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RESEARCH ARTICLE OPEN ACCESS

Association of serum lactate dehydrogenase and C-reactive protein with disease severity in hospitalised COVID-19 patients

Nsaif MM[1], Abdulhussein AA[1], Taher AY[2ID], Rasoul LM[3]

[1]College of Medicine, Al Iraqia University, Baghdad, Iraq
[2]Department of Chemistry and Biochemistry, College of Medicine, Al-Iraqia University, Baghdad, Iraq
[3]University of Baghdad, College of Science, Department of Biology, Baghdad, Iraq

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Abstract
Objective: Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, can lead to critical illness in hospitalised patients. Elevated levels of certain biomarkers are often associated with worse clinical outcomes. Two such biomarkers are lactate dehydrogenase (LDH), an enzyme found in nearly all body tissues that is released upon cell damage, and C-reactive protein (CRP), a protein produced by the liver in response to inflammation. This manuscript examines the relationship between LDH and CRP levels and their association with disease severity and clinical outcomes in critically ill patients with COVID-19.
Methods: A cross-sectional study was conducted on 200 hospitalised COVID-19 patients and 20 age- and sex-matched healthy controls. SARS-CoV-2 infection was confirmed by RT-PCR targeting the ORF1ab, E, and N genes. Serum LDH and CRP levels were measured using a Cobas C111 clinical chemistry analyser.
Results: COVID-19 patients had significantly higher median serum LDH and CRP levels [Provide values, e.g., LDH: 450 U/L (IQR: 350-580)] compared to healthy controls [LDH: 180 U/L (IQR: 150-210), $p<0.001$]. Both biomarkers showed a significant positive correlation with disease severity ($p<0.001$), with the highest levels observed in the severe patient group. Patients over 50 years old had significantly higher concentrations than younger patients.
Conclusion: Elevated serum LDH and CRP levels are associated with increased disease severity in hospitalised COVID-19 patients, suggesting their potential utility as accessible prognostic biomarkers.

Keywords: COVID-19, LDH, CRP, multiplex PCR, ELISA

Plain English Summar

COVID-19 is a disease caused by the coronavirus SARS-CoV-2. Doctors and scientists have been searching for simple blood tests that can help predict which patients are at risk of severe illness. In this study, we tested two blood markers: lactate dehydrogenase (LDH), an enzyme found in almost all tissues, and C-reactive protein (CRP), a protein made by the liver during inflammation.
We measured LDH and CRP levels in 200 hospitalised patients with COVID-19 and compared them with healthy people. Our results showed that patients with higher levels of these markers, especially those over 50 years old, were more likely to develop severe disease. Women in our study also had higher LDH values than men.

Correspondence:
Taher Aya Y
Department of Chemistry and Biochemistry, College of Medicine
Al-Iraqia University, Baghdad
Iraq
+96412179590, aya.y.taher@aliraqia.edu.iq

This means that testing for LDH and CRP in COVID-19 patients could help doctors identify patients at higher risk of complications, allowing for earlier treatment and better outcomes.

Introduction

Coronaviruses are a large family of viruses capable of causing disease in both humans and animals, ranging from the common cold to more severe illnesses such as severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS). A novel coronavirus (nCoV) is a new strain not previously identified in humans. The outbreak of SARS-CoV-2, first detected in Wuhan, China, in December 2019 (1). The severe strain COVID-19 placed on global healthcare systems, due to its high morbidity and mortality, highlighted the urgent need for novel therapeutic platforms, a field where oncolytic virotherapy—such as the engineered Newcastle Disease Virus has shown significant promise." (2). The identification of reliable biomarkers for predicting disease severity and mortality is therefore critical for the rational allocation of healthcare resources, early clinical intervention, and improved patient outcomes (3). The pathophysiology of severe COVID-19 is characterised by a pronounced inflammatory response. Elevated levels of various inflammatory mediators have been consistently associated with severe disease compared to mild cases. Among the promising prognostic biomarkers is lactate dehydrogenase (LDH), a cellular enzyme released upon tissue damage. Elevated LDH levels are a known predictor of poor outcomes in a range of viral infections (4, 5, 6), and early data in COVID-19 patients indicated significant differences in LDH levels between severe and non-severe cases (7). Similarly, C-reactive protein (CRP), a key acute-phase protein synthesised by the liver in response to inflammation, serves as a sensitive marker for infection and tissue damage. In COVID-19, elevated CRP levels are not only indicative of pneumonia but are also correlated with greater disease severity and the presence of extensive lung lesions (8, 9, 10). Furthermore, the prognostic value of both LDH and CRP has been observed in previous coronavirus outbreaks, including SARS and MERS, where their levels were linked to severity and mortality (11, 12, 13).

