Ospedale Luigi Sacco

AZIENDA OSPEDALIERA - POLO UNIVERSITARIO

COVID-19 E PATOLOGIA CARDIACA

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RESPIRATORY INFECTIONS AND CARDIAC INJURY

- Sepsis and other infections are associated with **CV events**, especially acute coronary syndromes
- In the early 20th century, an excess mortality during influenza and pneumonia epidemics was first recognized, but the specific **association** with influenza or other respiratory infections and MI was not described until decades later
- The risk of MI in the context of respiratory infectious disease reaches a **peak at the onset of infections** and is proportional to the severity of illness
- Respiratory infections—e.g., influenza A/B and previous SARS infections—are associated with CV events, cardiac arrhythmias, and especially ACS

ACS AND RESPIRATORY INFECTIONS

Table 2. Acute coronary syndromes and other acute respiratory infection—main studies.

Study, Year, Journal	Infection	Population and Timeline	Myocardial Infarction Diagnosis	Cases with Myocardial Infarction and Respiratory Infectious Disease
Smeeth et al., 2004, New England Journal of Medicine [42]	Systemic respiratory tract infection (pneumonia, acute bronchitis, chest infections, and influenza)	MI diagnosed 91 days after infection exposure	UK GPRD data (1495 cases were excluded because the date of the MI was uncertain)	MI: n = 3254 Respiratory infectious disease: n = 20,921
Kwong et al., 2018, New England Journal of Medicine [43]	Influenza A/B, RSV, adenovirus, CoV, enterovirus (including rhinovirus), HPIV, and HMPV	Admission for MI within 7 days after laboratory confirmation of influenza	ICD-10 diagnostic code	MI: n = 364 Respiratory infectious disease: n = 19,045
Warren-Gash et al., 2013, British Medical Journal [44]	Influenza A H1N1	Respiratory tract infection developed within one month before admission for MI	cTn elevation with ischemic symptoms or typical ECG changes, or by angiographic findings	MI: n = 134 Respiratory infectious disease: n = 13
Violi et al., 2017, Clinical infectious diseases [45]	CAP	MI during hospitalization for CAP	Third universal definition of AMI	MI: n = 89 (NSTEMI = 78 STEMI = 11) Respiratory infectious disease: n = 1182
Musher et al., 2007, Clinical infectious diseases [46]	Pneumococcal pneumonia	MI diagnosed at hospital admission for pneumonia	New ECG abnormalities (i.e., ST segment elevation or depression or Q waves) accompanied by cTn elevation	MI: n = 12 (NSTEMI = 9 STEMI = 3) Respiratory infectious disease: n = 170
Corrales-Medina et al., 2015, Journal of American Medical Association [47]	Pneumonia	MI and fatal coronary heart disease over 10 years after pneumonia hospitalization	Two algorithms based on symptoms, cardiac enzymes, and electrocardiographic evidence	MI: n = 247 Respiratory infectious disease: n = 1271
Vejpongsa et al., 2019, The American Journal of Medicine [48]	Acute influenza and other viral respiratory infections	Acute influenza and other viral infections in hospital admission for MI	ICD-9 diagnostic code	MI: n = 1,884,985 Respiratory infectious disease: n = 21,370 (Acute influenza = 9885 Other = 11,485)
Caussin et al., 2015, International Journal of Cardiology [49]	Wide spectrum of respiratory tract infection (flu-like illness with fever and sore throat), pneumonia or bronchitis	Possible exposure to respiratory infection within 35 days prior to admission for MI	Angiographically confirmed MI	MI: n = 578 Respiratory infectious disease: n = 123
Ruane et al., 2017, Internal Medicine Journal, [50]	Influenza	Association between STEMI and influenza epidemic	Angiographically confirmed STEMI (≤24 h) with at least ≥50% coronary stenosis	MI: n = 11,987 Respiratory infectious disease: n = NA (ERR 8.9)
Peiris et al, 2003, The Lancet [51]	SARS-CoV	Deaths for MI in hospitalized patients with SARS	Not reported	MI: n = 2 Respiratory infectious disease: n = 75
Chong et al., 2004, Archives of Pathology and Laboratory Medicine [52]	SARS-CoV	MI in post-mortem examinations for confirmed SARS infections	Post-mortem	MI: n = 2 Respiratory infectious disease: n = 8
No data available		MERS		NA

