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Relation between Hypercoagulability Effect of COVID-19 and the Occurrence of Acute Coronary Syndrome

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ABSTRACT

Background: The coronavirus illness of 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (COVID-2) (SARS-CoV-2). Although systemic inflammation and lung complications can result in significant morbidity and mortality, cardiovascular issues can also occur.

Aim of The Work: Reducing risk of myocardial infarction in patients with COVID-19.

Subjects and methods: This Case-control study was conducted in Shark El-Madina hospital in Alexandria on 129 covid-19 patients divided into group A: 43 suspected COVID-19 patients who developed Acute coronary syndrome (ACS), group B: 43 suspected COVID-19 patients who hasn`t developed ACS and group C: 43 patients with myocardial infarction who were not suspected for COVID-19. All patients underwent thorough general and local history taking, a physical exam, routine tests (CBC, CRP, ESR and blood gases) and CT chest as well as specialised tests like the ECG, ferritin, PT, PTT, INR, D. dimer, Troponin, and LDH.

Results: There was differences between the three groups in terms of Troponin level, D-dimer, Ferritin, CRP, ALT, AST and PT

Conclusion: Based on our study findings, we concluded that hypercoagulability of Acute coronary syndrome is more likely to manifest in people with Covid 19 infection.

Keywords: Acute coronary syndrome, Hypercoagulability, COVID-19.

INTRODUCTION

Lombardy has the largest population density (roughly 10 million people) in Italy. Four months after the first confirmed case of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection on February 21, 2020, the disease has been diagnosed in more than 90,000 people in Lombardy [(1)]. Sadly, more than 16,000 people died as the virus reached its height in March and April 2020. Then, in May and June, there was a slow but steady slide **[(2)].**

Time-dependent systems' efficacy and efficiency may be negatively impacted by emergencies like the COVID-19 epidemic, with potentially disastrous clinical outcomes [(3)]. Pandemic COVID-19 significantly decreased how many admissions there were for acute coronary syndromes (ACS) in Italy, which may have impacted the timing of primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction in individuals (STEMI) (PPCI), potentially increasing fatality and complication rates **[(4)].** National and international scientific bodies have offered recommendations on how to manage ACS patients, whether or not they have COVID-19 infection. These recommendations have been made in nations where there has been a significant virus outbreak **[(5, 6)].**

The Lombardy healthcare authorities issued a decree on March 8th urging a modification to all regional networks for the management of time-critical clinical and surgical emergencies (STEMI, stroke, major traumas, neurological, cardiac, and vascular surgical emergencies) are being developed in order to concentrate urgent activities in a small number of facilities, increase the number of intensive care beds designated for COVID-19 patients, and prevent other hospitals from closing down as a result of general overcrowding **[(7)].** Eight regions make up the Lombardy standard STEMI network, which has a total of 55 catheterization labs (caths-labs), the majority of which provide 24/7 PPCI **[(8)]**. Previous publications provide a thorough explanation of the changed network for STEMI during pandemics **[(9)].** Briefly stated, a one- or two-person model of centralization "Macro-Hubs" was used in each area based on the projected Time spent transporting patients, regional considerations, and the capacity to accept all incoming patients **[(10)].**

Additional requirements included performing PPCI on establishing separate pathways from triage to an isolated care unit for STEMI patients with suspected or proven COVID-19 (ensuring the availability of an interventional cardiology, nursing, and support personnel PPCI team) and accepting all arriving STEMI patients on a 24/7 basis. As a result, 13 "Macro-hubs" with various numbers of spoke centres were discovered **[(11)].**

PATIENTS AND METHODS

Sharks were the subject of this case-control study. El-Madina hospital in Alexandria on 129 covid-19 patients divided into group A: 43 suspected COVID-19 patients who developed ACS, group B: 43 suspected COVID-19 patients who hasn`t developed ACS and group C: 43

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patients with myocardial infarction who were not suspected for COVID-19.

Inclusion criteria: Patients suspected of having covid-19 infection and patients suspected of having myocardial infarction complicated by covid-19 infection not complicated with myocardial infection from both males and females.