Building upon this established context, the concurrent investigation of LDH, as a marker of cellular injury, and CRP, as a marker of systemic inflammation, provides a robust framework for assessing disease progression in COVID-19. Therefore, this study aims to evaluate the association of serum LDH and CRP levels with mortality in patients with COVID-19 (14, 15, 16). We hypothesise that elevated levels of both biomarkers at admission are independently and jointly associated with an increased risk of mortality, and that their combined assessment may offer superior prognostic value for stratifying high-risk patients.

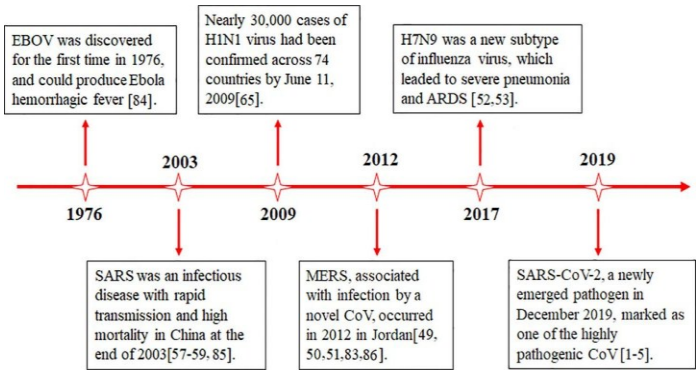

Figure 1: Research developments on numerous viral diseases over time. A severe form of acute respiratory syndrome is referred to as SARS.

The respiratory syndrome of the Middle East is referred to as MERS. Acute respiratory distress syndrome is referred to as ARDS (15).

In this study, we assess the levels of LDH and CRP in serum to see if these inflammatory mediators are involved in COVID-19 mortality.

Materials and Methods

200 Hospitalised Patients with COVID-19 infection took part in this study, and the local ethics committees approved it.

Participants' information was as follows

1. Study Dates and Enrollment Period

Patient Enrollment Period: Participant enrollment and sample collection took place over this entire period, from April 15, 2024, to September 30, 2024.
2. Participating Centres/Laboratories
Sample collection and analysis were performed at the following two public health laboratories:
The Public Health Laboratory of Al-Najaf Health Directorate. The Public Health Laboratory of Al-Diwaniyah Health Directorate.
3. Study Population and Inclusion/Exclusion Criteria
Study Population: The study included hospitalised adult patients with confirmed COVID-19.

Inclusion Criteria
Confirmed Diagnosis: Patients were included based on a positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) test from nasopharyngeal swabs.

Blood Sample Collection
Following the confirmation of the viral gene via RT-PCR, blood samples were drawn from the patients for biochemical analysis.

Clinical Presentation
Enrolled patients were symptomatic, with common clinical manifestations including oxygen desaturation, loss of taste, and loss of smell.

Patient Status
The study cohort included both patients in general wards and those admitted to the Intensive Care Unit (ICU).

Exclusion Criteria
Patients who had received any prior specific pharmacological treatment for COVID-19 before enrollment were excluded.
Pregnant women were excluded from the study.
Patients with known immunosuppression or significant chronic comorbidities were not included in this research.

