)	38 (20.8)	0.002
Selective calcium channel blocker n.(%)	546 (26.4)	382 (24.0)	164 (34.5)	< 0.001	111 (37.9)	53 (29.0)	0.046
Angiotensin II receptor blocker n.(%)	159 (7.7)	117 (7.3)	42 (8.8)	0.289	37 (12.6)	5 (2.7)	< 0.001
Angiotensin converting enzyme inhibitors n. (%)	31 (1.5)	24 (1.5)	7 (1.5)	0.954	4 (1.4)	3 (1.6)	0.809
Anticoagulant drugs n.(%)[b]	347 (16.8)	89 (5.6)	258 (54.2)	< 0.001	157 (53.6)	101 (55.2)	0.732
Antiplatelet drugs n.(%)[b]	243 (11.8)	162 (10.2)	81 (17.0)	< 0.001	55 (18.8)	26 (14.2)	0.197
Non-cardiovascular drugs							
Antiviral drugs n. (%)[b]	655 (31.7)	486 (30.5)	169 (35.5)	0.041	114 (38.9)	55 (30.1)	0.050
Immunoglobulin n. (%)	366 (17.7)	173 (10.9)	193 (40.5)	< 0.001	110 (37.5)	83 (45.4)	0.091
Immune modulators n. (%)[b]	54 (2.6)	21 (1.3)	33 (6.9)	< 0.001	29 (9.9)	4 (2.2)	0.001
Corticosteroids n. (%)	585 (28.3)	284 (17.8)	301 (63.2)	< 0.001	167 (57.0)	134 (73.2)	< 0.001
Multi vitamin complex n. (%)	551 (26.6)	339 (21.3)	212 (44.5)	< 0.001	137 (46.8)	75 (41.0)	0.218
Non-pharmacological therapy during hospitalization							
Oxygen n. (%)	1682 (81.3)	1212 (76.1)	470 (98.7)	< 0.001	288 (98.3)	182 (99.5)	0.270
NIV n. (%)	279 (13.5)	7 (0.4)	272 (57.1)	< 0.001	118 (40.3)	154 (84.2)	< 0.001
IMV n. (%)	168 (8.1)	0 (0.0)	168 (35.3)	< 0.001	56 (19.1)	112 (61.2)	< 0.001
CRRT n. (%)	55 (2.7)	0 (0.0)	55 (11.6)	< 0.001	24 (8.2)	31 (16.9)	0.004
VV/VA-ECMO n. (%)[c]	9 (0.4)	0 (0.0)	9 (1.9)	< 0.001	6 (2.0)	3 (1.6)	0.750
IABP n. (%)	3 (0.1)	0 (0.0)	3 (0.6)	0.002	1 (0.3)	2 (1.1)	0.313
Patients with cardiac events[d]							
Cardiac arrest n. (%)	77 (3.7)	0 (0.0)	77 (16.2)	< 0.001	5 (1.7)	72 (39.3)	< 0.001
Cardiac rhythm disturbances n. (%)[d]	151 (7.3)	13 (0.9)	138 (29.0)	< 0.001	63 (21.5)	75 (41.0)	< 0.001
Myocardial infarction n. (%)[d]	3 (0.1)	0 (0.0)	3 (0.6)	0.002	0 (0.0)	3 (1.6)	0.028
Overall mortality	183 (8.8)	0 (0)	183 (38.4)				

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; Ig, immunoglobulin; hs-cTnI, High-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; Mb, myoglobin; CK-MB, Creatine Kinase-MB; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-2R, interleukin-2 receptor; TNF-α, Tumor necrosis factorα; INR, international normalized ratio; GFR, glomerular filtration rate; ECMO, Extracorporeal Membrane Oxygenation; IABP, Intra-Aortic Balloon Pump; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation. Q1-Q3: first to third quartile.

[a] SARS-CoV-2-Specific antibodies were tested by a Chinese investigational kit since February 26th, 2020; the levels of SARS-CoV-2-Specific IgG antibodies were available in 344 non-critically ill patients, 36 critically ill survivors, and 1 critically ill non-survivor; the levels of SARS-CoV-2-Specific IgM antibodies were available in 345 non-critically ill patients, 36 critically ill survivors, and 1 critically ill non-survivor.

[b] Anticoagulant drugs include dabigatran, heparin, warfarin, rivaroxaban, and sulodexide. Antiplatelet drugs include aspirin, clopidogrel, ticagrelor, and dipyridamole; Anti-viral drugs include oseltamivir, lopianvir, ribavirin, ganciclovir, and peramivir; immue modulators include tocilizumab and pirfenidone.

[c] Of these, 3 out of 9 were VA-ECMO.

[d] Each cardiac event was counted independently. Cardiac rhythm disturbances include ventricular tachycardia, supraventricular tachycardia, atrial fibrillation, atrial flutter, second-degree (type 2) or third-degree atrioventricular block, and sick sinus syndrome. Myocardial infarction was confirmed by coronary angiography.

Elevation of biomarkers per se were not used as a factor in deciding on admission. We excluded patients younger than 18 years of age and those with recent history of acute myocardial infarction (< 1 month before admission), or patients without cardiac troponin tested on admission. Clinical characteristics of patients without cardiac troponin vs. patients with cardiac troponin that were included in this study are presented as Supplementary Table 1. Based on the Guidelines on the Diagnosis and Treatment of COVID-19 [24], patients were further categorized into two groups: non-critically ill (moderate and/or severe) and critically ill patients during the course of hospitalization. Among the critically ill patients, 294 out of 476 (61.8%) were critically ill on admission, whereas 182 out of 476 (38.2%) became critically ill during hospitalization. The median time from admission to become critically ill patients was 0 (interquartile range [Q1-Q3]: 0–2) day in those patients that on admission were not critically ill. All patients who died were critically ill at a certain point during hospitalization. Thus, critically ill patients were further differentiated in survivors vs. non-survivors (death or survival at last follow up; April 1th, 2020).

2.4. Biomarkers

All biomarkers were measured using standard hospital assays. We also explored other myocardial biomarkers of cardiac injury such as creatine kinase-myocardial band (CK-MB, URL 7.2 ng/mL), myoglobin (Mb, URL 154.9 pg/mL) and N-terminal pro-brain natriuretic peptide (NT-proBNP, URL 62.9 pg/mL) as marker of cardiac dysfunction or fluid overload. IL-6 (URL 7 pg/mL), IL-8 (URL 62 pg/mL), IL-10 (URL 9.1 pg/mL), IL-2 receptor (IL-2R, URL 710 U/mL), and tumor necrosis factor-α (TNF-α, URL 8.1 pg/mL), C-reactive protein (CRP, URL 35.4 mg/L) were used as markers of inflammation. At least one of the

abovementioned markers of inflammation was available at admission in 97.1% (2008/2068) of patients (IL-6 was available for 47.8% [989/2068] patients, IL-8 for 46.6% [964/2068] patients, IL-10 for 46.6% [964/2068] patients, IL-2R for 46.3% [957/2068] patients, TNF-α for 45.9% [949/2068] and CRP for 96.2% [1989/2068] of patients). As markers of coagulation we reported d-dimer levels (URL 0.5 μg/mL and an upper limit of 21 μg/mL of the kit), fibrinogen level (URL 4.0 g/L) and international normalized ratio (INR; normal range 0.8–1.2). A sensitivity subanalysis has been performed in 234 patients with available data on both hs-cTnI and IL-6 on admission, day 4–7, and day 8–14. Similarly, analyses were performed on 407 patients with available data on hs-cTnI and CRP, and 396 patients with available data on hs-cTnI and d-dimer at the same timepoints.

