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Diagnostic value of combined nucleic acid and antibody detection in suspected COVID-19 cases

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Abstract

Objectives: Nucleic acid testing is the gold standard method for the diagnosis of coronavirus disease 2019 (COVID-19); however, large numbers of false-negative results have been reported. In this study, nucleic acid detection and antibody detection (IgG and IgM) were combined to improve the testing accuracy of patients with suspected COVID-19.

Study design: The positive rate of nucleic acid detection and antibody detection (IgG and IgM) were compared in suspected COVID-19 patients.

Methods: A total of 71 patients with suspected COVID-19 were selected to participate in this study, which included a retrospective analysis of clinical features, imaging examination, laboratory biochemical examination and nucleic acid detection and specific antibody (IgM and IgG) detection.

Results: The majority of participants with suspected COVID-19 presented with fever (67.61%) and cough (54.93%), and the imaging results showed multiple small patches and ground-glass opacity in both lungs, with less common infiltration and consolidation opacity (23.94%). Routine blood tests were mostly normal (69.01%), although only a few patients had lymphopenia (4.23%) or leucopenia (12.68%). There was no statistical difference in the double-positive rate between nucleic acid detection (46.48%) and specific antibody (IgG and IgM) detection (42.25%) (P = 0.612), both of which were also poorly consistent with each other (kappa = 0.231). The positive rate of combined nucleic acid detection and antibody detection (63.38%) was significantly increased, compared with that of nucleic acid detection (46.48%) and that of specific antibody (IgG and IgM) detection (42.25%), and the differences were statistically significant (P = 0.043 and P = 0.012, respectively).

Conclusions: Nucleic acid detection and specific antibody (IgG and IgM) detection had similar positive rates, and their combination could improve the positive rate of COVID-19 detection, which is of great significance for diagnosis and epidemic control.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a new acute respiratory infectious disease, which first occurred in December 2019 in Wuhan, Hubei Province, China. COVID-19 quickly spread to several cities in other provinces in China, such as Shenzhen in Guangdong Province, and subsequently many countries around the world, causing wide concern. By early March 2020, more than 80,000 cases had been confirmed in China, with more than 30,000 deaths; in addition, there were more than 30,000 cases outside of China, with more than 700 deaths, mainly distributed in South Korea, Iran, Italy and France. The majority of patients experienced mild symptoms, with the death rate of about 2.38%, which mainly consisted of elderly men with underlying health conditions.

To date, the global pandemic is not yet under complete control. SARS-CoV-2 is mainly transmitted by respiratory droplet transmission, airborne transmission, contract transmission, facees-
mouth transmission and even maternal-foetal transmission.\(^2\) Currently, there is no treatment for COVID-19, and therefore, patients rely on support and alleviation of symptoms to recover. The Chinese Center for Disease Control and Prevention has designated COVID-19 as a ‘Class B’ infectious disease and recommends following prevention and control measures for ‘Class A’ infectious diseases, focussing on early diagnosis and early isolation to cut off the source of infection.\(^3\) At present, the standard method for the diagnosis and control of the epidemic is real-time fluorescent quantitative reverse transcription polymerase chain reaction (rRT-PCR) nucleic acid detection, which is highly specific and can immediately determine whether patients are infected with SARS-CoV-2 or not. However, nucleic acid detection from nasopharyngeal swabs showed high false-negative rates in clinical application, producing a number of patients with suspected COVID-19.\(^4\) It is very important to improve the diagnosis rate of suspected cases to ensure timely treatment for patients with confirmed COVID-19 to avoid the spread of infection, but also to avoid overtreatment of patients without COVID-19, thus reducing human and material resources. In this study, retrospective analysis was performed on 71 suspected COVID-19 cases, combined with nucleic acid detection, laboratory biochemical examination, imaging examination and specific antibody (IgG and IgM) detection, which can provide a clinical basis for improving the diagnosis of suspected COVID-19 cases.

Methods

Study participants

A total of 71 patients with suspected COVID-19, ranging in age from 2 to 65 years (mean age: 35.86 years), including 35 males and 36 females, were admitted to the seventh trial edition of the National Diagnosis and Treatment Protocol of Novel Coronavirus Pneumonia, with clinical information involving general information, clinical features, laboratory examination, imaging examination and COVID-19 antibody detection. Data were collected from the Hezheng ward, Shenzhen Hospital, Southern Medical University, China, between January 2020 and March 2020. The Hezheng ward was the admission site for patients with suspected COVID-19 designated by the Shenzhen City Government.