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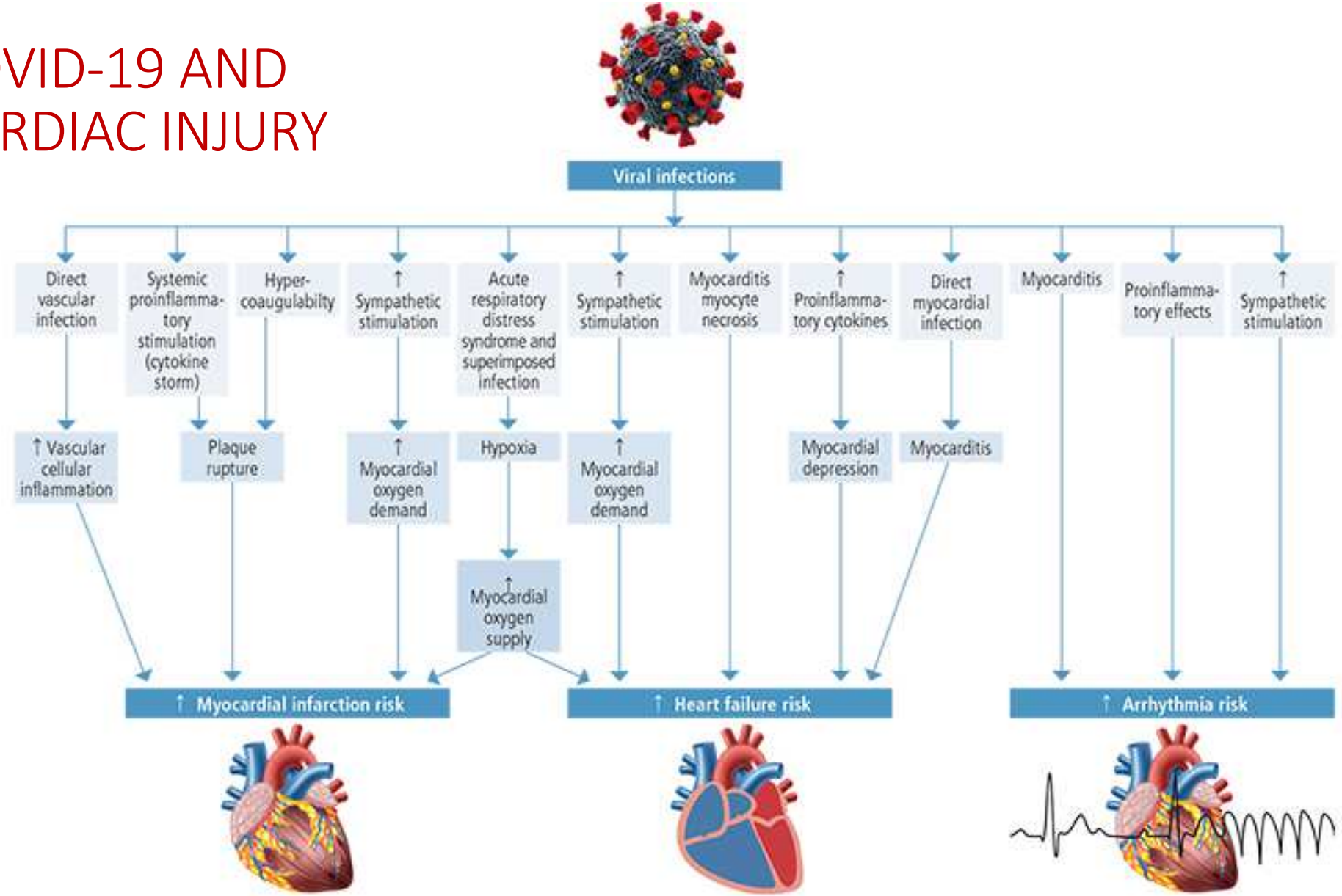
COVID-19 AND CARDIAC INJURY



COVID-19 AND MYOCARDIAL INFARCTION

Journal of *Clinical Medicine*

MDPI

Review

Acute Coronary Syndromes and Covid-19: Exploring the Uncertainties

Marco Schiavone [1,2,†], Cecilia Gobbi [2,†], Giuseppe Biondi-Zoccai [3,4], Fabrizio D'Ascenzo [5], Alberto Palazzuoli [6], Alessio Gasperetti [1], Gianfranco Mitacchione [1], Maurizio Viecca [1], Massimo Galli [7,8], Francesco Fedele [9], Massimo Mancone [9,*] and Giovanni Battista Forleo [1,2]

Cardiac complications in COVID-19 patients: Chinese experience

First published reports (early 2020)

Table 3. Myocardial injury and ACS in patients with Covid-19—main studies.

Study, Year, Journal.	Population	Evaluation and Timeline	Cases with Myocardial Injury	Suspected ACS	in Hospital Mortality
Huang et al., 2020, The Lancet [5]	*n* = 41 ICU = 13 Non-ICU = 28	Myocardial injury = increased cardiac biomarkers or new ECG—echo abnormalities during hospitalization	*n* = 5 (12%) ICU = 4 (31%) Non-ICU = 1 (4%)	NA	*n* = 6 (15%)
Wang et al., 2020, Journal of American Medical Association [1]	*n* = 138 ICU = 36 Non-ICU = 102	Myocardial injury = increased cardiac biomarkers or new ECG—echo abnormalities during hospitalization	*n* = 10 (7.2%) ICU = 8 (22.2%) Non-ICU = 2 (2%)	NA	*n* = 6 (43%)
Zhou et al., 2020, The Lancet [66]	*n* = 191 Non-survivor = 54 Survivor = 137	Myocardial injury = increased cardiac biomarkers or new ECG—echo abnormalities during hospitalization	*n* = 33 (17%) Non-survivor = 32 (59%) Survivor = 1 (1%)	First autopsy performed = findings were consistent with AMI	*n* = 54 (28.3%)
Shi et al., 2020, Journal of American Medical Association: Cardiology [6]	*n* = 416	Myocardial injury = increased cardiac biomarkers regardless of new ECG—echo abnormalities during hospitalization	*n* = 82 (19.7%)	ECG features consistent with myocardial ischemia—NSTEMI: *n* = 14 (3.36%)	*n* = 57 (13.7%) With cardiac injury = 42 (51.2%) Without cardiac injury = 15 (4.5%)

Abbreviations: ACS: acute coronary syndromes; AMI: acute myocardial infarction; ECG: electrocardiogram; ICU: intensive care unit; NA: not available; NSTEMI: myocardial infarction without ST-segment elevation; STEMI: ST-segment elevation myocardial infarction.

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COVID-19 AND MYOCARDIAL INJURY

Table 1. Mechanisms of myocardial injury. Adapted from Thygesen et al. Fourth universal definition of myocardial infarction (2018) [13].

Myocardial Injury		
Related to Primary Acute Myocardial Ischemia	**Related to Oxygen Supply/Demand Imbalance**	**Other Causes**
	Reduced myocardial perfusion	**Cardiac conditions**
Plaque rupture—erosion with occlusive thrombosis Plaque rupture—erosion with non-occlusive thrombosis	Coronary artery spasm Microvascular dysfunction Coronary embolism Coronary artery dissection Sustained bradyarrhythmia Hypotension or shock Respiratory failure with hypoxaemia Severe anaemia	Heart failure Myocarditis Cardiomyopathy (any type) Takotsubo syndrome Coronary revascularization procedure Cardiac procedure other than revascularization Catheter ablation Defibrillator shocks Cardiac contusion
	Increased myocardial oxygen demand	**Systemic conditions**
	Sustained tachyarrhythmia Severe hypertension with or without left ventricular hypertrophy	Sepsis, infectious disease Chronic kidney disease Stroke, subarachnoid hemorrhage Pulmonary embolism, pulmonary hypertension Infiltrative diseases, e.g., amyloidosis, sarcoidosis Chemotherapeutic agents Critically ill patients Strenuous exercise

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COVID-19 AND MYOCARDIAL INJURY

Myocardial injury = cardiac troponin?

