T-wave inversion as a manifestation of COVID-19 infection: a case series

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Abstract

Purpose Cardiac involvement with COVID-19 infection has become evident by elevated troponin, cardiac arrhythmias, ST segment elevation, myocarditis, fulminant heart failure, and sudden cardiac death. We aimed to describe the association of COVID-19 and T-wave inversion (TWI) in a large case series.

Methods We conducted an observational, retrospective study of confirmed COVID-19 cases with at least one electrocardiogram (ECG) in a large hospital in New York City (March 23, 2020–April 23, 2020). Patients with new TWI or pseudonormalization were further analyzed. Mortality and the need for invasive mechanical ventilation were the main outcomes.

Results A total of 3225 patients were screened; 195 (6%) were selected for further analysis: 181 with TWI and 14 with T-wave pseudonormalization. Mean age was 66 ± 7 years; 51% were male. TWI were more commonly noted in the lateral (71%), followed by anterior (64%), inferior (57%), and septal (26%) leads. A total of 44 patients (23%) had elevated troponin. A total of 50 patients died (26%). Mortality rates of 35%, and 52% were observed in patients with diffuse TWI, and elevated troponin, respectively. Mortality rate of 80% was observed in patients with both elevated troponin and diffuse TWI. Additionally, 30% of the entire cohort and 58% of patients with elevated troponin required invasive mechanical ventilation.

Conclusion Our study demonstrates that new TWI is a relatively common finding in COVID-19 patients. Importantly, our findings suggest that new TWI or T-wave pseudonormalization, particularly with elevated troponin, was associated with higher rates of mechanical ventilation and in-hospital mortality.

Keywords COVID 19 · T-wave inversion · Mortality · ECG abnormality

1 Introduction

In less than 6 months since its initial description, the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) responsible for the coronavirus disease 2019 (COVID-19) has caused a pandemic with an unprecedented impact on health systems and global economy. Rapid transmission of the virus has led to uncontrolled outbreaks in different regions of the world. Our understanding of the disease and its consequences on the virus–host interaction are evolving as the disease spreads widely [1]. Albeit, most infections are mild; COVID-19 is associated with significant morbidity and mortality, particularly among patients with advanced age, male sex, and/or previous medical conditions [2–4]. Mortality due to other causes has increased during the pandemic as well, possibly due to reduced access to health care [5]. Although acute hypoxemic respiratory failure is the most frequently recognized cause of clinical deterioration and death, cardiovascular compromise has been increasingly recognized in patients with COVID-19 and is associated with worse clinical outcomes [6]. Cardiac compromise is observed in 20–40% of patients and results in ST segment elevation, elevated

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troponin, cardiac arrhythmias, chest pain, fulminant heart failure, and sudden cardiac death [3, 6–8].

Nonetheless, the association of COVID-19 with T-wave inversion (TWI) has not been described in a large case series. TWI is defined as negative T-wave (≥ 1 mm in depth) in two or more contiguous leads excluding leads aVR, III, and V1, with clinical significance being highly dependent on their localization on the 12-lead electrocardiogram (ECG). TWI in the inferolateral leads is always abnormal and indicative of an underlying cardiac pathology [9, 10]. The incidence of TWI in the middle age population is approximately 0.7%, and it is associated with an increased risk of cardiac and arrhythmogenic death [11]. In patients with myocarditis, TWI is frequently seen, particularly in those patients with greater disease severity [12]. At the time of this study, New York has been one of the most affected areas by the COVID-19 pandemic. The association between TWI and COVID-19–related myocardial damage has not yet been reported. In this study, we describe results from a large case series of COVID-19 patients with TWI in a large healthcare system in New York.

