A systematic review of ECG findings in patients with COVID-19

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A B S T R A C T

Introduction: Since the epidemic of COVID-19 attracted the attention, reports were surrounding electrocardiographic changes in the infected individuals. We aimed at pinpointing different observed ECG findings and discussing their clinical significance.

Methods: We conducted a systematic search in PubMed, Embase, and Scopus databases. We included eligible original papers, reports, letters to the editors, and case reports published from December 2019 to May 10, 2020.

Results: The team identified 20 articles related to this topic. We divided them into articles discussing drug-induced and non-drug-induced changes. Studies reported an increased risk of QTc interval prolongations influenced by different therapies based on chloroquine, hydroxychloroquine, and azithromycin. Although these medications increased risks of severe QTc prolongations, they induced no arrhythmia-related deaths. In the non-drug-induced group, ST-T abnormalities, notably ST elevation, accounted for the most observed ECG finding in the patients with COVID-19, but their relation with myocardial injuries was under dispute.

Conclusion: This systematic review suggests that identifying ECG patterns that might be related to COVID-19 is vital. Provided that physicians do not recognize these patterns, they might erroneously risk the lives of their patients. Furthermore, important drug-induced ECG changes provide awareness to the health-care workers on the risks of possible therapies.

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1. Introduction

Coronavirus Disease 2019 (COVID-19) is a disease caused by Severe Acute Respiratory Syndrome–Coronavirus-2 (SARS-CoV-2) infection, considered as a “public health emergency of international concern” 1, and causing the current pandemic around the world.2 4 Facing this challenge requires immediate and strict action. This virus utilizes the Angiotensin-Converting Enzyme 2 (ACE2) as a functional receptor for cellular entry. Research demonstrates that various tissues, including the myocardium of the heart, express ACE2 protein on their cellular surface.5 This protein has described roles in the heart function and pathophysiology of diabetes mellitus (DM) and hypertension. SARS-CoV-2 might use this entry pathway as a trajectory to invade myocardial cells and directly damage them. Related studies suggest other mechanisms for the perceived cardiac injury, including cytokine storms and hypoxemia.6 7 Cardiac injuries correlate with a more detrimental outcome in patients with COVID-19, thus requiring adequate attention. All these effects potentiate cardiac injuries that might be detected as various patterns in an Electrocardiogram (ECG).8 9

Investigators are conducting studies on some medicines with a potential benefit in COVID-19 settings.10 11 Some proposed medications, most notably chloroquine, hydroxychloroquine, and azithromycin, have shown an increased risk of ECG changes in the settings of past diseases, specifically QTc interval prolongations.12 13 Nevertheless, as every problem needs to be addressed in its specific context, uncertainties still overshadow our...
clinical knowledge in this area. Therefore, careful studies ought to specifically address this problem. Expected adverse effects require appropriate diagnosis and intervention to maximize treatment benefits.

In this systematic review, we aimed to provide the researchers and clinicians with an update on the diverse patterns observed in the ECG of patients with COVID-19. We address ECG changes that might be attributed to the injuries imposed by the virus, and those caused by certain medications. As a global concern, COVID-19 requires worldwide collaboration and research toward an ever-growing understanding of the disease.

2. Methodology

2.1. Design

This systematic review aims to explain the ECG changes associated with novel coronavirus infection. This study involves reviewing the currently available evidence on the study objective to provide a better understanding of specific aspects of related knowledge. We conducted a systematic search, and the identified articles evaluated concerning the inclusion and exclusion criteria. We subsequently categorized the included studies and established a synthesis of the review analysis.

2.2. Research question

We aimed to answer the following main question:

- Which available ECG changes associated with novel coronavirus infection have been noted in recent studies?

2.3. Eligibility criteria for the selection of studies

Three researchers independently performed the selection of the studies. We included articles published from December 2019 to May 10, 2020.

The exclusion criteria were as follows:
- Duplicated results in databases.
- Ongoing projects, review articles that included ongoing studies, and papers addressing non-human studies or discussing COVID-19 intervention in general, without reference to ECG changes.