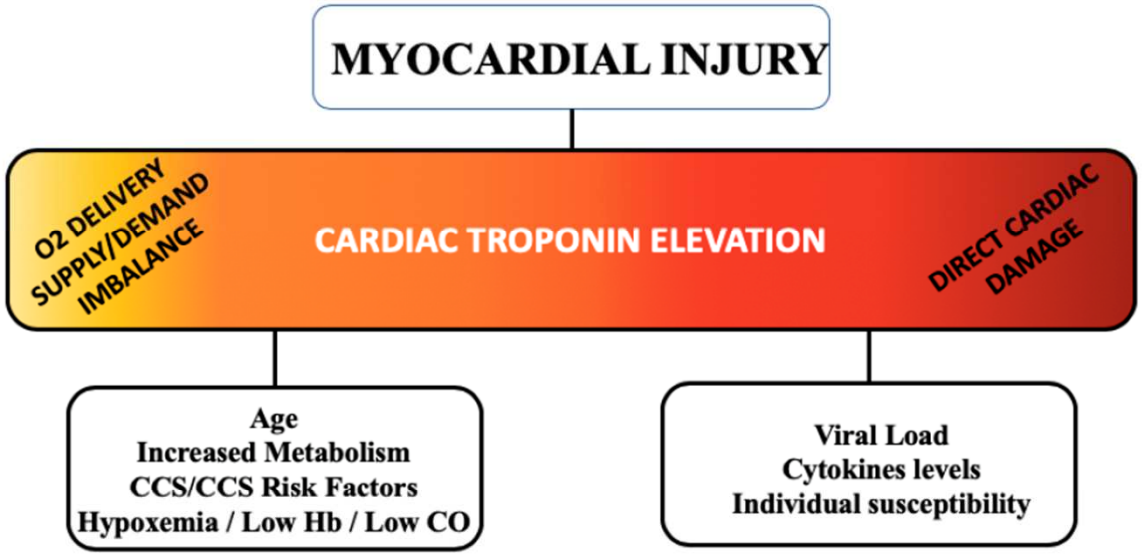

Figure 3. culprit mechanisms behind the development of myocardial injury in COVID-19. **Abbreviations**: CCS: chronic coronary syndromes; CO: cardiac output; Hb: hemoglobin.

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COVID-19 AND CARDIAC TROPONIN

What is the prognostic value of High-Sensitivity Troponin in COVID-19 Patients?

Does Coronary Artery Disease matters?

COVID-19, CARDIAC TROPONIN AND CAD

Journal of *Clinical Medicine*

MDPI

Article

Redefining the Prognostic Value of High-Sensitivity Troponin in COVID-19 Patients: The Importance of Concomitant Coronary Artery Disease

Marco Schiavone [1,†], Alessio Gasperetti [1,†], Massimo Mancone [2,*], Aaron V. Kaplan [3], Cecilia Gobbi [4], Giosuè Mascioli [5], Mattia Busana [6], Ardan M. Saguner [7], Gianfranco Mitacchione [1], Andrea Giacomelli [8], Gennaro Sardella [2], Maurizio Viecca [1], Firat Duru [7], Spinello Antinori [8,9], Stefano Carugo [4], Antonio L. Bartorelli [9,10], Claudio Tondo [10,11], Massimo Galli [8,9], Francesco Fedele [2] and Giovanni B. Forleo [1]

Redefining the Prognostic Value of High-Sensitivity Troponin in COVID-19 Patients: The Importance of Concomitant Coronary Artery Disease

Prior to this report, **no studies focused on clinical outcomes of myocardial injury in patients with and without chronic coronary syndromes (CCS)** were available

674 consecutive COVID-19 patients admitted to **four** different institutions were screened for enrolment

Patients were divided **into two groups (CCS vs. no-CCS)**

main study outcome: association with in-hospital mortality and related predictors

secondary outcomes myocardial injury and its predictors

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Table 1. Baseline characteristics of the study cohort.

	Overall (n = 674)	CCS (n = 112)	No-CCS (n = 562)	p
Age (years), mean ± s.d.	60.8 ± 15.9	75.3 ± 10.1	58.0 ± 15.2	**<0.001**
Sex (male), n (%)	406 (60.2)	75 (67)	331 (58.9)	0.111
Main cardiovascular risk factors, n (%)				
Hypertension	280 (41.5)	89 (79.5)	191 (31)	**<0.001**
Diabetes	101 (15.0)	40 (35.7)	61 (10.8)	**<0.001**
Dyslipidemia	145 (21.5)	64 (57.1)	81 (14.4)	**<0.001**
Smoke	130 (19.3)	71 (63.4)	59 (10.5)	**<0.001**
Comorbidities, n (%)				
Heart failure	111 (16.5)	76 (67.9)	35 (6.2)	**<0.001**
History of atrial fibrillation	53 (7.9)	26 (23.2)	27 (4.8)	**<0.001**
Chronic kidney disease	85 (12.3)	26 (23.1)	59 (10.5)	**<0.001**
Chronic obstructive pulmonary disease	46 (6.8)	16 (14.3)	30 (5.3)	**<0.001**
Cancer	43 (6.4)	15 (13.4)	28 (5)	**<0.001**
Drug therapy, n (%)				
ACE-inhibitors	102 (15.2)	44 (39.3)	58 (10.3)	**<0.001**
ARBs	111 (16.5)	45 (40.2)	66 (11.7)	**<0.001**
Beta-blockers	150 (22.3)	78 (69.6)	72 (12.8)	**<0.001**
Calcium-antagonists	73 (10.8)	22 (19.6)	51 (9.1)	**<0.001**
Diuretics	96 (14.2)	46 (41.1)	50 (8.9)	**<0.001**
VKAs	14 (2.1)	7 (6.2)	7 (1.3)	**<0.001**
DOACs	30 (4.4)	11 (9.8)	19 (3.4)	**0.003**
Antiplatelets	130 (19.3)	108 (96.4)	22 (3.9)	**<0.001**
Statins	156 (23.1)	93 (83.0)	63 (11.2)	**<0.001**
Prior revascularization (PCI and/or CABG), n (%)	86 (76.8)	86 (78.6)	NA	**NA**

Baseline characteristic of the study cohort

A total of 674 COVID-19 patients were enrolled, **112 (16.6%) with an established history of CCS**.