2.5. Statistical analysis

Continuous values were shown as medians and Q1-Q3 and categorical variables as counts and percentages. Wilcoxon or Kruskal-Wallis rank-sum tests were used to evaluate the differences in non-normal distributed continuous values, and Pearson's X^2 test was used to evaluate the differences in categorical variables. These tests were used appropriately to compare baseline characteristics between non-critically ill and critically ill patients, as well as survivors and non-survivors among critically ill patients. Furthermore, they were used appropriately across the same groups to test differences in median values of markers of myocardial injury, inflammation and coagulation at different time points during the hospitalization. Additionally, Spearman correlation analyses were used to assess the association the association of inflammatory and coagulative markers with myocardial injury biomarkers. We further quantified the independent association between hs-cTnI, IL-6 and d-dimer levels with mortality among critically ill patients by computing odds ratios (OR) and their 95% confidence intervals (CI), testing different time points. For regression analyses, variables were all log-transformed before modelling to reduce skewness observed in this population. To address the impact of potential confounders, we incorporated several variables into multivariable regression models: age, sex, history of arterial hypertension, diabetes mellitus, coronary heart disease, heart failure, arrhythmia, chronic obstructive pulmonary disease (COPD), cancer, stroke and renal disease. All statistical analyses were performed using R packages (version 3.1.4, Vienna, Austria).

3. Results

3.1. Baseline characteristics

We identified 2741 patients with a diagnosis of COVID-19 in our database. Of these, we excluded 3 who had an acute myocardial infarction within the previous month, 39 who were younger than 18 years old, and 631 cases with no data on hs-cTnI on admission (Supplementary Table 1). In total, 2068 patients were included in the analysis. Study population median age was 63 (Q1-Q3: 51–70) years, 51.4% of whom were women. On admission, cardiac injury was observed in 8.8% of admitted patients. Furthermore, CK-MB was increased in 2.6%, Mb in 11.2% and NT-proBNP in 64.3%. Among markers of inflammation recorded on admission, IL-6 was increased in 43.8%, IL-8 in 6.0%, IL-10 in 13.9%, IL-2R in 29.4%, TNF-α in 49.7% and CRP in 51.2%. Markers of coagulation were also increased in a large subset, d-dimer in 58.6%, fibrinogen in 58.0% and INR in 10.9% of cases. Overall mortality occurred in 183 patients (8.8%) (Table 1).

When compared to non-critically ill (N = 1592, 77.0%) patients, 476 critically ill COVID-19 patients (23.0%) were more likely to be older, male, with a higher prevalence of arterial hypertension, diabetes mellitus, history of coronary heart disease, heart failure, arrhythmia, cancer, stroke, COPD, renal disease, and a higher titer of SARS-CoV-2 IgG and IgM (IgG data available in 381 patients and IgM in 382 patients on admission) (Table 1). On admission, critically ill COVID-19 patients had a higher proportion of elevated levels of markers of cardiac injury, as defined by increased hs-cTnI, inflammation and coagulation compared with non-critically ill cases. Additionally, absolute values for each marker of cardiac injury, inflammation and coagulation were significantly increased in critically ill patients compared with non-critically ill patients; hs-cTnI was 15.9 (6.3–52.9) vs. 3.0 (1.9–7.0) pg/mL, IL-6 was 40.1 (18.2–85.9) vs. 3.1 (1.5–9.9) pg/mL, CRP was 72.7 (37.1–125.5) vs. 5.2 (1.2–31.0) mg/L, and d-dimer was 2.4 (1.2–8.1) vs. 0.5 (0.2–1.1) ug/mL, respectively ($p < 0.001$ for all) (Table 1). Finally, critically ill versus non-critically ill patients had a higher rate of fatalities (38.4% vs. 0%, $p < 0.001$).

Among, critically ill patients, non-survivors were older, and more frequently men, with 45.4% having cardiac injury compared to 20.8% in survivors ($p < 0.001$). On admission, the proportion of patients with markers Mb, CK-MB and NT-proBNP beyond the URL was significantly higher in non-survivors compared with survivors, as well as the following inflammatory markers: IL-6, IL8, IL-10 and CRP (Table 1). Among coagulation markers, d-dimer was above the URL in > 90% of critically ill patients but the proportion of cases with increased d-dimer was not different in non-survivors vs. survivor, whereas INR was increased in a larger proportion of non-survivors (Table 1). Finally, absolute values at admission of each marker of cardiac injury, inflammation and coagulation were significantly increased in critically ill non-survivors vs. survivors with the exception of TNF-α and fibrinogen (Table 2). Specifically, critically ill non-survivors vs. survivors had hs-cTnI of 28.7 (11.1–155.8) vs. 11.7 (5.2–30.3) pg/mL; IL-6 of 58.5 (30.4–174.7) vs. 30.4 (13.4–64.5) pg/mL, CRP of 102.7 (58.8–151.9) vs. 59.4 (26.6–109.2) mg/L, and d-dimer 3.4 (1.6–21.0) vs. 2.0 (1.0–4.1) ug/mL respectively ($p < 0.001$ for all).

3.2. Longitudinal changes in markers of myocardial injury, inflammation and coagulation during hospitalization

Hs-cTnI levels as well as other markers of cardiac injury (Mb, CK-MB and NT-proBNP) were higher at any time point (admission, day 1–3, day 4–7, day 8–14 and > 14) in critically ill compared to non-critically ill patients. Among non-critically ill patients, hs-cTnI, Mb, CK-MB, and NT-proBNP remained significantly lower compared with critically ill patients, and most of values were within URL throughout hospitalization. Higher levels of markers of cardiac injury were also confirmed at any time point in non-survivors compared with survivors (Fig. 1, Supplementary Fig. 1, and Table 2). Strikingly, in critically ill survivors, hs-cTnI, Mb, CKMB and NT-proBNP increased from admission to day 3, but then declined from day 4–7; on the other hand, non-survivors had an abrupt increase in hs-cTnI, Mb, CK-MB and NT-proBNP until death. Similar patterns were observed for IL-6, IL-8, IL-10, IL-2R, TNF-α, CRP and coagulation markers (d-dimer, fibrinogen and INR). Among critically ill survivors, peak level for each marker was observed on days 1–3, with progressive decrease from day 4–7 onward (Fig. 1, Supplementary Fig. 1, and Table 2). In critically ill non-survivors, almost all markers of inflammation and coagulation increased throughout the entire course of hospitalization. Of note, d-dimer levels peaked at day 1–3 and subsequently decreased both in survivors and non-survivors, although median values were persistently and significantly higher at any time point in non-survivors compared to survivors. Finally, when we assessed the levels of biomarkers on admission comparing non-survivors that died within 7 days (N = 69) vs. non-survivors that died beyond 7 days (N = 114) after admission, we observed that hs-cTnI, NT-proBNP, IL-6, INR were significantly increased in non-survivors that died within 7 days after hospitalization compared to those that died later (Supplementary Table 2).

Table 2
Dynamic changes in the levels of biomarkers throughout the hospitalization stratified by the severity of disease.