2.4. Search strategy

The systematic search was carried out in May 2020 using the PubMed (Medline), Scopus, and Embase. The search was limited to English-written articles, and published in the January 2020 to May 2020. We searched the keywords of electrocardiography, ECG, EKG, electrocardiogram, electrocardiograph, coronavirus, COVID-19, SARS-CoV-2, Novel Coronavirus, and 2019-nCoV on the following search strategy:

A [electrocardiography] (Title/Abstract) OR [ECG] (Title/Abstract) OR [EKG] (Title/Abstract) OR [electrocardiogram] (Title/Abstract) OR [electrocardiograph] (Title/Abstract).
B [Coronavirus] (Title/Abstract) OR [COVID-19] (Title/Abstract) OR [SARS-CoV-2] (Title/Abstract) OR [Novel Coronavirus] (Title/Abstract) OR [2019-nCoV] (Title/Abstract).
C [A] AND [B].

2.5. Literature selection

We screened the titles and abstracts of retrieved papers to identify studies meeting the eligibility criteria. We included the relevant full-text articles and discussed their results to make the final selection. After studying all eligible papers’ full text, the researchers made the final decision for each paper.

3. Results

After removing duplicates, abstract, and full-text screening, and adding a few articles manually, 20 studies were encompassed. In the full-text screening process, articles were excluded if their subjects or findings were irrelevant to our study. The PRISMA flow diagram is provided in Fig. 1, which illustrates a thorough presentation of the study selection process. The eligible articles comprised of eleven were case reports, two case series, three retrospective cohorts, two prospective cohorts and observational studies, one consecutive cohort, and one randomized clinical trial (RCT).

We categorized the studies into two groups based on the etiology of ECG abnormalities: drug-induced and non-drug-induced, where QTc prolongation was the mainstay of all studies reporting drug-induced abnormalities. The drug-induced group accounted for six studies discussed in Table 1, whereas other studies belonged to the non-drug-induced group summarized in Table 2. Fig. 2 describes the age distribution of the selected studies.

4. Discussion

COVID-19 incepted rapidly, affecting many different countries all over the world. The beneficiary aspects of this systematic review are extensive, as ECG is a tool utilized vastly worldwide. We discuss some findings that provided physicians do not recognize these patterns, they might erroneously risk their patients’ lives. Major ECG findings are as follows:

4.1. QTc prolongation

Prolonged QTc was mainly due to medication treatment. Six studies were recruited, and all studies exhibited significant QT-prolongation secondary to drug therapy (p < 0.05) with no prior QTc abnormalities in baseline ECG. The drug of choice was chloroquine/hydroxychloroquine either with (combination therapy) or without (monotherapy) azithromycin.

Two articles merely investigated the effects of chloroquine on QTc interval duration. One study presented that 23% of patients developed severe and significant QTc interval prolongation (QTc > 500 ms). Similarly, Borba et al. observed that higher doses of chloroquine resulted in QTc exceeding regular durations (QTc interval >500 ms was recorded in 11.1%, and 18.9% of low-dosage and high-dosage group, respectively).

The other four studies administered both monotherapy (chloroquine/hydroxychloroquine) and combination treatment for COVID-19 patients and confirmed that combination therapy is associated with a higher risk of QTc interval prolongation compared with monotherapy.

A cohort study in Boston assessed the effect of hydroxychloroquine with or without azithromycin on QTc prolongation in which QT prolongation was observed in 19% and 21% of monotherapy, and combination therapy cases, respectively. In a similar case series study, Bessiere and colleagues reported a broader difference in the two groups’ ECG outcomes, indicating 5% and 33% of patients developing QT prolongation in the monotherapy group and combination therapy, respectively.
A retrospective study, in which only combination therapy was administered, declared that 11% (nine patients) of COVID-19 patients had a QTc of more than 500 ms when given hydroxychloroquine with azithromycin (five of which had a normal baseline QTc).

Saleh et al conducted an observational study of 201 patients receiving either chloroquine or hydroxychloroquine with or without azithromycin. QTc >500 ms was noted in 8.6% of monotherapy-receiving patients versus 9.2% of the combination therapy group.

No records of Torsades de Pointes (TdP) were found in reviewed studies, except for the cohort mentioned above by van den Broek et al, which addressed a patient developing TdP three days after his premature discharge. He was later treated with lidocaine.

No arrhythmia-related sudden cardiac death was reported in any of the manuscripts of this group. However, in each study, some of the patients required early treatment termination due to risks of QTc prolongation and ventricular arrhythmia.