2 Methods

This retrospective, observational study was performed at Montefiore Medical Center/Albert Einstein College of Medicine, New York. Institutional review board approval was obtained for the research protocol of this study. All consecutive patients evaluated and admitted in our institution between March 23, 2020, and April 23, 2020, with laboratory confirmed SARS-CoV-2, were screened. To be eligible for inclusion in the analysis, the presence of a prior ECG for comparison was necessary, in addition to serial ECGs (i.e., one baseline ECG at admission and at least one 24–48 h thereafter) during the admission/hospitalization. Laboratory confirmation was defined as the presence of a positive reverse transcriptase–polymerase chain reaction (RT-PCR) assay from nasal or pharyngeal swabs in patients with symptoms compatible with COVID-19. ECGs were screened for the presence of new T-wave changes in the septal (i.e., leads V1 and V2), anterior (i.e., leads V3 and V4), lateral (i.e., leads I, aVL, V5, and V6), and inferior myocardial wall (i.e., leads II, III, and aVF) during the index hospitalization. TWI were considered new if they were present on the admission ECG but not prior ECGs in the medical records, or if serial ECGs revealed new TWI that were not present on the admission ECG. We excluded patients with known causes of TWI (i.e., ventricular preexcitation, right and left ventricular hypertrophy, ventricular paced rhythm, left and right bundle branch block). Moreover, we excluded patients who had no TWI, those who had TWI that were unchanged from the prior ECG that was used for comparison, or those who had no previous ECG for contrast. Patients with previously known TWI (verified on

prior ECG recordings) that displayed normalization of these inversions were classified as T-wave pseudonormalization. Medical records were reviewed to obtain baseline demographics and clinical data, including presence of baseline comorbidities, laboratory results (e.g., troponin I, D-dimer, serum electrolytes, creatine phosphokinase (CPK), fibrinogen, procalcitonin, C reactive protein), imaging studies (echocardiogram, cardiac magnetic resonance imaging [cardiac MRI], coronary angiography), invasive mechanical ventilation, length of hospital stay and treatment received. The clinical outcomes were discharge, death, or ongoing hospitalization at the time of data analysis.

2.1 Statistical analysis

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are expressed as number of patients (percentage) with 95% confidence intervals (CIs). Using a statistical software package, univariate and multivariate analyses were performed. Univariate associations between clinical characteristics and the study outcomes of death and intubation were assessed using Fisher's exact test for categorical variables or Student's t test for continuous variables, with the addition of the Cochran-Armitage test for trend for ordinal variables. Using variables found to be associated with these outcomes in univariate analysis, a multiple logistic regression was performed to assess for independent associations. For statistical tests, p values ≤ 0.05 were considered to be statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 Results

In our study period from March 23, 2020 to April 23, 2020,' a total of 3225 patients were admitted to Montefiore Medical Center for confirmed COVID-19 infection. A total of 129 patients (4%) with TWI were excluded because they had known causes of TWI (i.e., ventricular preexcitation, right and left ventricular hypertrophy, ventricular paced rhythm, left and right bundle branch block). Sixty-eight patients (2%) were excluded because no prior ECG was available for comparison, and 2833 patients (88%) were excluded because they either had no TWI or ECG displayed TWI that were present and unchanged from prior ECGs. Ultimately, a total of 195 (6%) patients were included in our analysis: T-wave inversions (n: 181) or T-wave pseudonormalization (n: 14). Overall, mean age of the study population was 66 ± 7 years, and 51% of patients were male. Mean body mass index was 29 ± 7 kg/m². Baseline characteristics are presented in Table 1. TWI was either noted at presentation (60%) or during the course of the hospitalization (40%). Distribution of TWI by cardiac walls is presented in Fig. 1a. TWI were more commonly observed in the lateral leads (71%),

Table 1 Characteristics of 195 patients with COVID-19 with T-wave inversion on 12-lead electrocardiography