	Total (n = 2068)		Non-critically ill (n = 1592)		Critically ill (n = 476)		p (non-critically ill vs. critically ill)	Critically ill				
								Survivors (n = 293)		Non-survivors (n = 183)		
	Patients with available data	Median (Q1-Q3)	Patients with available data	Median (Q1-Q3)	Patients with available data	Median (Q1-Q3)		Patients with available data	Median (Q1-Q3)	Patients with available data	Median (Q1-Q3)	p (survivors vs. non-survivors)
hs-cTnI (pg/mL)												
Admission	n = 2068	4.2 [1.9, 11.0]	n = 1592	3.0 [1.9, 7.0]	n = 476	15.9 [6.3, 52.9]	< 0.001	n = 293	11.7 [5.2, 30.3]	n = 183	28.7 [11.1, 155.8]	< 0.001
Day 1–3	n = 200	31.1 [7.7, 175.4]	n = 47	6.3 [2.2, 11.7]	n = 153	46.9 [17.9, 342.9]	< 0.001	n = 81	34.2 [7.5, 173.3]	n = 72	93.7 [28.8, 515.6]	0.006
Day 4–7	n = 511	6.8 [2.0, 26.1]	n = 275	2.6 [1.9, 7.1]	n = 236	25.6 [7.6, 146.3]	< 0.001	n = 148	13.4 [4.8, 49.7]	n = 88	117.3 [28.2, 467.2]	< 0.001
Day 8–14	n = 634	3.9 [1.9, 14.3]	n = 402	2.2 [1.9, 5.0]	n = 232	21.0 [4.5, 96.2]	< 0.001	n = 159	9.6 [3.2, 34.9]	n = 73	133.9 [31.7, 525.5]	< 0.001
Day > 14	n = 533	3.8 [1.9, 10.6]	n = 334	2.5 [1.9, 5.8]	n = 199	11.0 [3.4, 61.7]	< 0.001	n = 163	7.4 [2.7, 24.9]	n = 36	177.6 [57.6, 541.1]	< 0.001
Mb (ng/mL)												
Admission	n = 1556	40.7 [28.4, 73.8]	n = 1245	35.8 [26.9, 54.8]	n = 311	108.9 [59.1, 253.6]	< 0.001	n = 207	92.1 [50.8, 200.5]	n = 104	183.1 [92.8, 509.3]	< 0.001
Day 1–3	n = 153	96.8 [42.4, 312.2]	n = 39	39.0 [26.1, 57.9]	n = 114	142.1 [73.4, 496.7]	< 0.001	n = 63	100.5 [50.6, 288.9]	n = 51	251.8 [111.8, 807.5]	0.002
Day 4–7	n = 411	40.6 [26.1, 112.1]	n = 218	28.9 [23.2, 40.2]	n = 193	106.7 [48.1, 288.4]	< 0.001	n = 126	71.1 [36.5, 197.3]	n = 67	239.5 [87.4, 860.4]	< 0.001
Day 8–14	n = 508	33.8 [24.1, 69.0]	n = 321	28.3 [22.4, 36.4]	n = 187	88.9 [42.0, 348.9]	< 0.001	n = 130	60.7 [29.9, 124.9]	n = 57	345.9 [105.3, 1133.3]	< 0.001
Day > 14	n = 450	32.0 [24.3, 51.9]	n = 281	28.4 [23.1, 38.4]	n = 169	50.4 [27.6, 185.1]	< 0.001	n = 144	40.0 [26.0, 94.3]	n = 25	712.5 [224.8, 1200.0]	< 0.001
CK-Mb (ng/mL)												
Admission	n = 1539	0.8 [0.5, 1.3]	n = 1234	0.7 [0.4, 1.1]	n = 305	1.5 [0.8, 3.3]	< 0.001	n = 204	1.3 [0.7, 2.6]	n = 101	2.4 [1.0, 6.1]	< 0.001
Day 1–3	n = 151	1.6 [0.7, 3.9]	n = 38	0.6 [0.4, 1.1]	n = 113	2.2 [1.1, 5.0]	< 0.001	n = 62	1.8 [1.0, 3.2]	n = 51	3.7 [1.8, 7.4]	0.001
Day 4–7	n = 406	0.7 [0.4, 1.7]	n = 213	0.5 [0.3, 0.7]	n = 193	1.4 [0.7, 4.0]	< 0.001	n = 126	1.0 [0.5, 1.9]	n = 67	3.0 [1.6, 9.5]	< 0.001
Day 8–14	n = 507	0.7 [0.4, 1.3]	n = 321	0.5 [0.4, 0.8]	n = 186	1.5 [0.8, 4.2]	< 0.001	n = 129	1.1 [0.7, 1.8]	n = 57	4.4 [2.0, 12.0]	< 0.001
Day > 14	n = 446	0.6 [0.4, 1.2]	n = 278	0.6 [0.4, 0.8]	n = 168	1.0 [0.6, 2.7]	< 0.001	n = 143	0.8 [0.6, 1.6]	n = 25	7.3 [3.4, 21.8]	< 0.001
NT-proBNP (pg/mL)												
Baseline	n = 1858	108 [36, 370]	n = 1423	72 [28, 190]	n = 435	581 [230, 1674]	< 0.001	n = 270	505 [180, 1485]	n = 165	790 [311, 2468]	0.001
Day 1–3	n = 206	873 [348, 2960]	n = 45	278 [62, 451]	n = 161	1225 [496, 4756]	< 0.001	n = 91	845 [338, 3962]	n = 70	1624 [833, 4863]	0.008
Day 4–7	n = 493	340 [79, 1350]	n = 251	101 [40, 315]	n = 242	1043 [357, 3654]	< 0.001	n = 154	647 [283, 1829]	n = 88	2240 [825, 6895]	< 0.001
Day 8–14	n = 626	178 [51, 757]	n = 386	84 [37, 227]	n = 240	950 [253, 4434]	< 0.001	n = 163	445 [182, 1751]	n = 77	4228 [1189, 13,442]	< 0.001
Day > 14	n = 495	144 [54, 636]	n = 301	95 [41, 216]	n = 194	547 [133, 3807]	< 0.001	n = 158	319 [95, 1786]	n = 36	6443 [2043, 9898]	< 0.001
IL-6 (pg/mL)												
Admission	n = 989	5.0 [1.8, 24.1]	n = 770	3.1 [1.5, 9.9]	n = 219	40.1 [18.2, 85.9]	< 0.001	n = 141	30.4 [13.4, 64.5]	n = 78	58.5 [30.4, 174.7]	< 0.001
Day 1–3	n = 356	10.7 [2.4, 40.1]	n = 243	5.0 [1.7, 21.3]	n = 113	39.7 [11.8, 114.8]	< 0.001	n = 75	24.3 [8.7, 103.0]	n = 38	64.6 [23.9, 178.1]	0.007
Day 4–7	n = 431	7.7 [2.1, 31.6]	n = 267	3.7 [1.5, 11.1]	n = 164	33.1 [9.4, 106.1]	< 0.001	n = 113	19.1 [7.0, 68.9]	n = 51	83.9 [35.2, 226.8]	< 0.001

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Table 2 (*continued*)