Although the articles mentioned above found severe QT prolongation correlating to hydroxychloroquine with or without azithromycin, the absence of TdP and deaths related to arrhythmia observed in most studies raise some hope. However, it must be noted that the degree of QTc prolongation does not linearly correlate with TdP incidence, and TdP might occur even without prolongation of QTc.

When taking a holistic approach into account, studies should outline the medicines’ overall risks and benefits. Nevertheless, we should discuss these ECG changes to minimize the detrimental outcomes and look after must-not-miss patterns.

4.2. Cardiac arrest

Shao et al studied 136 patients with severe COVID-19 who experienced cardiac arrest during hospitalization. Initial ECG patterns and cardiac rhythms were ventricular fibrillation (V-fib) and pulseless V-tach (8, 5.9%), pulseless electrical activity (PEA) (6, 4.4%), and asystole (122, 89.7%). Cardiac arrest occurred after a median of 10 days into hospital admission. A total of 18 patients achieved the restoration of spontaneous circulation after resuscitation; six (75%) out of eight V-fib/V-tach patients, one (16.7%) out of six PEA patients, and 11 (9%) out of 122 asystole patients.

In this described setting of cardiac arrest, asystole accounted for the majority of patients. Unfortunately, much more reduced restoration rates of spontaneous circulation were observed in
Table 1
Description of the included studies in the drug-induced group.

| ID | First author (reference) | Type of study | Country | Study Population | Study Purpose | ECG findings |
|----|--------------------------|---------------|---------|------------------|---------------|--------------|
| 1  | Borba MG⁵                  | Randomized clinical trial | Brazil | 81 patients (male = 60, female = 21) mean age = 51.1y | To evaluate the efficacy and safety of chloroquine in patients with severe COVID-19. | Prolongation of the QTcF
- QTc interval >500 ms: high-dosage group: 7 of 37 (18.9%), low-dosage group: 4 of 36 (11.1%)
- QTc prolongation (mean = 35 ms (95%CI 28 – 43 ms) using computerized interpretation and 34 ms (95% CI 25 – 43 ms) using manual interpretation)
- No TdP
- QTc more than 500 ms in 22 patients (23%) during chloroquine treatment, with no records of prolonged QTc interval prior to the applying medication (p < 0.05)
- QTc prolongation:
  - Median increase in QTc = 21 (11–39) ms: 5.5 (∼14 to 31) ms in monotherapy, 23 (10 –40) ms in combination therapy, p = 0.03
  - QTc increase in: critically ill = 26.5, not critically ill = 16 (∼8 –35), p = 0.05
  - 10 had >60 ms increase in QTc after treatment (3 in monotherapy, 7 in combination therapy)
  - 18 had >500 ms (prolonged) QTc after treatment (7 in monotherapy, 11 in combination therapy)
- QTc ≥ 500 ms after treatment in: loop diuretic – 12 out of 39, no loop diuretic – 6 out of 51, likelihood p = 0.03
- QTc ≥ 500 ms after treatment in: patients with baseline QTc ≥ 450 ms: 15 out of 50, patients with baseline QTc < 450 ms: 3 out of 40, likelihood p = 0.008
- Loop diuretic and baseline QTc ≥ 450 ms remained independent for post-treatment prolonged QTc after controlling for 2 or more Systemic Inflammatory Response Syndrome criteria
  - Age, sex, simultaneous QTc prolonging drugs and comorbidities were not correlated with post-treatment prolonged QTc
- 10/90 stopped hydroxychloroquine before 5 days of treatment due to QTc prolongation
  - PVC* (possibly due to hydroxychloroquine)
  - RBBB* (possibly due to hydroxychloroquine)
  - TdP (1 case, 3 days after hydroxychloroquine + azithromycin discontinuation due to 499 ms QTc) which later developed other ventricular arrhythmias and was treated with lidocaine
- QT prolongation: 37 patients after antiviral therapy
  - PVC (possibly due to hydroxychloroquine)
  - RBBB (possibly due to hydroxychloroquine)
  - TdP (1 case, 3 days after hydroxychloroquine + azithromycin)
  - QTc prolongation: 37 patients after antiviral therapy
  - 14 prolonged QTc after 2–5 days of antiviral therapy; 10 ΔQTc > 60 ms, 7 QTc ≥ 500 ms (1 in monotherapy, 6 in combination therapy, p = 0.03)
  - Antiviral therapy stopped in 17 patients: 7 because of ECG changes, 10 because of acute renal failure
  - Baseline ECG: 46 had intraventricular conduction delay, incomplete or complete RBBB, LBBB or a ventricular paced rhythm – mean QTc = 439.5 ± 24.8 ms, 8 patients had > 500 ms QTc
- QTc prolongation:
  - Mean maximum QTc during cohort = 463.3 ± 42.6 ms: 453.3 ± 37.0 ms in monotherapy, 470.4 ± 45.0 in combination therapy, p = 0.004
  - Mean change from baseline to max QTc: 32.8 ± 28.6 ms in monotherapy,
  |  |  |  |  |  | (continued on next page) |
asystole cases than VF or pulseless VT cases. This trend illustrates the importance of developing and implementing careful preventive measures to reduce cardiac arrest risks in hospitalized patients with COVID-19.