Characteristic	Total (N = 195)
Male sex—no. (%)	100 (51)
Median age—year (IQR)	66 (57–77)
Risk factor—no. (%)	
DM	82 (43)
HTN	140 (72)
CKD	44 (23)
OSA	4 (2)
COPD	19 (10)
CAD	28 (14)
Median BMI (IQR)	27.6 (24–32.1)
Electrocardiographic findings—no. (%)	
Septal	51 (26)
Anterior	124 (64)
Lateral	139 (71)
Inferior	111 (57)
One wall	61 (31.3)
Two walls	64 (33)
Three walls	47 (24.1)
Four walls	23 (11.8)
QTc > 460 ms	36 (18)
TWI present on admission	117 (60%)
Echocardiography—no. (%)	57 (29)
Echocardiographic findings	
EF—mean (SD)	58.6 (12.4)
EF ≤ 50%—no. (%), [mean ± SD]	11/57 (19.3), [44.1 ± 5.3]
EF > 50%—no. (%), [mean ± SD]	46/57 (80.7), [62 ± 11]
Regional wall-motion abnormality—no. (%), [mean EF ± SD]	15/57 (26.3), [51.6 ± 12.7]
Median laboratory values (IQR)	
White cell count—k/ul [ref: 4.8–10.8]	8.2 (6–12.3)
Hemoglobin—g/dl [ref: 14–17.4]	11.9 (10.1–13.5)
Platelet count—k/ul [ref: 150–400]	234 (172.5–310.5)
Potassium—mEq/L [ref: 3.5–5]	4.2 (3.8–4.7)
Magnesium—mg/dl [ref: 1.7–2.8]	2.2 (2–2.5)
Calcium—mg/dl [ref: 8.5–10.5]	8.7 (8.3–9.2)
Troponin—ng/ml [ref: < 0.1]	0.01 (0.01–0.11)
Creatine kinase—U/L [ref: < 200]	249 (132–892)
D-dimer—µg/ml [ref: 0–0.5]	4.4 (1.7–10.1)
Procalcitonin—ng/ml [ref: < 0.1]	0.4 (0.1–1.5)
C-reactive protein—mg/dl [ref: < 0.8]	15 (7.8–25.5)
Fibrinogen—mg/dl [ref: 187–502]	707 (584–824)
Treatment—no. (%)	
Hydroxychloroquine	139 (71)
Ceftriaxone	80 (41)
Azithromycin	28 (14)
Hydroxychloroquine + azithromycin	
Steroids	87 (45)
Anticoagulation	124 (64)

Table 1 (continued)

Characteristic	Total (N = 195)
Median length of stay—days (IQR)	7 (4.25–13)
Invasive mechanical ventilation—no. (%)	58 (30)
Death in the hospital—no. (%)	50 (26)

DM Diabetes mellitus, *TWI* T-wave inversion, *IQR* interquartile range, *SD* standard deviation, *EF* ejection fraction, *Ref* reference value; *HTN* hypertension; *CKD* chronic kidney disease; *OSA* obstructive sleep apnea; *COPD* chronic obstructive pulmonary disease; *CAD* coronary artery disease

followed by anterior (64%), inferior (57%), and septal (26%) ECG leads (Fig. 1a). A total of 31%, 33%, 24%, and 12% patients had TWI corresponding to one, two, three and four myocardial walls on 12-lead ECG, respectively (Figs. 1b and 2a–d).

A total of 44 out of 195 included patients (23%) had elevated troponin levels. Peak troponin level was 0.28 (0.17–0.92, reference < 0.1) ng/mL. Echocardiography was performed in 57 (29%) patients, and mean left ventricular ejection fraction (LVEF) was 58 ± 12%. A total of 15 (27%) out of the 57 patients undergoing echocardiography demonstrated regional wall motion abnormalities.

The median leukocyte count was 8.2 [6–12.3, reference 4.8–10.8] k/µl, the median hemoglobin level was 11.9 [10.1–13.5, reference 14–17.4] g/dl, the median platelet count was 234 [172.5–310.5, reference 150–400] k/ul, the median C-reactive protein levels were 15 [7.8–25.525, reference < 0.8] mg/dL, the median procalcitonin was 0.4 [0.10–1.475, reference < 0.1] ng/mL, the median CPK was 249 [132–892, reference < 200] U/L, and the median D-dimer was 4.4 [1.7–10, reference 0–0.5] µg/mL. Additional laboratory results are also reported in Table 1.

3.1 Mortality

A total of 50 patients from this cohort died (26%). Patients with TWI and concomitant troponin elevation had a significantly higher mortality when compared with those with normal troponin values [23/44 (52%) vs. 17/119 (14%), p: < 0.001]. Patients with diffuse TWI (4 walls affected) were also noted to have higher mortality (35%) when compared with patients with involvement of one (26%), two (26%) or three (21%) myocardial walls. In patients with both diffuse TWI and elevated troponin levels, mortality rate was significantly higher than in the absence of both conditions (80% vs. 13%, p: 0.02) (Fig. 3).