	Total (n = 2068)		Non-critically ill (n = 1592)		Critically ill (n = 476)		p (non-critically ill vs. critically ill)	Critically ill				
								Survivors (n = 293)		Non-survivors (n = 183)		
Day 8–14	n = 694	4.9 [2.0, 17.3]	n = 485	3.2 [1.5, 6.8]	n = 209	26.4 [7.4, 100.0]	< 0.001	n = 158	18.3 [5.6, 55.7]	n = 51	126.0 [40.2, 389.6]	< 0.001
Day > 14	n = 668	4.8 [2.2, 12.7]	n = 463	3.6 [1.7, 7.4]	n = 205	15.1 [4.8, 76.0]	< 0.001	n = 176	10.8 [4.5, 41.4]	n = 29	226.2 [123.8, 634.7]	< 0.001
IL-8 (pg/mL)												
Admission	n = 964	10.6 [6.8, 19.0]	n = 754	9.0 [6.2, 14.8]	n = 210	21.9 [12.2, 44.6]	< 0.001	n = 133	19.4 [11.4, 38.7]	n = 77	25.3 [15.0, 52.3]	0.040
Day 1–3	n = 341	18.3 [11.2, 30.7]	n = 239	15.5 [9.8, 26.5]	n = 102	25.9 [17.0, 57.0]	< 0.001	n = 66	24.0 [16.8, 43.2]	n = 36	32.5 [18.3, 62.6]	0.195
Day 4–7	n = 416	10.0 [6.1, 21.5]	n = 262	7.7 [5.2, 11.9]	n = 154	22.1 [11.0, 48.7]	< 0.001	n = 103	17.5 [9.6, 31.9]	n = 51	45.2 [24.1, 121.5]	< 0.001
Day 8–14	n = 689	8.6 [5.2, 16.7]	n = 484	7.3 [5.0, 11.5]	n = 205	16.8 [8.2, 41.4]	< 0.001	n = 155	13.4 [7.6, 23.7]	n = 50	51.5 [21.4, 222.5]	< 0.001
Day > 14	n = 636	12.1 [7.3, 23.2]	n = 446	10.5 [6.4, 17.5]	n = 190	18.6 [11.1, 40.4]	< 0.001	n = 163	16.9 [10.3, 30.2]	n = 27	95.0 [30.9, 216.0]	< 0.001
IL-10 (pg/mL)												
Admission	n = 964	5.0 [5.0, 6.1]	n = 754	5.0 [5.0, 5.0]	n = 210	7.5 [5.0, 12.6]	< 0.001	n = 133	6.1 [5.0, 10.5]	n = 77	9.8 [6.4, 16.0]	< 0.001
Day 1–3	n = 341	5.0 [5.0, 6.5]	n = 239	5.0 [5.0, 5.1]	n = 102	6.3 [5.0, 13.1]	< 0.001	n = 66	6.1 [5.0, 11.5]	n = 36	8.4 [5.3, 16.6]	0.149
Day 4–7	n = 416	5.0 [5.0, 5.6]	n = 262	5.0 [5.0, 5.0]	n = 154	5.2 [5.0, 10.1]	< 0.001	n = 103	5.0 [5.0, 7.3]	n = 51	10.4 [5.0, 19.9]	< 0.001
Day 8–14	n = 689	5.0 [5.0, 5.0]	n = 484	5.0 [5.0, 5.0]	n = 205	5.0 [5.0, 9.4]	< 0.001	n = 155	5.0 [5.0, 7.0]	n = 50	12.6 [5.1, 22.1]	< 0.001
Day > 14	n = 636	5.0 [5.0, 5.1]	n = 446	5.0 [5.0, 5.0]	n = 190	5.0 [5.0, 8.8]	< 0.001	n = 163	5.0 [5.0, 7.0]	n = 27	10.1 [5.1, 49.1]	< 0.001
IL-2R (U/L)												
Admission	n = 957	464 [297, 783]	n = 749	400 [277, 619]	n = 208	972 [644, 1522]	< 0.001	n = 133	881 [595, 1432]	n = 75	1095 [706, 1587]	0.021
Day 1–3	n = 341	666 [397, 1024]	n = 239	528 [340, 805]	n = 102	1142 [716, 1440]	< 0.001	n = 66	1072 [617, 1386]	n = 36	1206 [885, 1595]	0.041
Day 4–7	n = 416	617 [383, 1025]	n = 262	464 [320, 708]	n = 154	987 [651, 1516]	< 0.001	n = 103	844 [563, 1296]	n = 51	1327 [987, 1619]	< 0.001
Day 8–14	n = 688	538 [338, 848]	n = 483	455 [298, 665]	n = 205	917 [565, 1290]	< 0.001	n = 155	777 [521, 1152]	n = 50	1202 [878, 1525]	< 0.001
Day > 14	n = 632	522 [348, 765]	n = 445	460 [322, 674]	n = 187	767 [496, 1040]	< 0.001	n = 160	723 [472, 962]	n = 27	1548 [808, 2838]	< 0.001
TNF-α (pg/mL)												
Admission	n = 949	8.0 [6.1, 10.6]	n = 739	7.6 [5.9, 9.7]	n = 210	10.4 [7.6, 13.8]	< 0.001	n = 133	9.8 [7.6, 13.4]	n = 77	11.3 [8.4, 15.1]	0.101
Day 1–3	n = 353	8.2 [6.0, 11.8]	n = 253	7.3 [5.7, 9.5]	n = 100	12.2 [8.6, 18.1]	< 0.001	n = 64	12.2 [8.9, 15.8]	n = 36	12.6 [7.7, 21.2]	0.755
Day 4–7	n = 416	8.4 [6.3, 12.0]	n = 261	7.5 [5.6, 9.6]	n = 155	11.5 [8.0, 16.7]	< 0.001	n = 104	9.7 [7.0, 14.8]	n = 51	15.0 [10.8, 23.1]	< 0.001
Day 8–14	n = 690	8.1 [5.5, 11.0]	n = 485	7.2 [5.0, 9.4]	n = 205	10.6 [7.7, 18.6]	< 0.001	n = 155	10.2 [7.3, 16.4]	n = 50	14.8 [9.3, 28.4]	< 0.001
Day > 14	n = 636	9.1 [6.6, 12.3]	n = 446	8.5 [6.2, 11.1]	n = 190	11.2 [8.1, 15.9]	< 0.001	n = 163	10.4 [7.8, 14.7]	n = 27	15.3 [12.3, 25.1]	0.001
CRP (mg/L)												

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Table 2 (*continued*)