4.3. Atrial fibrillation (A-fib)

A-fib existed in baseline ECG of 11% of van den Broek and colleagues’ study population. As for new-onset A-fib, Saleh et al. demonstrated 8.5% of patients developing atrial fibrillation after receiving treatment.

4.4. Ventricular tachycardia

In the mentioned cohort by Saleh et al., seven (3.5%) patients showed evidence of monomorphic non-sustained V-tach, and one (0.5%) had sustained hemodynamically stable monomorphic V-tach. Moreover, in Borba et al’s study, V-tach manifested on ECG records of two patients before their death, although no association between their death and the arrhythmia was proved.

4.5. ST-T abnormalities

In a retrospective cohort in Wuhan, China by Deng and colleagues, researchers assessed 112 hospitalized COVID-19 positive patients (67 classified in the severe group) for possible myocardial injury and identified fourteen (12.5%) as suspected myocarditis patients based on American Heart Association’s criteria. Abnormal ECG (i.e., ST-T changes) was observed in 22 cases (7 from the non-severe disease group, and 15 with severe disease), including two patients with possible myocarditis. However, ST-T changes were non-specific, considering high age and pre-existing comorbidities of the patients. Also, the study does not state whether the changes were focal or diffused. Based on echocardiography and ECG results, the authors concluded that the patients’ myocardial injury is probably due to the disease’s systemic effects rather than the COVID-19 virus itself. A case report in Italy also studied...
| ID | First author (reference) | Type of study | Country | Study Population | Study Purpose | ECG findings |
|----|--------------------------|---------------|---------|------------------|---------------|--------------|
| 1  | Shao F                   | Retrospective observational study | China   | 136 patients (female = 46, male = 90) | To describe characteristics and outcomes in severe COVID-19 patients with cardiac arrest | Initial rhythms: 8 (5.9%) V-fib/V-tach, 6 (4.4%) PEA, 122 (89.7%) asystole. Patients monitored prior to IHCA: 93.4%. ROSC achieved patients: 75% of patients with V-fib or pulseless V-tach, 5% of asystole group. ECG abnormality definition: ST-T changes. 22 patients with ECG abnormality (2 in suspected myocarditis group (n = 14)); 7 in non-severe disease group (n = 45), 15 in severe disease group (n = 67), p = 0.37. ECG changes generally non-specific. Typical ECG signs absent, suggesting myocardial injury as a result of systemic effects of the illness instead of the virus itself. ECG changes in fatalities (n = 14): ST-segment changes or Abnormal ST-T changes: 9 patients. LAD*: 4 patients. Q wave in inferior leads: 1 patient. ST-elevation: 14 focal, 4 diffuse. |
| 2  | Deng Q                   | Retrospective | China   | 112 hospitalized patients with COVID-19 (male = 57 (50.9%), female = 55 (49.1%)) | Description of findings — suspected myocardial injury | ECG abnormality definition: ST-T changes. 22 patients with ECG abnormality (2 in suspected myocarditis group (n = 14)); 7 in non-severe disease group (n = 45), 15 in severe disease group (n = 67), p = 0.37. ECG changes generally non-specific. Typical ECG signs absent, suggesting myocardial injury as a result of systemic effects of the illness instead of the virus itself. ECG changes in fatalities (n = 14): ST-segment changes or Abnormal ST-T changes: 9 patients. LAD*: 4 patients. Q wave in inferior leads: 1 patient. ST-elevation: 14 focal, 4 diffuse. |
| 3  | Bangalore S             | Case series   | USA     | 18 COVID-19 positive patients with ST-elevation on ECG (male = 15 (83%), female = 3 (17%)) | Findings description | Clinical manifestations of a COVID-19 patient with myocardial infection. ECG abnormality definition: ST-T changes. 22 patients with ECG abnormality (2 in suspected myocarditis group (n = 14)); 7 in non-severe disease group (n = 45), 15 in severe disease group (n = 67), p = 0.37. ECG changes generally non-specific. Typical ECG signs absent, suggesting myocardial injury as a result of systemic effects of the illness instead of the virus itself. ECG changes in fatalities (n = 14): ST-segment changes or Abnormal ST-T changes: 9 patients. LAD*: 4 patients. Q wave in inferior leads: 1 patient. ST-elevation: 14 focal, 4 diffuse. |