Inclusion criteria

Epidemiological history: Inclusion criteria based on epidemiological history are as follows: (1) patients with travel or residence history in Wuhan and the surrounding areas or other communities with reported cases within 14 days before the onset of COVID-19 symptoms; (2) patients with contact history with patients with COVID-19 (positive nucleic acid detection) within 14 days before the onset of COVID-19 symptoms; (3) patients who were in contact with individuals with respiratory symptoms or fever who came from Wuhan and the surrounding areas or communities with reported cases within 14 days before the onset of COVID-19 symptoms; and (4) clustering occurrence, i.e., two or more reported cases of fever or respiratory symptoms in small areas, such as the home, office or classroom, within 14 days before the onset of COVID-19 symptoms.

Clinical manifestations: Inclusion criteria based on clinical manifestations are as follows: (1) fever or respiratory symptoms; (2) imaging characteristics consistent with COVID-19; and (3) normal leucocyte count or lymphopenia or normal lymphocyte count or leucopenia in the early diagnosis.

Patients with COVID-19 were defined as those who met any criterion of the epidemiological history and any two clinical manifestations or who had any three clinical manifestations without any criterion of the epidemiological history.

COVID-19 nucleic acid detection

Two sterile swabs were used to wipe both pharyngeal tonsils and the posterior pharyngeal wall simultaneously. Then, the swab head was immersed in a tube with 3 ml of virus preservation solution, the tube cover was tightened and the specimen was sealed in an appropriate plastic bag to avoid cross-contamination. All tests were completed within 24 h of swab collection. Nucleic acid detection kits provided by GeneoDx and Sansure Biotech were used for nucleic acid detection in nasopharyngeal swabs on days 2–10 after COVID-19 infection, once every 1–2 days. Two kits were used to confirm the results, four times in a row. According to the instructions, the PCR solution was prepared by mixing 16 µl of the reaction solution and 4 µl of the enzyme mixture, which was then added into the PCR amplification tube with 20 µl of the extracted nucleic acid specimen. Positive and negative controls were set. FAM (ORF-1ab region) and ROX (N gene) channels were selected to test nucleic acids, and HEX channel was taken as the internal standard. The PCR procedure was conducted as follows: reverse transcription at 50 °C for 30 min, cDNA predenaturation at 95 °C for 1 min, denaturation at 95 °C for 15 s, annealing and elongation at 60 °C for 30 s for 45 cycles and cooling at 25 °C for 10 s. Negative control results are defined as follows: no Ct values for FAM, FOX and HEX channels or Ct > 40; positive control results are defined as follows: Ct < 35 for FAM, FOX and HEX channels. Both positive and negative control results should meet the requirements simultaneously; otherwise, the experiments are invalid. Positive SARS-CoV-2 results are defined when the S-type amplification curve is detected through FAM or ROX channel and Ct ≤ 40; whereas negative SARS-CoV-2 results are defined when the S-type curve is not detected through FAM or ROX or Ct > 40, but with the amplification curve in HEX channel and Ct ≤ 40.

COVID-19—specific antibody (IgG and IgM) detection

COVID IgM and IgG antibody kits (provided by Beijing Diagreet Biotechnologies Co., Ltd.) were used for testing 3–4 weeks after COVID-19 infection and were verified and approved by Beijing Institute of Medical Device Testing (BIMT). Whole blood samples of suspected patients were collected, and heparin was added for anticoagulation. The tests were completed within 24 h of blood sample collection. According to the instructions, 20 µl of the sample was added to a tube with phosphate-buffered saline. After homogeneously mixing, 80 µl of the mixture was added into the hole of the test card. The test card is composed of a card cover and a test strip; the test strip contains sample stage, glass fibre, cellulose nitrate film, IgG or IgM antibody, absorbent paper, PVC board, and sample pad. After reaction for 15 min, the relative content of IgG or IgM was detected under a fluorescence immunoassay analyser. IgM > 0.88 µL and IgG > 1.00 µL were defined as positive results based on the detection values from 242 healthy subjects, and the 95% confidence interval was labelled as negative.

Statistical analyses

SPSS, version 26.0, software was used for statistical analyses. Count data were expressed as percentage. The chi-squared test was
used for comparison between groups. \( P < 0.05 \) showed statistical significance.

**Results**

**Patient characteristics**

A total of 71 patients with suspected COVID-19, ranging in age from 2 to 65 years (mean age: 35.86 years), including 35 males and 36 females, participated in this study. The majority of patients were aged between 18 and 65 years (88.73%). Patients with a relatively clear epidemiological history, according to the inclusion criteria, accounted for 83.10% of the sample (see Table 1).

**Clinical features**

The majority of patients presented with fever (67.61%) and cough (54.93%), whereas a few had fatigue and shortness of breath, and some had diarrhoea, sore throat and other symptoms. The imaging findings showed multiple small patches and ground-glass opacity in both lungs, with less common infiltration and consolidation opacity (23.94%); chest computed tomography (CT) scans of some patients were normal (14.08%). Routine blood tests were mostly normal in the early stages (69.01%); however, a few patients had lymphopenia (4.23%), leucopenia (12.68%), leucocytosis (14.08%) and neutrophilic leucocytosis (14.08%) (see Table 2).