Disease Severity Classification
Disease severity was classified at admission according to the WHO COVID-19 Clinical Management Living Guidelines. Mild/Moderate: patients with clinical symptoms but without evidence of viral pneumonia or hypoxia. Severe: patients with clinical signs of pneumonia (fever, cough, dyspnea) plus one of: respiratory rate >30 breaths/min, severe respiratory distress, or SpO2 <90% on room air.
After a positive nasopharyngeal swab, all patients were studied, as were twenty age- and sex-matched healthy volunteers who had a negative nasopharyngeal swab.
"The primary objective of this study was to investigate the prognostic value of LDH and CRP for disease severity and mortality within a cohort of hospitalised COVID-19 patients. The inclusion of a small healthy control group (n=20) was not intended for direct statistical comparison but to establish a local, context-specific benchmark for normal biomarker levels, against which the markedly elevated levels in the patient group could be qualitatively appreciated. The statistical analyses were therefore powered and designed to detect differences between patient sub-groups (e.g., survivors vs. non-survivors), for which the sample size was adequate."

Molecular diagnosis of SARS-CoV-2 via multiplex PCR
The presence of SARS-CoV-2 RNA in patient specimens was determined using a multiplex real-time reverse transcription PCR (RT-PCR) assay. The test utilised specific primers and fluorescent probes to simultaneously target conserved regions of the SARS-CoV-2 genome.
To reconcile the gene targets mentioned throughout the manuscript, we clarify that the assay targeted the following genes:
Envelope (E) gene
Nucleocapsid (N) gene
Open Reading Frame 1ab (ORF1ab)
An internal control was included in each reaction to monitor for PCR inhibition and confirm successful nucleic acid extraction. Nucleic acids were extracted from oropharyngeal swab samples using a commercial viral RNA extraction kit, following the manufacturer's protocol. The RT-PCR reaction was performed using a pre-formulated master mix, and amplification was carried out on a real-time PCR instrument. A sample was considered positive for SARS-CoV-2 if characteristic amplification curves were observed for the specified target genes.

Analysis of Genetic Variation
During the screening process, a subset of positive samples exhibited atypical amplification profiles, specifically a loss of signal in the probe channel targeting the S-gene while maintaining robust signal in other gene targets (e.g., N and ORF1ab). This pattern is known to be associated with genetic variation in the probe-binding region of the S-gene.
Important Note: While such a shift in the qPCR curve is a strong indicator of a potential sequence variation, it is not a definitive confirmation of a specific mutation. Validation through sequencing (e.g., Sanger or Next-Generation Sequencing) is

required to identify the exact genetic change. Therefore, these samples are described as showing "signatures suggestive of S-gene variation" or "atypical S-gene amplification." Any claims of specific mutations in the results (e.g., in Figures 3, 4, 5, and Table 6) have been removed, as the described methodology does not support them (17, 18).

Determination of lactate dehydrogenase (LDH) in a patient's serum

Biochemical Assays

Serum levels of Lactate Dehydrogenase (LDH) and C-Reactive Protein (CRP) were analysed using a Cobas Integra 400 plus clinical chemistry analyser (Cobas).

Lactate Dehydrogenase (LDH): LDH activity was measured using a quantitative enzymatic biochemistry kit (Catalogue No. ACN 080), as per the manufacturer's instructions.

Using a Cobas Integra 400 Plus analyser (Roche Diagnostics, Mannheim, Germany), the Lactate Dehydrogenase acc. to IFCC ver.2 assay was used to evaluate serum LDH activity. The kinetic UV test principle serves as the foundation for the assay. LDH catalyses the oxidation of NADH to NAD^+ while also converting L-lactate to pyruvate. Kinetic measurements at 340 nm show that the rate at which absorbance decreases as a result of NADH consumption is exactly related to the sample's LDH catalytic activity. The test was conducted in compliance with the guidelines provided by the manufacturer (19).

C-Reactive Protein (CRP)

Using a Cobas Integra 400 Plus analyser (Roche Diagnostics, Mannheim, Germany), the Tina-quant® C-Reactive Protein IV immunoassay was used to quantitatively measure the levels of serum CRP. The assay relies on the principle of particle-enhanced immunoturbidimetry. Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies in this technique. The photometric measurement of the turbidity that results from the production of these immune complexes is proportional to the concentration of CRP in the sample. The manufacturer's instructions were followed when conducting the test (20).

Analysis of statistics

The Statistical Packages of Social Sciences -SPSS (2019) program was used to detect the effect of different factors on study parameters (distribution percentage). The t-test was used to significantly compare between means in this study (21).

Results

This study comprised a total of 200 instances of COVID-19 patients and 20 healthy participants (both males and females).