| 4  | Cai XQ                  | Case report   | China   | A 60-year-old male | Clinical manifestations of a COVID-19 patient with myocardial infection | ST elevation in leads II, III, and aVF. ST depression in leads V1–V6. Severe ischemia in the inferior wall (leads II, III, and aVF). Sinus tachycardia. Marked RAD*. ST elevation in leads II, III, aVF, and V6 (Inferior leads). |
| 5  | Loghin C                | Case report   | USA     | A 29-year-old male | Clinical features of Pseudo acute myocardial infarction in a young COVID-19 patient | ST elevation in leads II, III, aVF, and V6 (Inferior leads). |
| 6  | Dabbagh MF              | Case report   | USA     | A 67-year-old female | Development of Cardiac Tamponade and Takotsubo cardiomyopathy in a COVID-19 patient | Low voltage in limb leads. Non-specific ST changes. Deep T wave inversion in precordial leads. |
| 7  | Vidovich M              | Case report   | USA     | A 61-year-old male | Finding Transient Brugada-like ECG pattern in a COVID-19 patient | Brugada-type pattern in the right precordial leads. ST elevation in the right precordial leads. |
| 8  | He J                    | Case report   | China   | Patient 1: A 66-year-old female Patient 2: A 70-year-old male | ECG and cardiac manifestations in 2 patients diagnosed with COVID-19 | Patient 1 (sequence of events): Sinus rhythm with first-degree AV block. Sinus tachycardia, first-degree AV block with S1Q3T3. Mobitz type 1 s-degree AV block and atrioventricular junctional escape beat. High-grade (nearly complete) AV block with a junctional escape rhythm. First-degree AV block and recovery from S1Q3T3. Patient 2 (sequence of events): Sinus tachycardia with incomplete RBBB*. Slight ST elevation. V-tach. V-tach and ventricular fusion. Remarkable ST elevation in the form of a triangular QRS-ST-T waveform (in inferior and precordial leads). Sinus tachycardia and 1 mm upsloping ST elevations in leads I and aVL. Mild diffuse PR depressions and diffuse ST-T changes. |
| 9  | Minhas AS               | Case report   | USA     | A 58-year-old female | Clinical manifestations and outcomes of a patient with stress cardiomyopathy or Takotsubo cardiomyopathy in a COVID-19 patient | Sinus rhythm with first-degree AV block. Sinus tachycardia, first-degree AV block with S1Q3T3. Mobitz type 1 s-degree AV block and atrioventricular junctional escape beat. High-grade (nearly complete) AV block with a junctional escape rhythm. First-degree AV block and recovery from S1Q3T3. Sinus tachycardia with incomplete RBBB*. Slight ST elevation. V-tach. V-tach and ventricular fusion. Remarkable ST elevation in the form of a triangular QRS-ST-T waveform (in inferior and precordial leads). Sinus tachycardia and 1 mm upsloping ST elevations in leads I and aVL. Mild diffuse PR depressions and diffuse ST-T changes. |
| 10 | Casey K                 | Case report   | USA     | A 42-year-old COVID-19 positive male | Case report – acute segmental pulmonary emboli | T wave flattening in inferior leads. RAD. S1Q3T3. Low voltage in limb leads. Minimal diffuse ST elevation (most prominent in inferior and lateral leads). ST depression and T inversion in aVR and V1. |
| 11 | Inciardi RM             | Case report   | Italy   | A 53-year-old white woman | Case report – cardiac involvement | (continued on next page) |
myocarditis in the setting of COVID-19. ECG changes of the patient included minimal diffuse ST elevations, which were more significant in inferior, and lateral leads, and concurrent ST depression, and T inversion in V1 and aVR. After further evaluation, Lake Louise's criteria for acute myocarditis were fulfilled.