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Table 3. Drug therapy and clinical outcomes during hospital stay.

	Overall (n = 674)	CCS (n = 112)	No-CCS (n = 562)	p
Drug therapy, n (%)				
Antibiotics	327 (48.5)	58 (51.8)	269 (47.9)	0.448
Antivirals	367 (54.4)	56 (50)	311 (55.3)	0.3
Steroids	87 (12.9)	16 (14.3)	71 (12.6)	0.634
Hydroxychloroquine	520 (77.1)	86 (76.8)	434 (77.2)	0.92
Tocilizumab	126 (18.7)	13 (11.6)	113 (20.1)	**0.035**
Heparin	294 (43.6)	67 (59.8)	227 (40.4)	**<0.001**
Deaths, n (%)	105(15.6)	47 (42.0)	58 (10.3)	**<0.001**
Intensive care unit admission, n (%)	46 (6.8)	6 (5.4)	40 (7.1)	0.5

Table 3. *Cont.*

	Overall (n = 674)	CCS (n = 112)	No-CCS (n = 562)	p
Mechanical ventilation, n (%)	42 (6.2)	6 (5.4)	36 (6.4)	0.675
Non-invasive ventilation, n (%)	207 (30.7)	49 (43.8)	158 (28.1)	**<0.001**
Acute respiratory distress syndrome, n (%)	99 (14.7)	46 (41.1)	53 (9.4)	**<0.001**
Hospital length of stay (days), median [IQR]	10 [6–16]	11 [7–17]	10 [5–16]	0.189
Myocardial injury, n (%)	130 (19.3)	49 (43.8)	81 (14.4)	**<0.001**
Cardiac troponin (ng/L), median [IQR]	18 [8–40]	42 [21–75]	13 [6–27]	**<0.001**

Myocardial injury occurred in 43.8% patients with CCS vs. 14.4% patients without CCS, as confirmed by high-sensitivity cardiac troponin (hs-cTn) elevation on admission or during hospitalization. **The mortality rate in the CCS cohort was nearly three-fold higher**.

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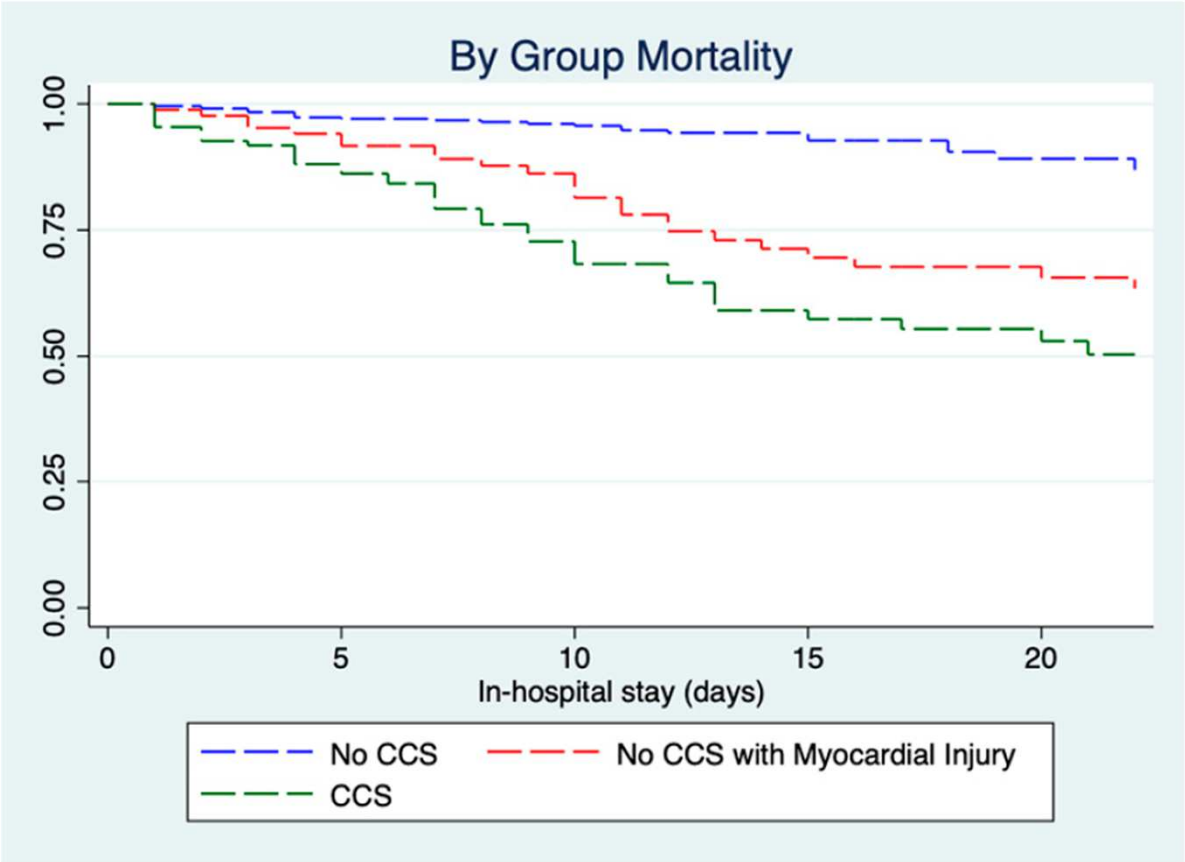
Kaplan–Meier survival curves for CCS patients, no-CCS patients, and no-CCS patients developing myocardial injury during in-hospital stay.