Exclusion criteria: Patients with ACS who do not have covid-19 suspicion infection and patients with hypercoagulable state as atrial fibrillation conditions, patients with history of previous thromboembolic events, dilated cardiomyopathy and advanced hepatic and renal diseases.

All patients were subjected to the following:

Thorough general and local history taking, physical exam, routine tests like the CBC, CRP, ESR, CT chest, blood gases, and blood gases, as well as specialised tests like the ECG, ferritin, PT, PTT, INR, D. dimer, troponin, and LDH.

Electrocardiogram (ECG):

Before the therapy for COVID-19 began, the patients' electrocardiograms (ECGs) in the supine and sleeping positions were recorded at a rate of 25 mm/sec using twelve leads. On-screen measurements were made manually for each measurement. The time between the start of the QRS complex and the end of the T wave is known as the QT interval. All leads were used for QT interval measurements, the longest QT interval with was noticed. The variance in many leads' largest and shortest QT intervals were identified as QT dispersion (QTd). The heart rate was calculated using the interval between R and R measurements.

completeness of the information about the type of therapy and its duration, including at least two ECG tests (one at baseline and at least one after patient recovery) [(12)].

Ethical consideration: The Institutional Review Board of Zagazig University approved the study.

Statistical analysis

All data were collected, tabulated, and statistically evaluated using version 23.0 of IBM SPSS statistics for Windows (Statistical Package for the Social Sciences, IBM Corp., based in Armonk, New York). The Receiver Operating Characteristic (ROC) curve, the Student's t-test, the Mann Whitney U-test, the Wilcoxon Signed Ranks Test, the Kruskall Wallis Test, and the Chi-square Test were used.

RESULTS

Our study was conducted on three groups A, B and C in each group 43 patients. The mean age for group A was 44 and 42.5 for group B but for group C was 43.5. We found that 60 % of cases were males in group A, 53% in group B and for group C 58% of patients were males. There was no statistical difference between the three groups except for SBP (Table 1).

Table (1): Demographic data

	Group A	Group B	Group C	Test of sig.	P value
Age (years)	44±5	42.5±4.2	43.5±5.2	F=10.124	0.856
Sex(m)	26(60.4)	23(53.4)	25(58)	X^2=7.364	0.660
BMI	26±2	25±2.1	26±4.1	F=4.756	0.798
HR	79±20	86±16	85±17	F=0.043	0.957
SBP	147±27	136±24	134±26	F=12.7	>0.001*

There was no statistically significant difference between our three groups regarding any comorbidities (Table 2).

Table (2): Comorbidities distribution

Comorbidities	Group A	Group B	Group C	Test of sig.	P value
PCI	24(56)	20(47)	0(0)	X^2=6.203	0.903
HF	11(26)	19(44)	3(7)	X^2=4.326	0.770
Angina	10(25)	10(25)	2(6)	X^2=2.985	0.854
Hypercholesterolaemia	21(50)	17(48)	8(24)	X^2=5.563	0.639

Table (3) showed that the three groups differed significantly in important ways with respect to Troponin level, D-dimer, ferritin, CRP, ALT, AST and PT.

Table (3): Lab findings

	Group A	Group B	Group C	Test of sig.	P value
Creatinine	1±0.196	1.03±0.193	1.123±0.495	F=19.630	0.986
Troponin	172±71	8±0.45	0.25±0.7	F=4.22	>0.001*
D-dimer	972±105	858±66	260±161	F=3.95	>0.001*
S.ferritin	941±99	924±94	59±14	F=1.98	>0.001*
CRP	67±5	64±5	80±4	F=1.14	>0.001*
ALT	94±8	50±6	66±5	F=14.56	<0.001*
AST	80±6	63±7	84±7	F=11.6	<0.001*
PT	12±2	12±1	15±3	F=5.12	>0.001*
PTT	32±9	32±10	36±13	F=14.86	0.956
INR	1±0.2	1±0.2	1±0.55	F=16.32	0.986

DISCUSSION

In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) to be a pandemic. A recent article has underlined the importance of cardiac injury in mortality and critically ill pneumonia in COVID-19 patients, despite the fact that the new virus (SARS-CoV-2) is usually linked with respiratory symptoms [13].