3.1.1 Invasive mechanical ventilation and length of stay

A total of 58 patients (30%) required invasive mechanical ventilation. Patients with TWI and concomitant troponin elevation had significantly higher rates of invasive mechanical ventilation when compared with those with TWI and normal troponin values [23/44 (52%) vs. 25/121 (21%), p: < 0.001].
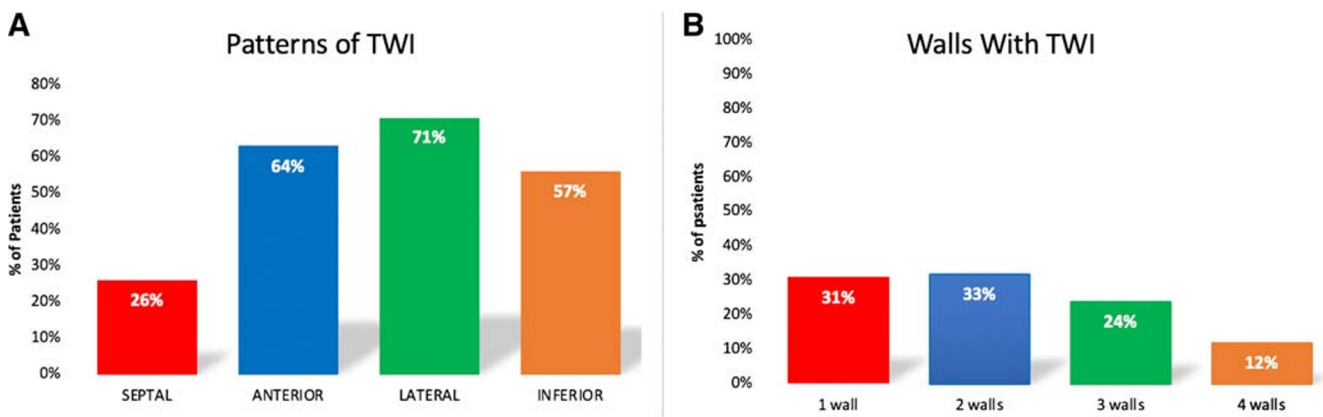
Fig. 1 **a** Distribution of T-wave inversion (TWI) on 12-lead ECG. **b** Number of cardiac walls involved with TWI on 12-lead ECG. ECG: electrocardiogram, TWI: T-wave inversion

The length of hospitalization was 7 (4.3–13) days. At the time of data analysis, 138 (71%) patients had been discharged from the hospital, 50 (26%) patients died, and 7 (3%) patients remained hospitalized.

3.2 Univariate and multivariate analysis

In univariate analysis, in which clinical characteristics were used, death was found to be associated with age, history of diabetes and CKD, elevated WBC count, hemoglobin, serum potassium, serum magnesium, troponin elevation, D-dimer, and C-reactive protein. Treatment with hydroxychloroquine, ceftriaxone, and steroids were also associated with death (Online Resource 1). Using the above significant variables, multiple logistic regression revealed that only age, troponin elevation, and C-reactive protein were independently associated with death (Table 2).

Similarly, in univariate analysis, mechanical ventilation was found to be associated with history of diabetes, TWI present on admission, elevated WBC count, hemoglobin, serum calcium, troponin elevation, D-dimer, and C-reactive protein. Likewise, treatment with ceftriaxone, steroids, and anticoagulation was also associated with mechanical ventilation (Online Resource 1). After multiple logistic regression analysis, only history of diabetes, WBC count, and troponin elevation were independently associated with endotracheal intubation (Table 2).

4 Discussion

In this large case series of COVID-19 patients in a tertiary care hospital in New York, new TWI/ T-wave pseudonormalization was observed in a considerable proportion of patients without known coronary artery disease, which is 10-fold higher than the expected for the general population [11]. Our results showed that COVID-19 patients that develop new TWI, particularly if

diffuse or accompanied by elevated troponin levels or both have 35%, 52%, and 80% mortality, respectively (Fig. 3). This study adds to the increasing pool of evidence linking COVID-19 infection with myocardial damage.