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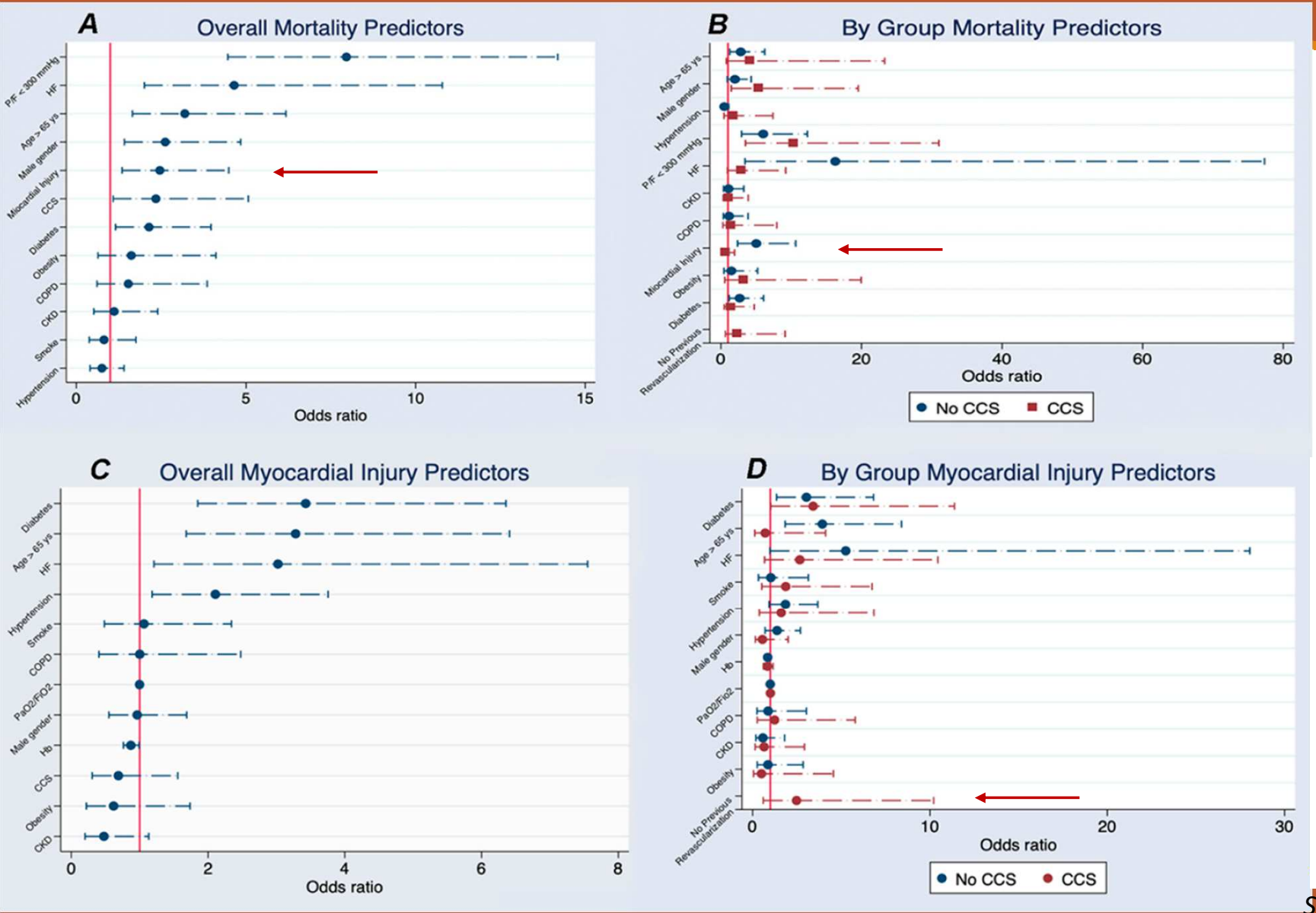

Panel A: overall multivariate logistical regression for mortality. Panel B: stratification of in-hospital mortality between CCS and non-CCS patients. Panel C: overall multivariate logistical regression for myocardial injury. Panel D: stratification of myocardial injury between CCS and non-CCS

After adjusting for disease severity, **myocardial injury resulted significantly associated with in-hospital mortality in the no-CCS group but not in CCS patients.**

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MYOCARDIAL INJURY AND MORTALITY IN CCS

CONCLUSION:

Although myocardial injury has been shown to be associated with worse outcomes in COVID-19, hs-cTn elevation had an independent prognostic value in non-CCS patients, while it was **not predictive of poor outcomes in patients with CCS**.

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MYOCARDIAL INJURY AND CARDIAC ARRHYTHMIAS

Serious cardiac arrhythmias may be:

1. The **consequence of direct effects of COVID-19 infection** → critically ill COVID-19 patients often have comorbidities that can trigger life-threatening ventricular arrhythmias, while acute myocardial injury increases the prevalence of arrhythmias
2. The outcome of the deleterious effects of systemic illness and **the adverse proarrhythmic reactions to drugs employed** in the treatment of this virus