The cytokine storm, a component of the host's immune response, and direct viral harm are likely the causes of the COVID-19 myocarditis' pathogenesis [14, 15]. Prior research has shown that ventricular arrhythmias are extremely common in viral myocarditis or pericarditis [16] and during influenza epidemics, patients with implantable cardioverter defibrillators showed a considerable increase in the frequency of these arrhythmias [17]. According to a recent meta-analysis, 19% of COVID-19 patients experienced arrhythmias and their presence was linked to a worse result [18].

In diverse clinical contexts, including myocarditis, some new electrocardiography (ECG) markers, such as T peak-to-T end (Tp-e), QT dispersion (QTd), and Tpe/QT ratio, have been demonstrated to indicate transmural ventricular repolarization heterogeneity or repolarization dispersion [19, 20, 21].

Sadly, there are yet no medications that have been licensed for either treating or preventing COVID-19. Azithromycin-coated antimalarial drugs that have previously shown efficacy against SARS-CoV and MERS-CoV, as well as COVID-19, have been the subject of numerous investigations aimed at developing effective antimalarial drugs [22].

The QT interval could be prolonged by these drug types, which could result in a deadly arrhythmia. Since beta-blockers are -adrenergic receptor (-AR) antagonists, they can stop the sympathetic tone from rising, which is the main arrhythmia trigger. Treatment for cardiac rhythm problems with azithromycin, chloroquine, and hydroxychloroquine demonstrates that the cardio-selective beta-blocker bisoprolol is helpful in treating QT interval prolongation in COVID-19 patients [23].

Recent research and case studies have clarified the possibility of abrupt cardiac damage in COVID-19-infected people. The coronavirus associated with Middle Eastern respiratory disease (MERS CoV) can result in myocarditis and cardiac failure **[24].** Myocardial injury is a symptom of both COVID19 and MERSCoV, which has led to increasing complexity in patient care due to their comparable pathogenicity **[25].** In one case report, a COVID-19 patient without any indications or symptoms of respiratory tract illness came with left ventricular failure and acute pericarditis **[26].**

In COVID-19 patients, we sought to lower the risk of myocardial infarction to look into how COVID-19 might affect cardiovascular disease, especially if it has the ability to make people more prone to hypercoagulability, which could result in myocardial infarction. Our study was conducted on three groups A, B and C in each group 43 patients. The average age of group A was 44, group B was 42.5, whereas group C was 43.5. We found that 60 % of cases were males in group A, 53% in group B and for group C 58% of patients were males. These outcomes are in line with those of **Yenerça *et al.*** **[27]** who discovered that the mean age of the COVID-19 patients under study was 55.5 ± 17.1 years, and that 52% of the patients were men. 37% of people were smokers, 52% had hypertension, and 36% had diabetes mellitus. **Ztürk** **[28]** discovered that the average age of Covid19 patients was 47.9, 14.9, and that 56% of them were male.

Tai *et al.* **[29]** investigated patients with mild COVID-19 for the connection between underlying CV issues and disease development. 327 people, 200 of them were females (61.2%), with age ranged from 40 to 59. **Shi *et al*** **[30]** looked into the relationship between COVID-19 patients' mortality and heart injury. The age of these 229 individuals ranged from 22 to 90, 130 (56.2%) of them were females.

Guo *et al.* [31] investigated the relationship between myocardial damage and underlying cardiovascular disease (CVD) and death outcomes in COVID-19 patients. 43 patients (23%) died, and 144 patients (77%) with verified COVID-19 were made public with 58.50 ± 14.66 years old.