4.1 Cardiac manifestations in COVID-19

Richardson et al. [13] recently reported an overall mortality rate of 21% among 2634 COVID-19 patients hospitalized in New York City that is lower than our cohort (i.e., 26%). The percentage of patients that required invasive mechanical ventilation and the median length of hospital stay were also significantly higher in our study (i.e., 30% vs. 12.2% and 7 vs. 4 days, respectively) [13]. A recent meta-analysis by Santoso et al. [14] including 2389 patients from 13 studies noted cardiac injury (evidenced by elevated troponin) to be associated with increased mortality (RR 7.95 {5.12, 12.34}, $p = 0.001$; I^2: 65%, $p = 0.009$), intensive care unit (ICU) care (RR 7.94 {1.51, 41.78}, $p = 0.01$; I^2: 79%, $p = 0.009$) and severe COVID-19 (RR 13.81 {5.52, 34.52}, $p = 0.001$; I^2: 0%, $p = 0.38$). While cardiac manifestations of COVID-19 infection like ST segment elevation, elevated troponin, cardiac arrhythmias, myocarditis, and fulminant heart failure have been reported before, presence of new TWI or T-wave pseudonormalization is novel and has not been explored. ST segment elevation has been recently described in patients with COVID-19 infection, with a high prevalence of nonobstructive coronary artery disease [7, 8]. Wall motion abnormalities have been reported in 62% of patients with ST segment elevation [7]. In our study, the proportion of patients with regional wall motion abnormalities was relatively lower (~27%). It is possible that the mechanism of ST segment elevation differs from the mechanism underlying TWI or T-wave pseudonormalization.
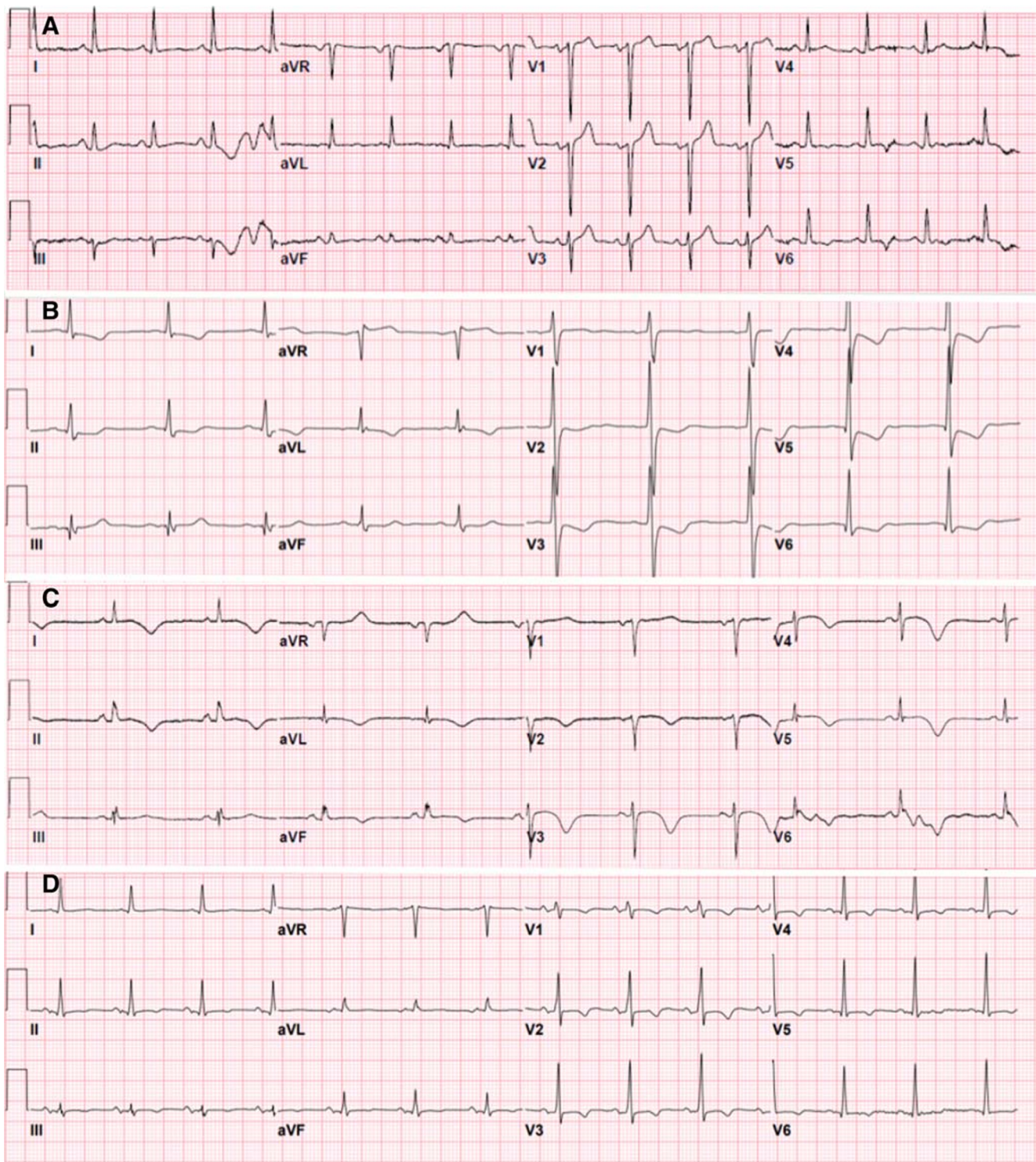
Fig. 2 **a** ECG showing T-waves inversion (TWI) in one cardiac wall (lateral leads), **b** ECG with TWI in two cardiac walls (anterolateral leads), **c** TWI in three cardiac walls (anterolateral with inferior leads), **d** TWI in all cardiac walls. ECG: electrocardiogram, TWI: T-wave inversion