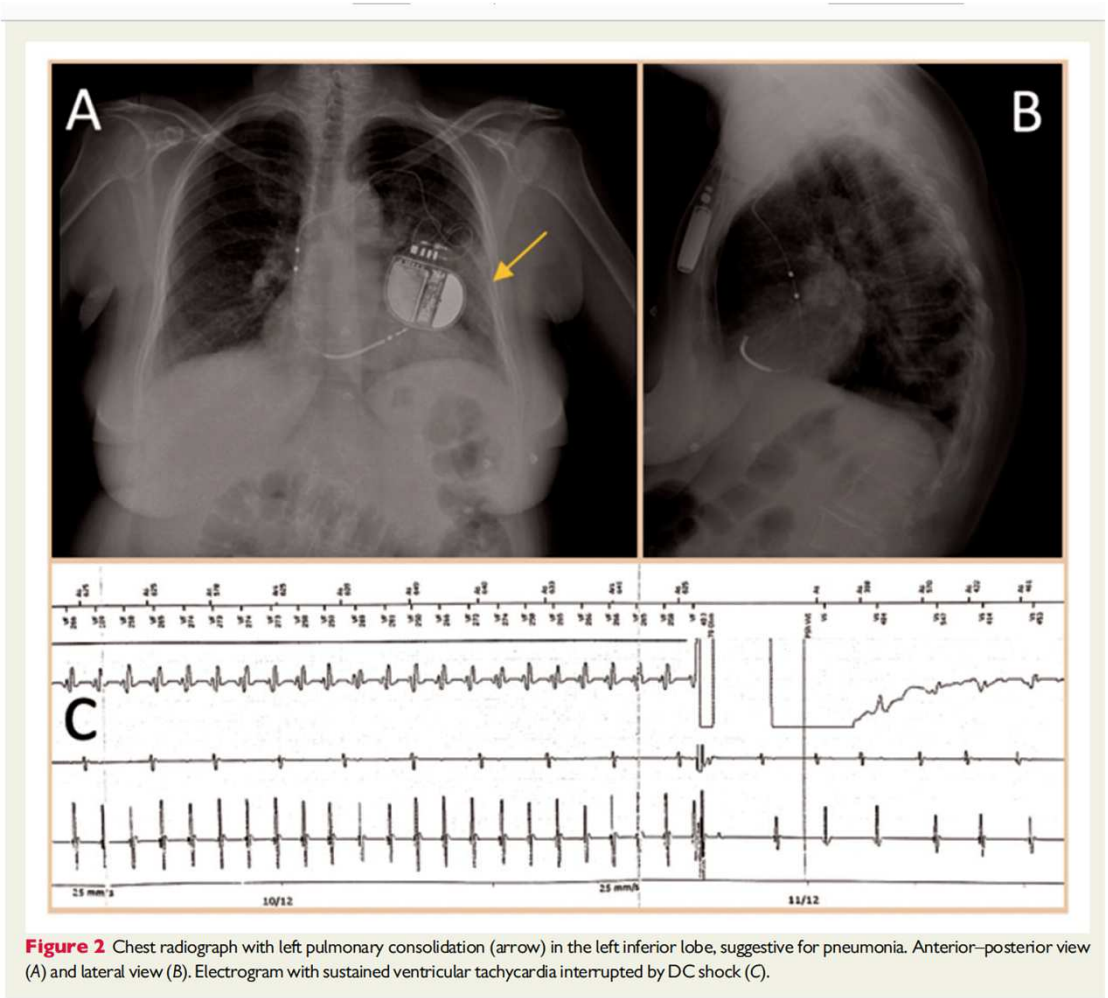

Figure 2 Chest radiograph with left pulmonary consolidation (arrow) in the left inferior lobe, suggestive for pneumonia. Anterior–posterior view (*A*) and lateral view (*B*). Electrogram with sustained ventricular tachycardia interrupted by DC shock (*C*).

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European Heart Journal - Case Reports
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CASE REPORT
Arrhythmias/Electrophysiology

Ventricular tachycardia storm management in a COVID-19 patient: a case report

Gianfranco Mitacchione *†, **Marco Schiavone** †, **Alessio Gasperetti, and Giovanni B. Forleo**

ARRHYTHMIC CONSEQUENCES OF COVID INFECTION?

ARRHYTHMIC CONSEQUENCES OF COVID INFECTION?

Timeline

20 days before admission	Symptom onset (cough and dizziness).
6 days before admission	Persistent fever unresponsive to antipyretic drugs and gradually worsening shortness of breath.
Admission	Diagnosis of pneumonia, suspected for coronavirus disease (COVID-19), with two real-time reverse transcription–polymerase chain reaction (RT–PCR) assays on nasopharyngeal swabs negative for SARS-CoV-2 infection.
Day 1–7	Non-invasive ventilation and antibiotic therapy.
Day 8	Electrical storm due to sustained episodes of ventricular tachycardia (VT) in absence of acute cardiac precipitating factors. Device detection of sustained and non-sustained VT episodes, started from the onset of COVID-19-related symptoms.
Day 9	Substrate-based VT catheter ablation targeting local abnormal ventricular activity (LAVA) with a remote magnetic navigation system.
Days 10–14	Absence of VT recurrence. Third nasopharyngeal swab positive for SARS-CoV-2 infection. Resolution of COVID-19 pneumonia.
Day 15	Discharge in home isolation.
Two months after discharge	Absence of ICD shocks.

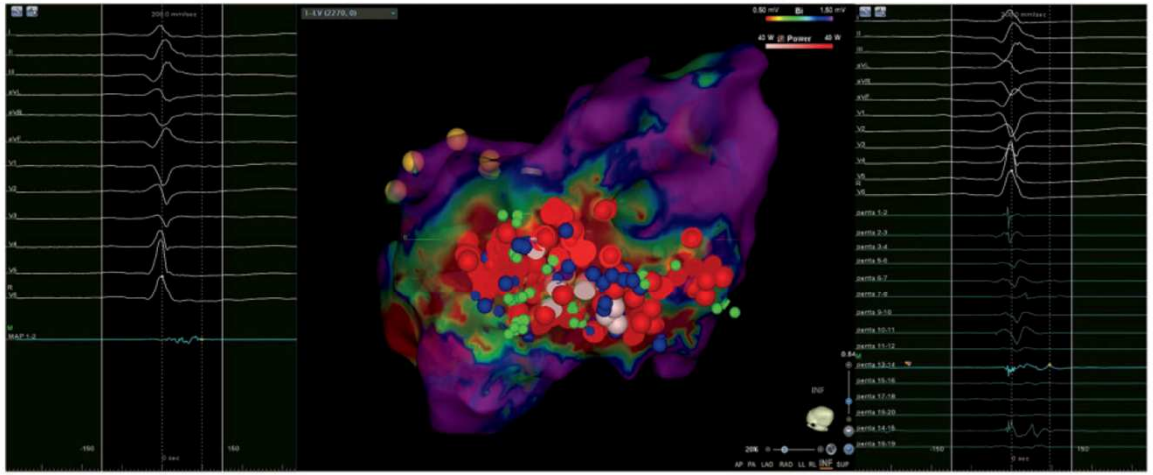

Figure 4 Three-dimensional bipolar voltage map of the left ventricle (LV) showing a low voltage scar in the inferolateral wall. Red regions represent scar (bipolar voltage 0.5 mV), and purple regions represent normal myocardium (bipolar voltage 1.5 mV). Other regions represent abnormal myocardial regions (bipolar voltage between 0.5 and 1.5 mV). Red and pink dots (VisiTag) represent radiofrequency pulses. Green and blue dots represent local abnormal ventricular activity (LAVA) points tagged with a Pentaray catheter (right) or ablation catheter (left), respectively.