Detection of SARS-CoV-2 infection through the spike (S) gene and nucleocapsid (N) gene

The molecular diagnosis was confirmed by using RT-PCR; Even though the kit used a multiplex PCR approach, spike (S) gene and nucleocapsid (N) gene specific primers were used, incorporating the upstream and downstream ends of specific primers. Results are shown in Figure 2 below

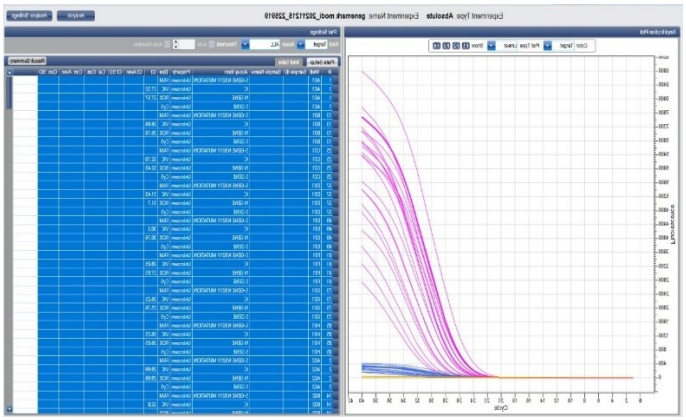

Fig. 2: RT-PCR amplification plot of the spike (S) gene and (N) gene using the Log graph type.

Distribution of SARS-CoV-2 infection among patients according to age factor

The age group 60-70 years is the most common in the infection rate. Although people of all ages can contract COVID-19, older adults are more likely to suffer from severe illness due to ageing-related physiological changes and other underlying health conditions. and the result was also statistically

highly significant according to (p≤0.01) as shown in Table 4.

Age-based COVID-19 infection distribution among patients' groups is shown in Table 4. below.

Table (4): Patient distribution based on age factor

Age group (year)	No. of patients	Percentage %	Number of patients with severe symptoms
10-20	10	5.0 d	2
20-30	17	8.5 cd	0
30-40	16	8.0 cd	3
40-50	30	15.0 bc	3
50-60	45	22.2 ab	15
60-70	60	30.0 a	30
70-80	22	11.0 cd	15
Total	200	100%	68
T-test (P-value)	---	8.633 ** (0.0001)	---

** (P≤0.01).

** Highly significant=less than 0.01.

Distribution of SARS-CoV-2 infection among patients according to gender

Our results show a statistical difference in the distribution of COVID-19 infection according to (P≤0.01), where males were (64%) and females were (36%).

Distribution of COVID-19 infection among patients according to gender is shown in Table 5 below:

Table (5): Distribution of patients according to gender

Gender	No. of patients	Percentage (%)
Males	128	64 a
Females	72	36 b
Total	**200**	**100**
T-test (P-value)	¬¬¬¬¬	9.021 ** (0.0004)

** (P≤0.01).

** Highly significant=less than 0.01.

LDH among the studied group according to the age factor in relation to the severity of infection

According to the statistical analysis, results are non-significant in relation to the age factor and severity of infection, where all patients showed a high level of LDH in the serum (Chi-Square (χ2) = 1.075)

Table (6): LDH value among SARS-CoV-2 patients according to age factor and severity of infection.

Age group	Total no. of patients	Number of patients with high concentrations of LDH	Severity of infection	Percentage (%)
10-20	10	2	Mild	1.0 b
20-30	17	6	Mild	3.0 ab
30-40	16	3	Mild	1.5 b
40-50	30	9	Moderate	4.5 ab
50-60	45	9	Severe	4.5 ab
60-70	60	14	Severe	7.0 a
70-80	22	6	Severe	3.0 ab
Total	**200**	**49**		**24.5**
T-test (P-value)	---	---	---	4.695 * (0.0358)

* (P≤0.05).

* Significant=less than 0.05.

LDH value among the studied group according to Gender

Statistical analysis (Chi-Square (χ2) = 5.194) showed a significant difference between LDH level and gender in patients' serum, where females with a high level of LDH showed 33.333% compared to males 17.968% according to (P≤0.05).