4.2 Mechanism of cardiac injury

The exact mechanism underlying cardiac damage in COVID-19 is currently unknown. Although initial studies reported a lack of direct myocardial damage (attributed troponin elevation to be a consequence of systemic compromise or demand ischemia) [15], more recent studies have revealed either direct (i.e., SARS-CoV-2 myocarditis) or indirect myocardial damage. Indirect myocardial damage can have multiple mechanisms, many of them attributable to severe
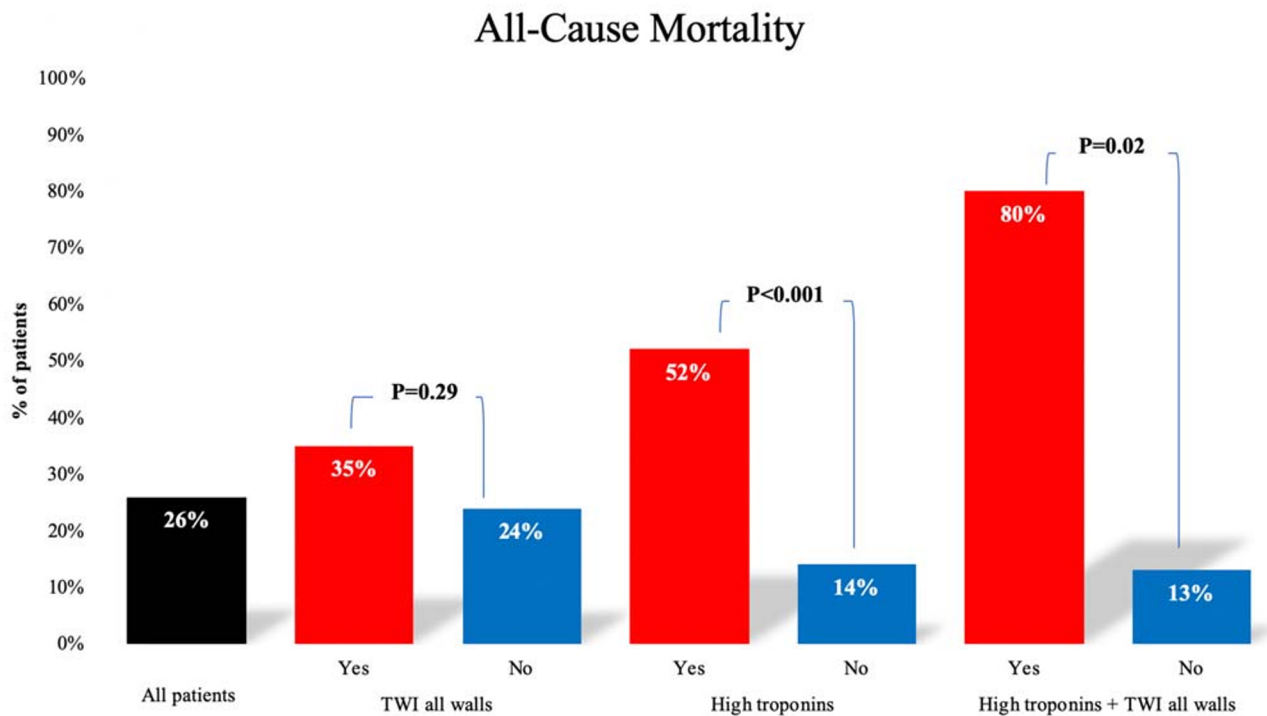
All-Cause Mortality