	Total (n = 2068)		Non-critically ill (n = 1592)		Critically ill (n = 476)		p (non-critically ill vs. critically ill)	Critically ill				
								Survivors (n = 293)		Non-survivors (n = 183)		
Admission	n = 1989	11.1 [1.7, 57.9]	n = 1537	5.2 [1.2, 31.0]	n = 452	72.7 [37.1, 125.5]	< 0.001	n = 279	59.4 [26.6, 109.2]	n = 173	102.7 [58.8, 151.9]	< 0.001
Day 1–3	n = 240	55.8 [13.5, 106.8]	n = 84	25.4 [4.3, 55.4]	n = 156	74.8 [32.9, 134.4]	< 0.001	n = 93	61.5 [21.6, 98.0]	n = 63	117.9 [65.2, 179.4]	< 0.001
Day 4–7	n = 828	8.6 [1.9, 39.3]	n = 569	3.7 [1.2, 14.9]	n = 259	48.4 [13.7, 105.8]	< 0.001	n = 169	34.0 [9.6, 72.7]	n = 90	93.8 [46.9, 190.3]	< 0.001
Day 8–14	n = 1074	3.5 [1.2, 17.0]	n = 784	2.2 [0.9, 7.0]	n = 290	23.3 [5.5, 97.0]	< 0.001	n = 215	10.3 [3.6, 50.5]	n = 75	160.5 [64.8, 213.9]	< 0.001
Day > 14	n = 802	3.5 [1.2, 14.8]	n = 580	2.4 [1.0, 6.5]	n = 222	16.4 [4.5, 79.3]	< 0.001	n = 190	11.8 [3.4, 44.7]	n = 32	167.1 [112.2, 231.3]	< 0.001
INR												
Admission	n = 1994	1.1 [1.0, 1.1]	n = 1534	1.0 [1.0, 1.1]	n = 460	1.1 [1.1, 1.2]	< 0.001	n = 282	1.1 [1.0, 1.2]	n = 178	1.2 [1.1, 1.4]	< 0.001
Day 1–3	n = 236	1.2 [1.1, 1.3]	n = 80	1.1 [1.0, 1.2]	n = 156	1.2 [1.1, 1.4]	< 0.001	n = 86	1.2 [1.1, 1.3]	n = 70	1.3 [1.2, 1.6]	< 0.001
Day 4–7	n = 641	1.1 [1.0, 1.2]	n = 388	1.1 [1.0, 1.1]	n = 253	1.2 [1.1, 1.4]	< 0.001	n = 155	1.1 [1.1, 1.2]	n = 98	1.4 [1.2, 1.6]	< 0.001
Day 8–14	n = 825	1.1 [1.0, 1.1]	n = 559	1.0 [1.0, 1.1]	n = 266	1.2 [1.1, 1.3]	< 0.001	n = 180	1.1 [1.1, 1.2]	n = 86	1.4 [1.2, 1.5]	< 0.001
Day > 14	n = 664	1.1 [1.0, 1.1]	n = 438	1.0 [1.0, 1.1]	n = 226	1.1 [1.0, 1.2]	< 0.001	n = 190	1.1 [1.0, 1.2]	n = 36	1.4 [1.2, 1.9]	< 0.001
D-Dimer (ug/mL)												
Admission	n = 1970	0.7 [0.3, 1.8]	n = 1524	0.5 [0.2, 1.1]	n = 446	2.4 [1.2, 8.1]	< 0.001	n = 275	2.0 [1.0, 4.1]	n = 171	3.4 [1.6, 21.0]	< 0.001
Day 1–3	n = 240	3.0 [1.1, 14.1]	n = 81	0.9 [0.3, 3.1]	n = 159	6.2 [2.2, 21.0]	< 0.001	n = 88	3.3 [1.6, 14.1]	n = 71	13.9 [2.9, 21.0]	< 0.001
Day 4–7	n = 642	1.6 [0.6, 5.2]	n = 389	0.8 [0.4, 2.0]	n = 253	5.5 [2.2, 19.1]	< 0.001	n = 157	2.7 [1.4, 8.4]	n = 96	16.3 [5.4, 21.0]	< 0.001
Day 8–14	n = 812	1.1 [0.4, 2.9]	n = 542	0.6 [0.3, 1.4]	n = 270	3.8 [1.6, 11.7]	< 0.001	n = 184	2.7 [1.1, 7.2]	n = 86	12.1 [5.3, 21.0]	< 0.001
Day > 14	n = 663	0.9 [0.4, 2.4]	n = 435	0.6 [0.3, 1.3]	n = 228	2.5 [1.1, 5.0]	< 0.001	n = 192	1.9 [0.9, 3.6]	n = 36	7.0 [4.3, 9.7]	< 0.001
Fibrinogen (g/L)												
Admission	n = 1860	4.4 [3.3, 5.6]	n = 1451	4.2 [3.3, 5.4]	n = 409	5.1 [3.9, 6.3]	< 0.001	n = 261	5.2 [4.0, 6.3]	n = 148	5.0 [3.6, 6.3]	0.329
Day 1–3	n = 233	4.4 [3.2, 5.5]	n = 78	4.3 [3.4, 5.5]	n = 155	4.4 [3.1, 5.5]	0.401	n = 85	4.5 [3.5, 5.7]	n = 70	4.1 [2.4, 5.4]	0.066
Day 4–7	n = 633	4.3 [3.3, 5.5]	n = 382	4.2 [3.3, 5.4]	n = 251	4.5 [3.4, 5.8]	0.094	n = 155	4.7 [3.6, 5.9]	n = 96	4.3 [3.1, 5.7]	0.127
Day 8–14	n = 817	4.1 [3.3, 5.2]	n = 553	3.9 [3.3, 4.8]	n = 264	4.7 [3.6, 5.8]	< 0.001	n = 180	4.4 [3.6, 5.5]	n = 84	5.0 [3.5, 6.4]	0.093
Day > 14	n = 662	4.0 [3.4, 5.0]	n = 437	3.9 [3.3, 4.7]	n = 225	4.7 [3.6, 5.8]	< 0.001	n = 189	4.5 [3.6, 5.5]	n = 36	6.4 [4.1, 6.9]	< 0.001

Abbreviations: hs-cTnI, High-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; Mb, myoglobin; CK-MB, Creatine Kinase-MB; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-2R, interleukin-2 receptor; TNFα, Tumor necrosis factor-α; INR, international normalized ratio.