Mitacchione et al. 2020

ADVERSE PROARRYTHMIC DRUG REACTIONS?

› Curr Clin Pharmacol. 2020 Dec 24. doi: 10.2174/1574884715666201224155042.
Online ahead of print.

QT Interval Monitoring and Drugs Management During COVID-19 Pandemic

Alessio Gasperetti [1], Marco **Schiavone** [1], Claudio Tondo [2], Gianfranco Mitacchione [1], Maurizio Viecca [1], Massimo Galli [3], Piercarlo Sarzi-Puttini [4], Giovanni Battista Forleo [1]

Affiliations + expand

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ADVERSE PROARRYTHMIC DRUG REACTIONS?

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Europace (2020) **0**, 1–9
doi:10.1093/europace/euaa216

CLINICAL RESEARCH

Arrhythmic safety of hydroxychloroquine in COVID-19 patients from different clinical settings

Alessio Gasperetti [1,2†], Mauro Biffi[3†], Firat Duru[2], Marco Schiavone[4], Matteo Ziacchi[3], Gianfranco Mitacchione[4], Carlo Lavalle[5], Ardan Saguner[2], Antonio Lanfranchi[4], Giacomo Casalini[6], Marco Tocci[5], Davide Fabbricatore[7], Francesca Salghetti[7], Marco Valerio Mariani[5], Mattia Busana[8], Alfonso Bellia[9], Chiara Beatrice Cogliati[10], Pierluigi Viale[1,11], Spinello Antinori[6], Massimo Galli[6], Nazzareno Galiè[3], Claudio Tondo[1,12,*‡], and Giovanni Battista Forleo[4‡]

ESC European Society of Cardiology
Europace (2020) 0, 1–9
doi:10.1093/europace/euaa216
CLINICAL RESEARCH

Arrhythmic safety of hydroxychloroquine in COVID-19 patients from different clinical settings

METHODS

Seven Hospitals involved (2 in Milan, 2 in Rome, 1 in Bologna, 1 in Brescia, 1 in Zurich)

ECG tracings were defined according to the time of retrieval as follows:

- T0—baseline ECG: recorded within 5 days before the first dose of HCQ;
- T1—first ('early') ECG control: recorded at least 36–72 h after the first HCQ dose;
- T2—second ('late') ECG control: recorded at least 96 h after the first HCQ dose.

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CLINICAL RESEARCH

METHODS

Arrhythmic safety of hydroxychloroquine in COVID-19 patients from different clinical settings

Patients were enrolled from three different clinical settings, defined as follows:

i. Home management (HM)

ii. Medical ward (MW) management

iii. Intensive care unit (ICU) management

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Europace (2020) 0, 1–9
doi:10.1093/europace/euaa216

POPULATION

Arrhythmic safety of hydroxychloroquine in COVID-19 patients from different clinical settings

Clinical setting,	
Home management, *n* (%)	126 (19.4)
Medical ward, *n* (%)	497 (76.3)
Intensive care unit, *n* (%)	28 (4.3)
Loading dose at HCQ therapy start, *n* (%)	380 (58.6)
Posology scheme, *n* (%)	
200 mg b.i.d., loading dose, 7 days, *n* (%)	350 (53.9)
200 mg b.i.d., no loading dose, 7 days, *n* (%)	160 (24.7)
200 mg b.i.d., loading dose, 14 days, *n* (%)	30 (4.6)
200 mg b.i.d., no loading dose, 14 days, *n* (%)	100 (15.4)
200 mg t.i.d., no loading dose, 14 days, *n* (%)	9 (1.4)
Electrolytes at HCQ beginning	
Na^+ (mEq/L), mean ± SD	137.9 ± 4.0
K^+ (mEq/L), mean ± SD	3.9 ± 0.5
Cl^- (mEq/L), mean ± SD	101.6 ± 4.6
Ca^{2+} (mEq/L), mean ± SD	8.7 ± 1.2
Additional potentially QT-prolonging drugs, *n* (%)	
Macrolides, *n* (%)	147 (22.7)
Azithromycin, *n* (%)	130 (20.0)
Fluoroquinolones, *n* (%)	10 (1.5)
Antifungal agents, *n* (%)	3 (0.5)
Antiviral agents, n (%)	157 (24.2)
Lopinavir/ritonavir, *n* (%)	125 (19.3)
Antiarrhythmics, *n* (%)	18 (2.8)
Class Ic, *n* (%)	7 (1.1)
Class III, *n* (%)	11 (1.7)
Antidepressants, *n* (%)	45 (6.9)
Antipsychotics, *n* (%)	36 (5.5)
Antihistamine agents, *n* (%)	2 (0.3)
Metoclopramide, *n* (%)	6 (0.9)
Number of QT-prolonging medications, median (IQR)	1 (1–2)
HCQ alone, *n* (%)	349 (53.8)
Two QT-prolonging drugs, n (%)	197 (30.4)
HCQ + azithromycin, *n* (%)	64 (9.9)
HCQ + lopinavir/ritonavir, *n* (%)	63 (9.7)
Three QT-prolonging drugs, *n* (%)	88 (13.6)
HCQ + azithromycin + lopinavir/ritonavir, *n* (%)	34 (5.2)

Gasperetti A et al. 2020

RESULTS

Table 2 QT risk score characteristics, as assessed by the Tisdale risk score from Tisdale *et al.*[11]