For group A and band C, respectively, we found means of BMI were 26.2, 25.2, and 26.4.1kg/m^2, while SBP was 134.27 mmHg. These results are better than those of **Yenerça *et al.*** [27] who discovered that the mean heart rate and BMI of the COVID-19 patients under study were 74.9 beat/min and 24.1 kg/m^2 respectively. **Ece *et al.*** [32] determined the SBP to be 104.5 ± 10.9 whereas the DBP was found to be 62.3 ± 7.03 mmHg. According to our findings, there were 26% cases of heart failure among the COVID19 patients who were investigated, 25% cases of anginal discomfort, and 56% cases of previous PCI. The findings revealed PCI to be the most common comorbidity. Regarding any comorbidities, there was no statistical difference between our three groups (PCI, angina and hypercholesterolemia). In contrast, there was a big disparity in SBP between the research groups.

Guo *et al.* [31] investigated the relationship between myocardial damage and underlying cardiovascular disease (CVD) and death outcomes in COVID-19 patients. Regarding comorbidities, 52 patients (27.2%) had myocardial damage as seen by high TnT levels, and 66 (35.3%) of the participants had underlying CVD, such as cardiomyopathy, hypertension, and coronary heart disease. Regarding comorbidities, there is a considerable difference between the two groups.

Ztürk *et al.* [28] discovered that diabetes mellitus and hypertension were also present in two of the three dead patients, which is consistent with our study's findings. They were 69 and 74 years old, respectively. All three of the victims were males. When the ECG data from diseased individuals were analysed, it was found that despite the fact that QTC readings were high, they were not high enough to be the cause of an abnormal heart rhythm. **Shi *et al.*** [30] aimed to investigate whether cardiac damage and mortality in COVID-19 patients were related. The most prevalent concomitant conditions were found to be diabetics (60 patients; 14.4%) and hypertension (127 patients; 30.5%). 44 (10.6%) and 22 (5.3%) of the 416 patients had coronary heart disease or cerebrovascular illness, respectively. **Matsushitall *et al.*** [33] **in** metanalysis studies found a positive connection between hypertension and severe COVID-19. The majority of studies that were considered showed a correlation between severe COVID-19 and diabetes. Similar to this, the majority of studies that were considered eligible demonstrated a favourable correlation between severe COVID-19 and past CVD, with a 3.58 combined relative risk (2.06-6.21).

Rivas *et al.* [34] reported that, in terms of comorbidities, 9612 patients (23%) had obesity, 11879 patients (28.4%) had diabetes, and 19405 patients (46.3%) had hypertension. Last but not least, while 2022 is still in progress, there were a total of 34573 patients during the first two years, with 16565 patients in 2020 (48%), and 18008 patients in 2021 (52%). The mortality rates for patients with comorbidities including diabetes and hypertension were shown to be four times higher in a recent research with 46321 hospitalised COVID-19-positive individuals (with CVD's) [34]. Our study, which concentrated on patients who had CVDs, found that diabetes and hypertension had comparable patterns (OR: 1.744, p 0.001) and that 92% of deaths were related to both.

Li *et al.* [35] revealed that a meta-analysis of six studies with 1527 participants with COVID-19 were conducted, investigated the frequency of CV diseases and found that hypertension, heart and cerebrovascular disease, and diabetes were all more common than expected, with respective prevalences of 17.1%, 16.4%, and 9.7% respectively. In The three groups in the current study, there was a significant difference in terms of Troponin level, D-dimer, S. ferritin, CRP, ALT, AST and PT.

Guo *et al.* [31] aimed to assess the correlation between fatal outcomes in individuals with myocardial injury, underlying cardiovascular disease (CVD), and COVID-19. Additionally, Patients with higher TnT levels experienced noticeably longer prothrombin times (12.4 [12.0-13.0] vs. 13.3 [12.2-15.3] seconds; P=.005) and significantly higher levels of D-dimer (0.29 [0.17-convert to nanomoles per mL: 3.85 [0.51-25.58] g/mL vs. 0.60 [0.60] liter by multiplying by 5.476; P=.005). Inflammatory indicators included high-sensitivity C-reactive protein median [IQR], 8.55 [4.87-15.165] versus 3.13 [1.24-5.75] mg/dL. In keeping with our findings, **Yenerça *et al.*** [27] discovered that Covid19 patients had increased CRP and WBC levels.