Fig. 3 Overall mortality in the study and mortality rates in different subgroups. TWI: T-wave inversion

inflammation and autoimmune responses. Huang et al. [16] reported increased levels of cytokines in patients requiring ICU admission compared with patients who did not require ICU admission, probably related to an increased T-helper 1 (Th1) response. This cytokine storm has been found to increase mortality in other respiratory viruses, including severe acute respiratory syndrome (SARS) [17], Middle Eastern respiratory syndrome (MERS) [18], and influenza [19, 20].

Alterations in coagulation have also been described in patients with COVID-19 including thromboembolic complications, myocardial infarction, stroke, and disseminated intravascular coagulation [21]. In patients with overt coagulopathy, use of anticoagulant treatment has been associated with improved outcomes [22]. Although these mechanisms could explain in part the presence of new TWI, we believe a direct mechanism may also be responsible for TWI in COVID-19 patients.

Table 2 Multiple logistic regression analysis for study outcomes using covariates found to be associated in univariate analysis

Characteristic	All-cause mortality OR	95% CI	p value	Mechanical ventilation OR	95% CI	p value
Age (OR for 10-year change in age)	1.66	1.17–2.34	$p = 0.004$	–		
DM	1.53	0.66–3.54	$p = 0.324$	3.05	1.48–6.31	$p = 0.003$
CKD	1.12	0.40–3.14	$p = 0.835$	–		
TWI present on admission	–	–	–	0.56	0.27–1.15	$P = 0.114$
White cell count (OR for 1 k/ul change)	1.04	0.97–1.10	$p = 0.264$	1.08	1.02–1.15	$p = 0.014$
Hemoglobin (OR for 1 g/dl change)	0.91	0.76–1.10	$p = 0.342$	0.95	0.81–1.11	$p = 0.515$
Potassium (OR for 1 mEq/L change)	1.59	0.94–2.69	$p = 0.084$	–		
Magnesium (OR for 0.1 mg/dl change)	1.06	0.96–1.17	$p = 0.242$	–		
Calcium (OR for 1 mg/dl change)	–			0.66	0.40–1.09	$p = 0.104$
Troponin (≥ 0.1 ng/ml)	3.13	1.34–7.35	$p = 0.009$	2.67	1.24–5.78	$p = 0.013$
D-dimer (OR for 1 μg/ml change)	0.97	0.91–1.03	$p = 0.294$	0.99	0.94–1.04	$p = 0.633$
C-reactive protein (OR for 5 mg/dl change)	1.26	1.08–1.48	$p = 0.004$	1.12	0.97–1.29	$p = 0.114$

IQR Interquartile range, *DM* diabetes mellitus, *CKD* chronic kidney disease

Evidence of direct myocardial damage by coronavirus is amounting. In a rabbit model, coronavirus infection led to focal myocyte necrosis and interstitial edema with predominant lymphocyte infiltration [23]. This evidence of direct myocardial damage (myocarditis) has been recently demonstrated in humans. In a recent report by Tavazzi et al. [24], endomyocardial biopsy (EMB) was performed in one patient with severe COVID-19 infection and cardiogenic shock, demonstrating low-grade interstitial and endocardial inflammation with viral particles observed in interstitial cells with loss of cytoplasmic membrane integrity. There was no evidence of artery obstruction on coronary angiography, thus demonstrating that cardiogenic shock was directly related to myocarditis. A similar case was reported by Sala et al. [25], with demonstration of lymphocytic infiltrates and interstitial edema on EMB of a patient with Takotsubo syndrome associated with COVID-19 myocarditis.