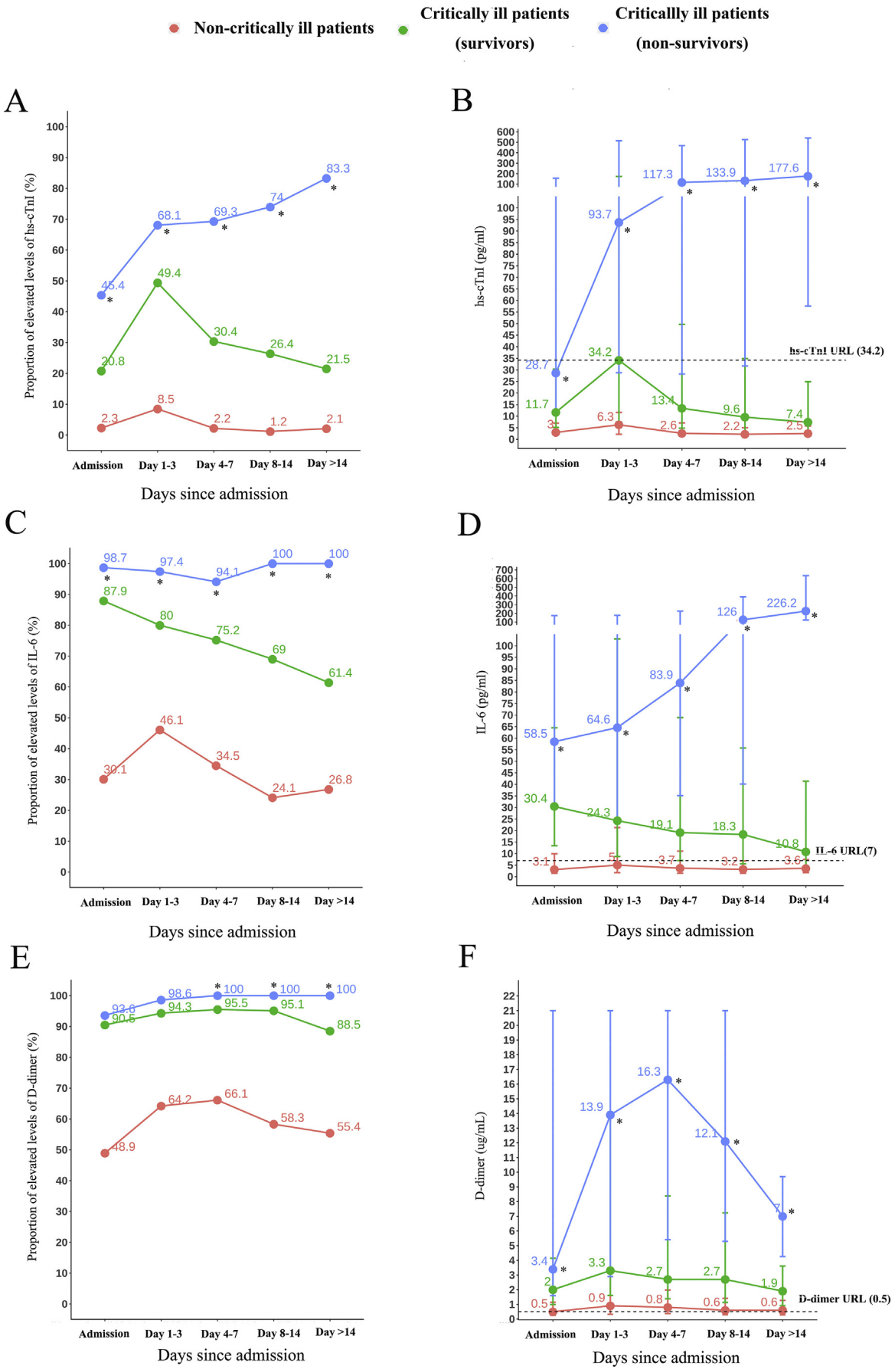

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Fig. 1. Proportions of patients with elevated biomarkers and the absolute levels of biomarkers during hospitalization. A) Proportion of patients with elevated high sensitivity cardiac troponin I (hs-cTnI). B) Hs-cTnI absolute level. C) Proportion of patients with elevated interleukin (IL)-6. D) IL-6 absolute level. E) Proportion of patients with elevated d-dimer. F) d-dimer absolute level. Asterix indicates at least $p < 0.05$ (see Table 1 for details).

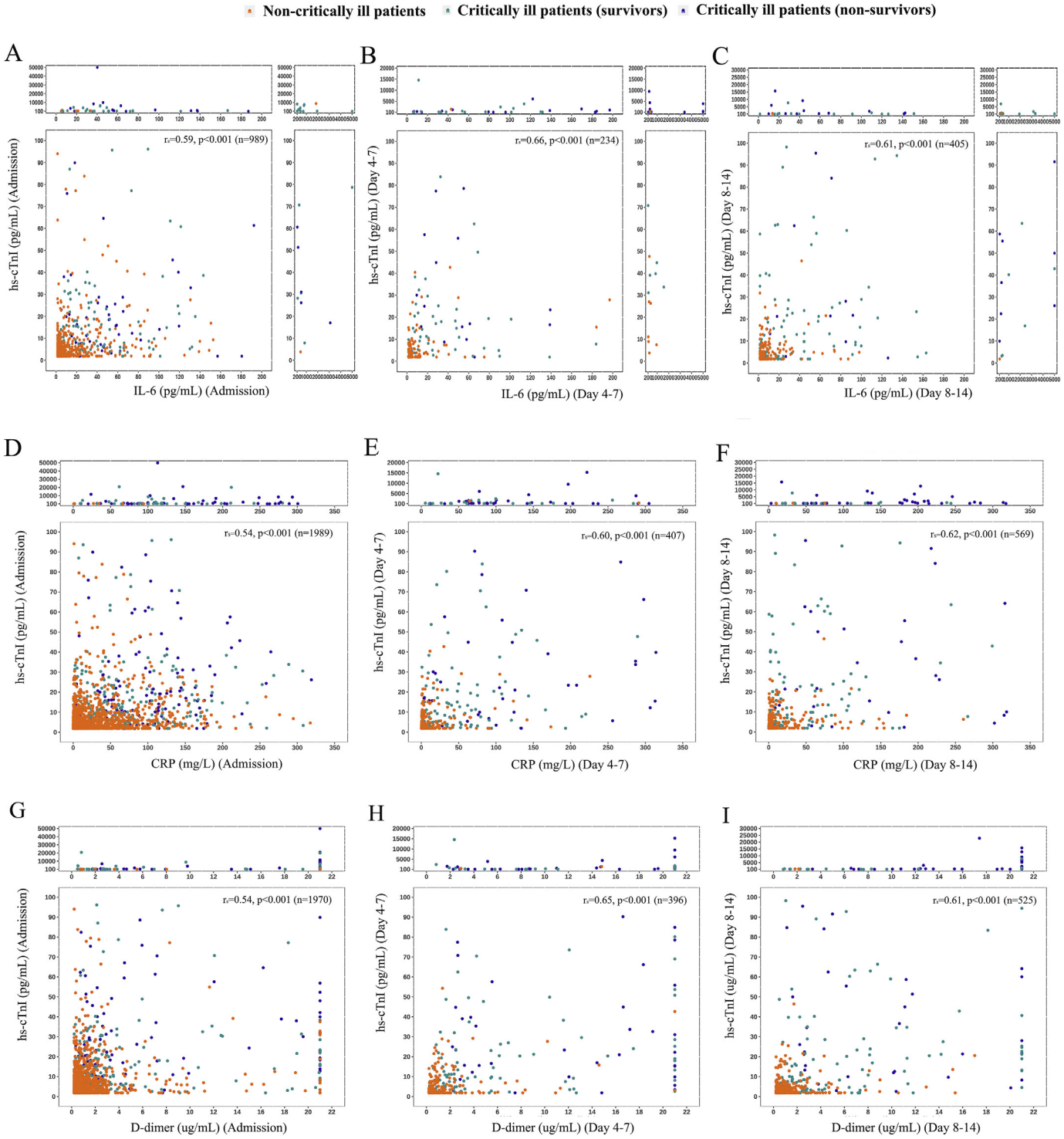

Fig. 2. Spearman correlations of high sensitivity cardiac troponin I (hs-cTnI) with interleukin (IL)-6, C-reactive protein (CRP), and d-dimer on admission, in the time interval between day 4–7 and in the time interval between day 8–14. A) hs-cTnI and IL-6 on admission. B) Hs-cTnI and IL-6 values in the time interval between day 4 and 7. C) Hs-cTnI and IL-6 values in the time interval between day 8 and 14. D) Hs-cTnI and CRP on admission. E) Hs-cTnI and CRP values in the time interval between day 4 and 7. F) Hs-cTnI and CRP values in the time interval between day 8 and 14. G) Hs-cTnI and d-dimer on admission. H) Hs-cTnI and d-dimer values in the time interval between day 4 and 7. I) Hs-cTnI and d-dimer values in the time interval between day 8 and 14.

Table 3
Correlations between markers of myocardial injury markers of inflammation and coagulation on admission, at day 4–7, and day 8–14 of hospitalization in COVID-19 patients.