Shi *et al.* [30] looked into the relationship between COVID-19 patients' cardiac damage and mortality. Procalcitonin levels were 0.07 [0.04-0.15] ng/L on average, and C-reactive protein levels were 4.5 [1.4-8.5] mg/dL (multiply by 10 to translate to milligrams per liter) were higher among the 416 patients who comprised the study's overall sample.

Levels of The median [IQR] for procalcitonin was 0.27 [0.10-1.22] ng/mL against 0.06 [0.03-0.10] ng/mL, while the median [IQR] for C-reactive protein was 10.2 [6.4-17.0] mg/dL versus 3.7 [1.0-7.3] mg/dL. CRP has been linked to the Tp-e interval, the Tp-e interval/QT rates, and predictors of ventricular arrhythmia in numerous investigations [19, 27].

CONCLUSION

Based on our study findings, we concluded that hypercoagulability caused by Covid-19 in Covid-19-infected individuals made them more likely to have acute coronary syndrome.

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REFERENCES

1. **Siudak Z, Grygier M, Wojakowski W *et al.* (2020):** Clinical and procedural characteristics of COVID-19 patients treated with percutaneous coronary interventions. Catheter Cardiovasc Interv., 96(6): 568-575.
2. **De Rosa S, Spaccarotella C, Basso C *et al.* (2020):** Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. European heart journal, 41 (22): 2083-2088.
3. **Hauguel-Moreau M, Pillière R, Prati G *et al.* (2021):** Impact of Coronavirus Disease 2019 outbreak on acute coronary syndrome admissions: four weeks to reverse the trend. Journal of Thrombosis and Thrombolysis, 51 (1): 31-32.
4. **Zeng J, Huang J & Pan L (2020):** How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People's Hospital. Intensive care medicine, 46 (6): 1111-1113.
5. **Huber K, Gersh J, Goldstein P *et al*. (2014):** The organization, function, and outcomes of ST-elevation myocardial infarction networks worldwide: current state, unmet needs and future directions. European heart journal, 35 (23): 1526-1532.
6. **Chieffo A, Stefanini G, Price S *et al.* (2020):** EAPCI position statement on invasive management of acute coronary syndromes during the COVID-19 pandemic. European heart journal, 41 (19): 1839-1851.
7. **Stefanini G, Montorfano M, Trabattoni D *et al*. (2020):** ST-elevation myocardial infarction in patients with COVID-19: clinical and angiographic outcomes. Circulation, 141 (25): 2113-2116.
8. **Tam F, Cheung S, Lam S *et al.* (2020):** Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment–elevation myocardial infarction care in Hong Kong, China. Circulation: Cardiovascular Quality and Outcomes, 13 (4): e006631. https://www.ahajournals.org/doi/full/10.1161/CIRCOUTCOMES.120.006631
9. **Ferlini M, Andreassi A, Carugo S *et al.* (2020):** Centralization of the ST elevation myocardial infarction care network in the Lombardy region during the COVID-19 outbreak. International Journal of Cardiology, 312: 24-26.
10. **Ardati K & Mena Lora J (2020):** Be prepared. Circulation: Cardiovascular Quality and Outcomes, 13 (4): e006661. https://www.ahajournals.org/doi/full/10.1161/CIRCOUTCOMES.120.006661
11. **Deng Q, Hu B, Zhang Y *et al.* (2020):** Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. International journal of cardiology, 311: 116-121.
12. **Bianco M, Biolè A, Campagnuolo S *et al*. (2020):** COVID-19 therapies and their impact on QT interval prolongation: A multicentre retrospective study on 196 patients. IJC Heart & Vasculature, 30: 100637. https://www.sciencedirect.com/science/article/pii/S2352906720303353
13. **Santoso A, Pranata R, Wibowo A *et al.* (2020):** Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: A meta-analysis. Am J Emerg Med., 44: 352-357.
14. **Siripanthong B, Nazarian S, Muser D *et al.* (2020):** Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Hear Rhythm, 17: 1463-1471.
15. **Lazzerini E, Boutjdir M, Capecchi L (2020):** COVID-19, Arrhythmic Risk, and Inflammation: Mind the Gap! Circulation, 142 (1): 7-9.
16. **Baksi J, Kanaganayagam S, Prasad K (2015):** Arrhythmias in Viral Myocarditis and Pericarditis. Card Electrophysiol Clin., 7: 269-281.
17. **Madjid M, Connolly T, Nabutovsky Y *et al.* (2019):** Effect of High Influenza Activity on Risk of Ventricular Arrhythmias Requiring Therapy in Patients With Implantable Cardiac Defibrillators and Cardiac Resynchronization Therapy Defibrillators. Am J Cardiol., 124 (1): 44-50.
18. **Pranata R, Huang I, Raharjo B (2020):** Incidence and impact of cardiac arrhythmias in coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Indian Pacing Electrophysiol., 20 (5): 193-198.
19. **Ucar M, Ozturk C, Yllmaztepe A (2019):** Evaluation of Tpe interval, Tp-e/QT ratio and Tp-e/QTc ratio in patients with acute myocarditis. BMC Cardiovasc Disord., 19: 232-239.
20. **Tse G, Chan F, Keung W *et al.* (2017):** Electrophysiological mechanisms of long and short QT syndromes. Int J Cardiol Heart Vasc., 14: 8–13.
21. **Prenner B, Shah J, Goldberger J *et al.* (2016):** Repolarization Heterogeneity: Beyond the QT Interval. J Am Heart Assoc., 5: e003607. https://www.ahajournals.org/doi/full/10.1161/JAHA.116.003607
22. **Lythgoe P , Middleton P (2020):** Ongoing clinical trials for the management of the COVID-19 pandemic. Trends in pharmacological sciences, 41 (6): 363-382.
23. **Heriansyah T, Nur Chomsy I, Febrianda L *et al*. (2020):** The potential benefit of beta-blockers for the management of Covid-19 protocol therapy-induced QT prolongation: a literature review. Scientia Pharmaceutica, 88 (4): 55-64.
24. **Alhogbani T (2016):** Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. Ann Saudi Med., 36: 78-80.