Table (7): LDH among the studied group according to Gender

Gender	Total no. of patients	No. of patients with high conc. Of LDH	Percentage (%)
Males	128	23	17.968 b
Females	72	24	33.333 a
Total	**200**	**47**	**51.301**
T-test (P-value)	--	--	6.813 * (0.0386)

* (P≤0.05).

* Significant=less than 0.05.

Relation of CRP with age factor, gender, and severity of infection

Table 8 shows the mean level of C-reactive protein (CRP), which was statistically ultra-significant in all patients of different age groups and genders.

Note: 20 healthy individuals were included in this study, and all of them showed normal values of LDH and CRP in their serum.

Table (8): The mean serum level of CRP (mg/L) in patients infected with COVID-19

Age group	Males	Females	Total no. of patients	Severity of infection	Serum level of CRP	Normal value of CRP
10-20	7	3	10	Mild	All patients showed a high level of CRP in serum	males (0-5 mg/l)
20-30	11	6	17	Mild		females (0-5 mg/l)
30-40	10	6	16	Mild		
40-50	15	15	30	Moderate		
50-60	23	22	45	Severe		
60-70	47	13	60	Severe		
70-80	15	7	22	Severe		

Discussion

A major hazard to human health worldwide, the COVID-19 pandemic has increased the annual death toll from infectious diseases (22). According to SARS-CoV-2 molecular diagnostics, the coronaviral genome encodes the spike(S), nucleocapsid(N), membrane(M), as well as envelope(E) proteins, which are necessary for the creation of a structurally complete viral particle. (23).

"The COVID-19 pandemic has underscored the critical need for accessible prognostic biomarkers to identify patients at high risk of severe disease. Our study confirms that serum levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP)—markers of tissue damage and systemic inflammation, respectively—are significantly elevated in hospitalised COVID-19 patients and are strongly associated with disease severity. This aligns with the broader principle that understanding host inflammatory pathways is key to managing severe disease, a concept also central to advancing therapies in other fields, such as the use of immunomodulatory cytokines like IL-15 in oncology (23, 24, 25).

The most salient finding of our study is the marked increase in both LDH and CRP levels in patients with severe COVID-19 compared to those with mild or moderate disease (25-27). This aligns consistently with the existing literature, where LDH, as a marker of cellular injury, and CRP, as an indicator of systemic inflammation, have been established as robust predictors of poor outcomes (7, 25, 26).

The elevated LDH likely reflects widespread tissue damage, particularly pulmonary involvement that can progress to acute respiratory distress syndrome, a common feature of critical COVID-19

(27, 28, 29). Similarly, the sharp rise in CRP is a well-documented response to the cytokine-mediated inflammatory cascade characteristic of severe SARS-CoV-2 infection (30, 31, 32). Our findings reinforce the utility of these biomarkers in a clinical setting, providing objective measures to complement clinical assessment for risk stratification. In two separate trials, elevated LDH levels were linked to a higher chance of a severe COVID-19 outcome (24, 26). Cells in practically every organ system contain the intracellular enzyme LDH, which catalyses the simultaneous interconversion of NADH and NAD+ as well as the conversion of pyruvate and lactate (33). Humans possess five different isozymes of this enzyme. The main isoforms include LDH-1 found in heart muscle cells, LDH-2 located in the reticuloendothelial system, LDH-3 present in lung cells, LDH-4 in the kidneys and pancreas, and LDH-5 primarily in the liver and skeletal muscles (A & B). Even though high levels of LDH have been linked to heart injury since the 1960s, harm to other organs, decreased oxygenation, and activation of the glycolytic pathway can also contribute to their occurrence. An acidic extracellular pH, resulting from elevated lactate levels due to infection and tissue damage, triggers the activation of metalloproteases and enhances macrophage-driven angiogenesis (27).

Serious infections could have two possible side effects: LDH release and cytokine-induced tissue injury (28). Given that LDH is present in lung tissue, individuals suffering from severe COVID-19 infections are likely to exhibit elevated LDH levels in their blood. This elevation is linked to the severe interstitial pneumonia associated with the disease, often progressing to acute respiratory distress syndrome, involving isozyme 3. However, the specific roles of the different LDH isoenzymes in the observed LDH increase in COVID-19 cases have not yet been clarified (27). LDH has been demonstrated in numerous studies (3, 28) to be a predictor of worse outcomes for patients who are hospitalised. Many of the COVID-19 prognostic markers and treatments now being researched have their roots in the (SARS) and other respiratory illnesses. Patients with MERS had increased LDH levels as well (27).