	hs-cTnI		NT-proBNP		Mb		CK-Mb	
	r_s	p	r_s	p	r_s	p	r_s	p
Admission								
IL-6	0.59	< 0.001	0.63	< 0.001	0.50	< 0.001	0.26	< 0.001
IL-10	0.39	< 0.001	0.36	< 0.001	0.32	< 0.001	0.16	< 0.001
IL-8	0.42	< 0.001	0.44	< 0.001	0.35	< 0.001	0.28	< 0.001
TNF-α	0.35	< 0.001	0.33	< 0.001	0.36	< 0.001	0.27	< 0.001
IL-2R	0.55	< 0.001	0.60	< 0.001	0.49	< 0.001	0.32	< 0.001
CRP	0.56	< 0.001	0.56	< 0.001	0.51	< 0.001	0.23	< 0.001
INR	0.36	< 0.001	0.45	< 0.001	0.36	< 0.001	0.26	< 0.001
D-dimer	0.54	< 0.001	0.65	< 0.001	0.46	< 0.001	0.31	< 0.001
Fibrinogen	0.32	< 0.001	0.34	< 0.001	0.31	< 0.001	0.08	0.002
Day 4–7								
IL-6	0.66	< 0.001	0.65	< 0.001	0.66	< 0.001	0.54	< 0.001
IL-10	0.50	< 0.001	0.51	< 0.001	0.47	< 0.001	0.45	< 0.001
IL-8	0.57	< 0.001	0.57	< 0.001	0.59	< 0.001	0.59	< 0.001
TNF-α	0.53	< 0.001	0.49	< 0.001	0.54	< 0.001	0.52	< 0.001
IL-2R	0.55	< 0.001	0.61	< 0.001	0.5	< 0.001	0.46	< 0.001
CRP	0.60	< 0.001	0.65	< 0.001	0.61	< 0.001	0.48	< 0.001
INR	0.59	< 0.001	0.57	< 0.001	0.65	< 0.001	0.52	< 0.001
D-dimer	0.65	< 0.001	0.63	< 0.001	0.61	< 0.001	0.53	< 0.001
Fibrinogen	0.04	0.454	0.10	0.046	0.08	0.154	0.01	0.912
Day 8–14								
IL-6	0.61	< 0.001	0.63	< 0.001	0.56	< 0.001	0.51	< 0.001
IL-10	0.36	< 0.001	0.38	< 0.001	0.4	< 0.001	0.34	< 0.001
IL-8	0.48	< 0.001	0.47	< 0.001	0.45	< 0.001	0.45	< 0.001
TNF-α	0.41	< 0.001	0.45	< 0.001	0.45	< 0.001	0.44	< 0.001
IL-2R	0.47	< 0.001	0.57	< 0.001	0.51	< 0.001	0.39	< 0.001
CRP	0.61	< 0.001	0.63	< 0.001	0.57	< 0.001	0.48	< 0.001
INR	0.51	< 0.001	0.56	< 0.001	0.57	< 0.001	0.46	< 0.001
D-dimer	0.61	< 0.001	0.63	< 0.001	0.56	< 0.001	0.47	< 0.001
Fibrinogen	0.24	< 0.001	0.26	< 0.001	0.27	< 0.001	0.15	0.001

Abbreviations: hs-cTnI, High-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; Mb, myoglobin; CK-MB, Creatine Kinase-MB; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-2R, interleukin-2 receptor; TNF-α, Tumor necrosis factor-α; INR, international normalized ratio. Spearmen correlation was used.

3.3. Correlations between myocardial injury and markers of inflammation and coagulation

To further assess the correlation between myocardial and inflammation biomarkers, as well as myocardial and coagulation biomarkers, we analyzed these makers among patients for whom one-to-one data were available at individual time points during hospitalization (Fig. 2). Scatter plots demonstrated a moderate magnitude and statistically significant correlation of hs-cTnI with IL-6 levels (ranging between $r = 0.59$ to 0.66, all $p < 0.001$), hs-cTnI with CRP levels (ranging between $r = 0.54$ to 0.62, all $p < 0.001$), as well as with d-dimer levels (ranging between $r = 0.54$ to 0.65, all $p < 0.001$) on admission, middle (day 4–7), and beyond the first week of hospitalization (day 8–14; Fig. 2). We also observed significant correlations between the levels of hs-cTnI and other markers of cardiac injury with other inflammatory and coagulation markers across different time points (Table 3)Correlations at further time points reported consistent results (day 1–3 and day > 14; Supplementary Table 3). To reduce the risk of inconsistencies in number of samples at each time point, we performed a sensitivity subanalysis in patients with complete data on admission, day 4–7 and day 8–14 for the correlations between hs-cTnI with IL-6 levels ($N = 234$, ranging between $r = 0.52$ to 0.66, all $p < 0.001$), hs-cTnI with CRP levels ($N = 407$, ranging between $r = 0.54$ to 0.62, all $p < 0.001$) and hs-cTnI with d-dimer ($N = 396$, ranging between $r = 0.55$ to 0.65, all $p < 0.001$) confirmed the results obtained with the larger sample size (Supplementary Fig. 2).

3.4. Cardiac events, ECG and echocardiographic data in patients with cardiac injury

We further assessed whether hs-cTnI elevation on admission correlated with cardiovascular events in critically ill patients during hospitalization. Critically ill patients with hs-cTnI elevation had significant higher rate of serious cardiovascular events compared with critically ill patients without hs-cTnI elevation: including higher risk for cardiac arrest (25.7% vs. 12.0% $p < 0.001$), cardiac rhythm disturbances (42.4% vs. 23.2%, $p < 0.001$), and myocardial infarction (2.1% vs 0%, $p = 0.027$), and mortality (57.6% vs. 30.1%, $p < 0.001$) (Table 4). These differences still held if the criteria were changed to hs-cTnI elevation on admission and during hospitalization (Table 4). To better characterize the cardiovascular manifestations in 267 patients with hs-cTnI elevation on admission or during hospitalization, including non-critically ill patients, we identified 118 patients who had electrocardiogram (ECG) and 49 patients who had echocardiographic data. Abnormal ECG was defined as presence of T wave depression/inversion, ST segment depression/elevation and new onset of pathogenic Q waves. Overall, 51 (43.2%) patients had ECG abnormalities, including 28 (54.9%) patients with T wave depression/inversion, 37 (72.5%) patients with ST segment depression/elevation, and 6 (11.8%) patients with pathogenic Q waves. On the other hand, of those patients who had an echocardiogram, median left ventricular ejection fraction (LVEF) was 58% with only 5 (10.2%) patients having at least moderate left ventricular dysfunction (LVEF ≤40%). Interestingly pericardial effusion was observed in 12 (24.5%) echocardiograms examined.

Table 4
The rate of incident cardiovascular events among critically ill patients stratified by without/with elevated high sensitivity cardiac troponin I (hs-cTnI) level.

	Patients without elevated hs-cTnI level on admission (n = 332)	Patients with elevated hs-cTnI level on admission (n = 144)	p	Patients without elevated hs-cTnI level on admission + during hospitalization (n = 249)	Patients with elevated hs-cTnI level on admission + during hospitalization (n = 227)	p
Cardiac events						
Cardiac arrest n. (%)	40 (12.0)	37 (25.7)	< 0.001	18 (7.2)	59 (26.0)	< 0.001
Cardiac rhythm disturbances[a] n. (%)	77 (23.2)	61 (42.4)	< 0.001	31 (12.4)	107 (47.1)	< 0.001
Myocardial infarction[a] n. (%)	0 (0)	3 (2.1)	0.027	0 (0)	3 (1.3)	0.108
Mortality n. (%)	100 (30.1)	83 (57.6)	< 0.001	46 (18.5)	137 (60.4)	< 0.001

[a] Cardiac rhythm disturbances include ventricular tachycardia, supraventricular tachycardia, atrial fibrillation, atrial flutter, second-degree (type 2) or third-degree atrioventricular block, and sick sinus syndrome. Myocardial infarction was confirmed by coronary angiography.

3.5. Associations between myocardial injury, IL-6 and d-dimer with mortality in critically ill patients

We next explored the prognostic value of hs-cTnI elevation in relation to, and independent of inflammatory and coagulation markers. As shown in Supplementary Table 4, we confirmed a significant independent association of elevated levels of hs-cTnI with the mortality among critically ill patients. In the demographically adjusted model (Model 1), 1 per standard deviation increase in hs-cTnI indicated a 1.29-fold higher risk of death among critically ill patients on admission. The associations remained significant after adjustment for traditional cardiovascular risk factors (Model 2) and IL-6 and d-dimer levels (Model 3). Similarly, hs-cTnI was independently associated with death among critically ill patients throughout hospitalization, both on day 4–7 and day > 14. Furthermore, the associations of IL-6 and d-dimer levels at different time points with the occurrence of death were also evaluated and displayed in Supplementary Table 4. Both IL-6 and d-dimer had an independent association with mortality after adjustment for the previous models.