25. **Zheng Y, Ma T, Zhang Y *et al.* (2020):** Reply to: 'Interaction between RAAS inhibitors and ACE2 in the context of COVID-19.'Nat Rev Cardiol., 17: 313–314.
26. **Inciardi M, Lupi L, Zaccone G *et al.* (2020):** Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA cardiology, 5 (7): 819-824.
27. **Yenerçağ M, Arslan U, Ceylan A *et al.* (2020):** Evaluation of Tp-e interval and Tp-e/QT ratio in major burn patients. J Electrocardiol., 60: 67–71.
28. **Öztürk F, Karaduman M, Çoldur R *et al*. (2020):** Interpretation of arrhythmogenic effects of COVID-19 disease through ECG. Aging Male ,23 (5): 1362-1365.
29. **Tai S, Tang J, Yu B *et al.* (2020):** Association between cardiovascular burden and requirement of intensive care among patients with mild COVID-19. Cardiovascular therapeutics, 15 (1): 77-83.
30. **Shi S, Qin M, Shen B *et al.* (2020):** Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA cardiology, 5 (7): 802-810.
31. **Guo T, Fan Y, Chen M *et al.* (2020):** Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA cardiology, 5 (7): 811-818.
32. **Ece İ, Koçoğlu M, Kavurt V *et al.* (2021):** Assessment of cardiac arrhythmic risk in children with Covid-19 infection. Pediatric cardiology, 42 (2): 264-268.
33. **Matsushita K, Ding N, Kou M *et al.* (2020):** The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: a systematic review and meta-analysis. Global heart, 15 (1): 19-33.
34. **Rivas R, Delgado-Gallegos L, Garza-Treviño G *et al.* (2022):** Association between Mortality and Cardiovascular Diseases in Vulnerable Mexican Populations, A Retrospective Study of the COVID-19 Pandemic. https://pubmed.ncbi.nlm.nih.gov/36438268
35. **Li Y, Yao L, Li J *et al*. (2020):** Stability issues of RT-PCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19. J Med Virol., 92 (7): 903-908.