Furthermore, our data reveal that older patients (aged 50 years and above) presented with significantly higher concentrations of both biomarkers. This is a clinically intuitive finding, as advanced age is a well-established risk factor for severe COVID-19, often compounded by age-related physiological changes and a higher prevalence of comorbidities (25). The correlation between increasing age and rising LDH/CRP levels underscores the need for heightened vigilance and early intervention in this vulnerable demographic (29).

An interesting observation from our study was the difference in LDH levels between genders. We found that female patients had significantly higher median LDH levels than males. While some studies have reported a higher incidence of severe disease and mortality in males, the relationship with biomarkers like LDH is complex and may be influenced by hormonal factors, differences in immune response, or the specific pattern of organ involvement (29). This finding warrants further investigation in larger, prospective cohorts.

Our findings regarding C-reactive protein (CRP) further substantiate the central role of a hyperinflammatory state in severe COVID-19. As demonstrated in Table 8, serum CRP levels were markedly elevated across all patient groups, with concentrations rising in tandem with clinical disease severity, from mild to moderate and severe cases. This ultra-significant elevation ($p < 0.001$) aligns with the established pathophysiology of SARS-CoV-2 infection, which is characterised by a dysregulated immune response and a pronounced "cytokine storm" (30, 31, 32). CRP, as a key acute-phase reactant produced by the liver in response to interleukin-6 (IL-6) and other pro-inflammatory cytokines, serves as a sensitive barometer of this systemic inflammation. The consistently high CRP levels in our cohort, particularly in patients with severe outcomes, reinforce its utility as a robust prognostic marker. This is consistent with a large body of literature where elevated CRP has been independently associated with an increased risk of respiratory failure, intensive care unit admission, and mortality in COVID-19 (34, 35). The measurable increase in CRP provides clinicians with an accessible and cost-effective tool to gauge the intensity of the inflammatory cascade and identify patients who may benefit from more aggressive anti-inflammatory or immunomodulatory therapies.

The strengths of our study include a well-characterised cohort of hospitalised patients and the use of standardised, automated assays for biomarker quantification. However, our findings must be interpreted in the context of several limitations. First, the cross-sectional design prevents us from establishing a causal relationship between biomarker levels and disease outcomes; we can only report associations. Second, the sample was drawn from hospitals in a single region (Baghdad), which may limit the generalizability of our findings to other populations with different

genetic backgrounds or healthcare infrastructures. Third, we focused on LDH and CRP, and a broader panel of inflammatory and immunological markers might provide a more comprehensive prognostic picture. Finally, the relatively small size of our healthy control group limited the power for more robust comparative analyses. Future prospective multicenter studies that include longitudinal biomarker measurement and adjust for potential confounders, such as specific comorbidities, are needed to validate the independent predictive value of LDH and CRP.

Conclusion

Elevated LDH and CRP levels are strongly associated with severe COVID-19. These biomarkers can serve as accessible, cost-effective tools for predicting disease progression and guiding clinical management in resource-limited settings.

Declarations

Ethics Approval and Consent to Participate

Approved by the Bioethics Committee of the Department of Biology, University of Baghdad, College of Science (Reference No. CSEC/0221/0095). Written informed consent was obtained from all participants.

Consent for Publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution Non-Commercial 4.0 license.

Availability of Data and Materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

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Authors' contributions

NMM and RLM: Designed the study
NMM: Collected data
TAY and AAA: Performed statistical analysis and funding.
RLM: writing, editing, and revising.
All authors approved the final manuscript.

List of abbreviations:

CRP: C-reactive protein
ELISA: Enzyme-linked immunosorbent assay
LDH: Lactate dehydrogenase
MERS: Middle East respiratory syndrome
PCR: Polymerase chain reaction
RT-PCR: Reverse transcription polymerase chain reaction
SARS: severe acute respiratory syndrome
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
UTM: Universal transport medium

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