4.3 ECG changes in COVID-19

Interestingly, ECG changes were common in animal models of coronavirus infections, including sinus tachycardia, reduced R-wave voltages, reduction in T-wave voltages, ST segment changes (elevation and depression), premature atrial beats, and prolongation of the QT interval [23]. Additionally, QT interval prolongation was relatively uncommon in our series of patients with COVID-19 infection (i.e., 18%). A recently published study including 201 patients with COVID-19 treated with chloroquine/hydroxychloroquine ± azithromycin did not find significant QT prolongation with the former, and only substantial QT prolongation with the latter combination [26].

TWI has been reported in 27% of patients with myocarditis; although it is not associated with a greater troponin elevation or left ventricular dysfunction, the presence of TWI is associated with myocardial edema on cardiac MRI [27]. Moreover, localization of TWI has a good correlation with the localization of segments with transmural edema which appears to be a prerequisite for TWI, and therefore may be an indicator of the underlying myocardial injury in these segments. On the other hand, diffuse TWI may be associated with global myocardial injury, as well as fulminant myocarditis in some cases, in which other findings such as PR depressions, ST elevations, QT prolongation, or new bundle-branch block patterns may be seen. Interestingly, myocardial fibrosis assessed with delayed contrast enhancement was not associated with TWI suggesting the occurrence of TWI during the acute setting [28]. On the contrary, wall motion abnormalities are not a prerequisite for TWI [29, 30], which explains why in our case series wall motion abnormalities were infrequent. In COVID-19 patients, TWI could be a sign of early myocarditis, and the need for invasive coronary angiography could be avoided in the absence of regional wall motion abnormalities.

4.4 Management

The optimal management for myocardial injury associated with COVID-19 has not been determined. Thus, the management of patients with myocardial injury, including clinically suspected myocarditis should be focused on supportive care. Whether or not anticoagulation and/or steroids improve outcomes in these patients remains to be elucidated. In patients with COVID-19 with suspected myocarditis, the decision on whether to proceed with further evaluation of myocarditis with cardiac MRI and possible EMB is based on the likelihood of a diagnosis that would alter therapy. Identification of ECG patterns suggestive of myocardial compromise is cost effective, and could have potential prognostic impact on identifying patients with a higher risk of mechanical ventilation or death. Subsequently, they can be utilized in devising a prognostication model for patients admitted with COVID-19.

5 Limitations

This study has several limitations that must be noted. First, it does not include a control group for comparison. Therefore, it does not describe the differences in patterns of TWI and pseudonormalization in COVID-19 patients compared with a healthy cohort. However, the ECG changes described in this study are 10-fold higher than the expected in the general population. In addition, although we propose several mechanisms of myocardial injury that may have contributed to these findings, the exact mechanism remains unknown; additional research is necessary to determine the pathophysiology of cardiac injury and interventions that can reduce mortality. Furthermore, this study does not in itself provide a full prognostication model for COVID-19 patients based on presenting ECG findings.

6 Conclusion

In this large case series, new TWI or T-wave pseudonormalization was common in patients admitted with COVID-19. Importantly, these finding were associated with higher mechanical ventilation and mortality rates, particularly in the presence of troponin elevation. Appropriate identification of this ECG pattern could play an important role in identifying COVID-19 patients at higher risk of adverse events such as intubation and death.

Compliance with ethical standards

Medtronic, Atricure, Pfizer, and Biotronik. The remaining authors report no conflicts of interest.

Ethics approval Institutional review board of Montefiore Medical Center approved the research protocol for this study.

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