	Overall (*n* = 649)	HM (*n* = 126)	MW (*n* = 495)	ICU (*n* = 28)
Tisdale score (points), median (IQR)	6 (4–8)	4 (4–5)	7 (5–8)	8 (6–9)
Tisdale score risk class:				
Low risk, *n* (%)	359 (55.3)	111 (88.1)	237 (47.9)	11 (39.2)
Moderate risk, *n* (%)	250 (38.5)	15 (11.9)	223 (45.0)	12 (48.9)
High risk, *n* (%)	40 (6.2)	0	35 (7.1)	5 (17.9)
Categories:				
Age >68 years, *n* (%)	266 (41.0)	34 (27.0)	221 (44.7)	11 (39.3)
Female, *n* (%)	350 (53.9)	78 (61.9)	264 (53.3)	8 (28.6)
Loop diuretics, *n* (%)	80 (12.3)	4 (3.2)	66 (13.3)	10 (35.7)
Diabetes, *n* (%)	73 (11.3)	6 (4.8)	58 (11.8)	9 (32.1)
Potassium ≤3.5 meq/L, *n* (%)	81 (12.5)	5 (4.0)	73 (14.8)	3 (10.7)
Admission QTc >450 ms, *n* (%)	188 (29.0)	24 (19.1)	154 (31.1)	10 (35.7)
Acute MI, *n* (%)	13 (2.0)	0	9 (1.8)	4 (14.3)
One QT-prolonging drug, *n* (%)	361 (55.6)	119 (94.4)	232 (46.9)	10 (35.7)
≥2 QT-prolonging drugs, *n* (%)	288 (44.4)	7 (5.6)	263 (53.1)	18 (64.3)
Heart failure, *n* (%)	25 (3.8)	1 (0.8)	21 (4.2)	3 (10.7)
Sepsis, *n* (%)	7 (1.1)	0	2 (0.4)	5 (17.9)

HM, home management patient; ICU, intensive care unit patient; MI, myocardial infarction; MW, medical ward patient.

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RESULTS

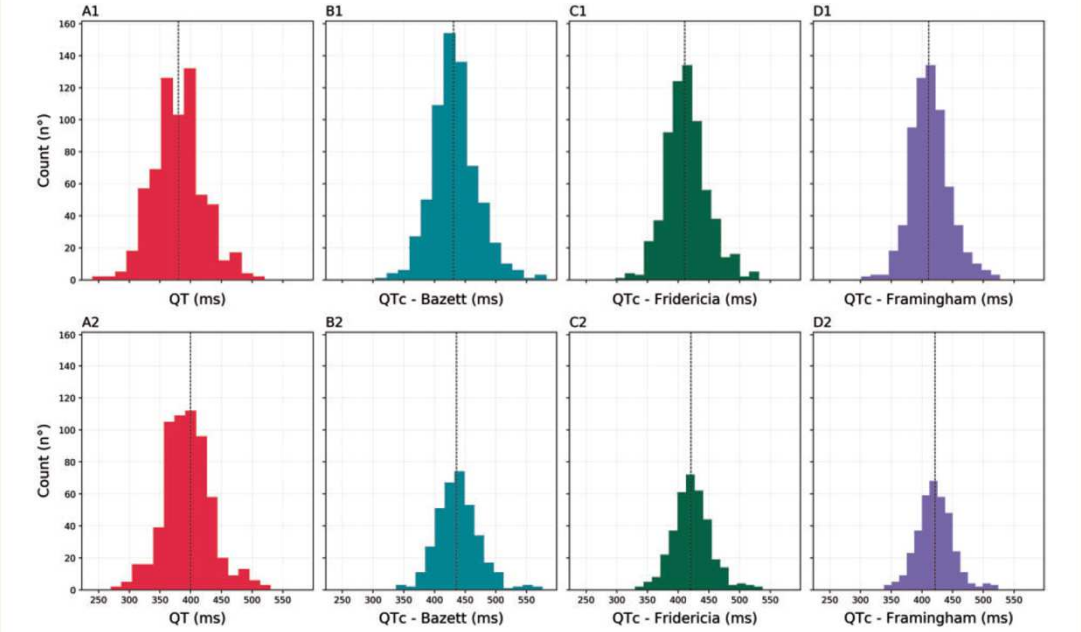

Figure 1 QT/QTc distribution at T_0 (upper panels) and at the last available ECG (lower panels) on hydroxychloroquine for the cohort. (*A1/A2*) QT interval (ms); (*B1/B2*) QTc Bazett (ms); (*C1/C2*) QTc Fridericia (ms); (*D1/D2*) QTc Framingham (ms).

Following HCQ administration, we observed only **modest QT/QTc changes from baseline**, regardless of the linear rate correction formula used.

Greater prolongation of QT/QTc on HCQ treatment was not associated with a longer baseline value, mostly due to the changing conditions of patients with an acute illness and due to a lower QT/QTc reserve.

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RESULTS

Table 4 **Outcome during HCQ therapy**

	Overall (*n* = 649)	HT (*n* = 126)	MW (*n* = 495)	ICU (*n* = 28)
Follow up time (days), median [IQR]	16 (9–20]	15 [8–20]	16 (9–210	19 (6–23)
HCQ suspension due to QT prolongation, *n* (%)	5 (0.8)	0	2 (0.4)	3 (10.7)
Sustained VT during HCQ, *n* (%)	4 (0.6)	0	2 (0.4)	2 (7.1)
VF during HCQ, *n* (%)	3 (0.5)	0	0	3 (10.7)
TdP during HCQ, *n* (%)	0	0	0	0
AF/AFl episodes, *n* (%)	15 (2.3)	2 (1.6)	6 (1.2)	7 (25.0)
Bradycardia episodes, *n* (%)	9 (1.4)	0	4 (0.8)	5 (17.8)
Overall mortality, *n* (%)	42 (6.5)	2 (1.6)	30 (6.1)	10 (35.7)

AF, atrial fibrillation; AFl, atrial flutter; HCQ, hydroxychloroquine; VT, ventricular tachycardia.

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KEY POINTS

1) Our study captured HCQ effects in **a real-life population** treated in three different clinical settings: ICU, hospital ward, and home treatment, according to the individual patient's risk profile.
2) HCQ administration (alone or in combination) **appears safe during the short-term** treatment used in COVID-19 patients in all clinical settings, provided that patients' screening and ECG recordings are available and that an adequate a priori patient-tailored risk assessment has been performed.
3) Low rate of major ventricular arrhythmia events was deemed to be due to termination of HCQ and other Qtprolonging drugs upon detection of QT prolongation at ECG monitoring.
4) **We did not assess HCQ efficacy in COVID-19.**

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