A case series of 18 patients with COVID-19 and ST elevation\textsuperscript{25} showed local changes in four (22%), and diffuse changes in 14 (78%) cases. ST elevations were either upon presentation (10, 56%) or after a median of 6 days after hospitalization (8, 44%). Myocardial infarction (MI) was observed in 8 (44%) patients, whereas 10 (56%) patients had a non-coronary myocardial injury. Nine (50%) patients underwent angiography, where six showed signs of coronary obstruction. The fatality rate was 72% (13 patients), of which nine died due to non-coronary myocardial damage, and four due to MI. One other study\textsuperscript{26} also reported ST-elevation myocardial infarction (STEMI) in a COVID-19 infected patient. ST-elevation was observed in leads V1–V6, and marked right axis deviation (RAD) were also detected. However, pretests indicated low MI probability, and imaging showed no signs of coronary calcifications. Therefore, coronary angiography was not performed, and the patient received conservative treatments.

Diffuse concave ST elevation was noted in a patient in Turkey\textsuperscript{28} who showed healthy coronary arteries on angiography. CT scan revealed ground-glass opacities associated with COVID-19. Therefore, the patient was diagnosed with possible COVID-19 associated myopericarditis.

ST-T changes were also observed in two patients with Takotsubo syndrome,\textsuperscript{29,30} which included ST elevation in leads I, and aVL, diffuse non-specific ST-T changes, and low voltage limb leads. One of the two patients experienced cardiac tamponade with hemorrhagic effusion before the identification of Takotsubo cardiomyopathy.

T inversion was a pattern observed in some studies. A patient with Takotsubo cardiomyopathy presented deep T inversion in precordial leads of her ECG.\textsuperscript{23} Moreover, T inversion in leads V1 and aVR has been observed in a patient with acute myocarditis.\textsuperscript{27} Doyen and colleagues\textsuperscript{31} observed T inversion in ECGs of a COVID-19 infected patient, which was first limited to anterior leads but was later presented diffusely on a second ECG when the patient was admitted to ICU. Due to the high Global Registry of Acute Coronary Events (GRACE) score, non-ST elevation MI was suspected. However, the diagnosis ruled out with coronary angiography, and myocarditis was suggested based on late gadolinium enhancement imaging.

Various patterns of ST-T abnormalities were the most reported ECG findings, probably not related to medications. Other reported ECG findings might also ensue the potential injuries belong to the virus, but the evidence is still under dispute. These patterns might display the manner of cardiac involvement and alleviate healthcare providers in the diagnosis and management of COVID-19 patients. Howbeit, the variety of ECG findings requires strict attention. Nevertheless, larger study populations adjusting their findings for specific confounders, such as cardiac comorbidities, have to establish these findings’ reliability.

4.6. Brugada pattern

Two case reports in the US\textsuperscript{32,33} reported Brugada patterns in patients with COVID-19.

4.7. S1Q3T3

Two studies\textsuperscript{34,35} reported the S1Q3T3 pattern in their patients. One was a case of pulmonary embolism in a patient with COVID-19 infection. The other two were more complicated and are discussed in the following sections.
precardial ST elevation was developed later on, which advanced into a triangular QRS-T pattern with V-tach episodes during this transition. Unfortunately, the patient deceased within 24 h of the first V-tach occurrence.

One major shortcoming of this systematic review was the limitation in the number of studies, and sample populations. Even in this small number of studies case reports account for a significant proportion of them. Hopefully, the rapidly evolving nature of the research in this field might provide us with increased useful information. We presented these case reports in a different section, as they could produce no firmly accountable evidence.

5. Conclusion

Overall, not only COVID-19 should not be ruled out in the presented ECG findings, but they might also raise clinical suspicions towards it, especially in the situation of an outbreak. Furthermore, due to potential adverse outcomes, recognizing some patterns is even more vital and should be considered, especially in the patients using certain medications.

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Declaration of competing interest

The authors confirm that they have no conflict of interest.

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