4. Discussion

In this large population-based study, 8.8% of COVID-19 patients have elevation in hs-cTnI on admission, increasing to 30.3% among critically ill patients, the latter associated with an in-hospital mortality rate of 38.4%. Longitudinal follow-up of hs-cTnI suggests significant divergence between critically ill survivors compared with critically ill patients who died. Importantly, our data suggest that hs-cTnI is an independent prognostic marker of mortality at baseline and at later timepoints independently of several variables including inflammatory and coagulative markers, supporting the value to monitor hs-cTnI in critically ill COVID-19 patients. Cardiac injury on admission was associated with increased serious cardiac events including cardiac arrest, arrhythmias and acute myocardial infarction among critically ill patients. In addition to hs-cTnI, median levels of inflammatory markers, in particular IL-6 and CRP, peak at day 3 and gradually decreased between day 4 and 7 of hospitalization in critically ill survivors while they continuous increased among non-survivors. Similarly, d-dimer, as a marker of coagulation, remained significantly increased in non-survivors compared with survivors at all timepoints.

We observed consistent positive correlation between levels of hs-cTnI and inflammation markers, including CRP, IL-6, IL-8, IL-10, TNF-α and IL-2R at each explored timepoint. The strongest correlations (r ranging from 0.54 to 0.66) were observed on admission, day 4–7 and day 8–14 among hs-cTnI, IL-6 and CRP levels. This association further holds when considering other marker of cardiac injury such as Mb, CK-MB or NT-proBNP. The overall interplay between inflammatory cytokines and cardiac injury in this study suggests the possibility that cardiac damage occurs as a result of hyperinflammatory disorder triggered by the SARS-CoV-2 and resembling cytokine release syndrome observed after treatment with cancer immunotherapies, such as chimeric antigen receptor T cells [25]. Our comprehensive biomarker phenotyping presented in this large COVID-19 population at several timepoints during hospitalization can provide a framework for future interventional studies aimed to attenuate the inflammatory response that is associated with cardiac injury. Finally, observational studies that report a potential therapeutic effect of corticosteroids and low molecular weight heparin in specific settings of severe COVID-19 patients [8,21], support the idea that markers of inflammation and activation of coagulation can guide intervention trials in high risk patients.

In the present study, cardiac injury was based on elevated hs-cTnI. We show that serious cardiac events were more common in critically ill patients with cardiac injury compared to those without cardiac injury. These data suggest that hs-cTnI elevation does have cardiovascular disease manifestations and consequences. To further assess the nature of cardiac disease, we assessed ECG and echocardiograms when

available. ECG abnormalities were present in 43.2% of cases. On the other hand, echocardiogram showed at lease moderate LVEF impairment in only 10.2% of patients. On the other hand, 25.8% of cases had pericardial effusion. While merely hypothesis-generating, the presence of ECG abnormalities, pericardial effusion, and reduced LVEF are potentially compatible with an inflammatory cardiac injury [26], at least in a proportion of COVID-19 patients with elevated hs-cTnI. In addition, these data suggest that the nature of cardiac manifestations in critically ill COVID-19 patients is more arrhythmogenic than classic cardiomyopathy and acute pump failure, in agreement with previous observations [11,13].

Previous studies that assessed the prognostic value of cardiac injury in COVID-19 patients reported ECG abnormalities in 14 out of 22 (63.6%) patients with available ECG [10], or did not report ECG data [11]. These limitations reflect the real clinical practice that healthcare personnel have to face during COVID-19 outbreak. In fact, physicians' choices are mainly guided by laboratory tests, vital signs and basic radiological assessment, limiting the use of more sophisticated diagnostic tools with the aim to reduce the personnel exposure to potentially contagious patients. In this view, prognostic information derived by biomarkers is of paramount importance.

Our data suggest potential insights into the mechanisms of cardiac injury in COVID-19 patients. There have been a number of proposed explanations for cardiac injury in COVID-19 patients including the potential for SARS-CoV-2 to infect cardiomyocytes, pericytes and fibroblasts via the angiotensin converting enzyme (ACE)-2 pathway leading to direct myocardial injury [27]. Alternatively, myocardial injury may be due to cytokine excess and/or antibody mediated mechanisms. Currently, limited data exist from endomyocardial biopsy or autopsies [17,18,20], or cardiac imaging in COVID-19 patients. Although acute myocarditis associated with COVID-19 has been described in isolated cases [15,16,28], a much larger body of literature suggests little resemblance to classic viral myocarditis with inflammatory cellular infiltration [17,18]. Our data show a consistent correlation between markers of inflammatory response, as well as coagulative activation and cardiac injury suggesting that myocardial injury could be mediated by the cytokine release syndrome. Other studies support our data for unlikelihood of a direct virus-mediated myocardial infection in most of cases of COVID-19. For example, among COVID-19 patients, SARS-CoV-2 was detected in blood in less than 1% of blood specimens [29]. Other studies have shown no evidence of SARS-CoV-2 in the cardiomyocytes with suspected myocarditis [17,18]. Another possibility is that critically ill COVID-19 patients present with more severe lung injury and hypoxia, leading to myocardial ischemia.

There are a number of limitations in our study. Data were not collected prospectively. Additionally, long-term clinical outcomes of survivors are not yet available. We did not have results of all biomarkers at any time point. Furthermore, the type and degree of anti-cardiac immune-mediated injury, including levels of antibody response to anti-cardiac epitopes, were not available, which would provide a proper insight into the pathophysiological stage of the cardiac injury from viral infection to the immune mediated autoreactivity. Finally, the impact of therapies, for instance initiation of corticosteroids or the effect of angiotensin II receptor blocker were not reported. Therapies could affect the clinical course (e.g. viral entry) and cytokine levels, but in a retrospective trial these variables cannot be completely controlled. For instance, in this series, drugs such as corticosteroids or anticoagulant drugs have been frequently initiated late in the course of hospitalization and in patients that developed clinical complications as observed also in other reports of critically ill patients [9,12]. Nevertheless, our study is the largest to date to longitudinally follow cardiac, inflammatory and coagulation biomarkers and correlate these with outcomes during hospitalization. Our data also provide hypotheses regarding mechanism of cardiac injury. Future prospective studies should aim to define if the early use of immunomodulating drugs such as corticosteroids or IL-6 receptor and IL-1 inhibitors may have an impact on prognosis by hampering the cytokine storm, reducing cardiac injury, thus improving the disease outcomes.

In conclusion we analyzed the dynamic changes in biomarkers of cardiac injury, inflammation and coagulation in hospitalized COVID-19 patients and correlated these to patient outcome. Myocardial injury not only occurs in the late stages of the disease, but a subclinical elevation of hs-cTnI already starts at the initial stages of infection. We found that changes in the biomarkers of myocardial injury in the first week largely determine the clinical outcome of COVID-19 patients, even when we focus only on critically ill patients. Interplay analysis of hs-cTnI with IL-6, and d-dimer suggests nonspecific cytokine-mediated cardiotoxicity in the context of a cytokine release syndrome as a possible mechanism of myocardial injury.

Contributors' statement

Study design: CL, DWW; data collection: CL, JJ, FW, NZ; data analysis: CL; data interpretation: CL, JJM, EA, DWW; writing: CL, JJM, EA; Revision: GV, DWW

Data and code sharing

The data and code that supporting the findings of the present study are available via the corresponding author under reasonable request.

Declaration of Competing Interests

JM has served on advisory boards for Pfizer, Novartis, Bristol Myers Squibb, Takeda, GSK and AstraZeneca and is supported by the National Institutes of Health (R01HL141466).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yjmcc.2020.08.008.

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