**Comparison between nucleic acid detection and antibody (IgG and IgM) detection**

The incubation period of SARS-CoV-2 infection is generally 3–7 days. Patients with suspected COVID-19 only come to the hospital when they started to experience typical clinical symptoms, such as fever or cough; therefore, it is difficult to determine the specific time of infection. The results showed that 22 patients were tested positive once in nucleic acid detection in nasopharyngeal swabs, 11 patients were tested positive twice in nucleic acid detection and a total of 33 patients were tested positive in nucleic acid detection; 38 patients were tested negative in nucleic acid detection in nasopharyngeal swabs, leading to an overall positive detection rate of 46.48%. In addition, 30 patients were double positive, and 41 were tested negative in specific (IgG and IgM) antibody detection approximately 3–4 weeks after SARS-CoV-2 infection, resulting in a positive detection rate of 42.25%. There was no statistical difference in the positive rate between both the two detection methods (\( P = 0.612 \)), both of which were also poorly consistent with each other (kappa = 0.231) (see Table 3). Among 33 patients tested positive in nucleic acid detection, 18 were double positive in IgG and IgM antibody detection; the remaining 15 patients were single positive in IgG (\( n = 10 \)) or single positive in IgM (\( n = 5 \)) antibody detection.

**Comparison between single detection and combined detection**

Analysis showed that the positive detection rate of COVID-19 was 63.38% in the combined nucleic acid detection and antibody detection, compared with 46.48% in single nucleic acid detection and 42.25% in single specific antibody detection; thus, the diagnosis rate was increased by about 20%, and the difference was statistically significant (\( P = 0.043 \) and \( P = 0.012 \), respectively; see Table 4).

**Discussion**

SARS-CoV-2 is the seventh new human coronavirus discovered so far, which belongs to the betacoronavirus family and has a high homology with the SARS-CoV epidemic in 2003. Such viruses belong to the RNA virus family, which evolves quickly, mutates greatly and is highly infectious, with a latency of generally 3–7 days, ranging from 1 to 24 days.\(^5,6\) SARS-CoV-2 nucleic acid detection is a key technical support to help

| Table 1 | Characteristics of patients with suspected COVID-19. |
|---------|---------------------------------------------------|
| Characteristic | n | % |
| Gender | | |
| Male | 35 | 49.30 |
| Female | 36 | 50.70 |
| Epidemiological history | | |
| Y | 59 | 83.10 |
| N | 12 | 16.90 |
| Age in years | | |
| < 18 | 5 | 7.04 |
| 18–45 | 49 | 69.01 |
| >45–65 | 14 | 19.72 |
| >65 | 3 | 4.23 |

COVID-19 – coronavirus disease 2019.

| Table 2 | Clinical features of patients with suspected COVID-19. |
|---------|---------------------------------------------------|
| Feature | n | % |
| Clinical symptoms | | |
| Fever | 48 | 67.61 |
| Cough | 39 | 54.93 |
| Fatigue | 5 | 7.04 |
| Shortness of breath | 4 | 5.63 |
| Others (sore throat, diarrhoea and so on) | 15 | 21.13 |
| Imaging findings | | |
| Characteristic changes\(^a\) | 17 | 23.94 |
| Normal | 10 | 14.08 |
| Blood test results | | |
| Lymphopenia | 3 | 4.23 |
| Leucopenia | 9 | 12.68 |
| Leucocytosis | 10 | 14.08 |
| Neutrophilic leucocytosis | 10 | 14.08 |
| Normal | 49 | 69.01 |

\( ^a \) Characteristic changes of imaging findings include the following: multiple small patch and ground-glass opacity in both lungs, infiltration and consolidation opacity in the lung.

| Table 3 | Comparison between nucleic acid detection and antibody detection. |
|---------|---------------------------------------------------|
| Nucleic acid detection | Antibody (IgG and IgM) detection | Total |
| | Positive | Negative | | |
| Positive | 18 | 15 | 33 |
| Negative | 12 | 26 | 38 |
| Total | 30 | 41 | 71 |

\( ^a \) Antibody (IgG and IgM) detection: positive means IgG and IgM are double positive.

| Table 4 | Diagnosis detection rates of COVID-19. |
|---------|---------------------------------------------------|
| Detection method | Positive cases | |
| | n | % |
| Nucleic acid detection | 33 | 46.48 |
| Antibody (IgG and IgM) detection | 30 | 42.25 |
| Combined detection | 45 | 63.38 |

COVID-19 – coronavirus disease 2019.
prevent and control the COVID-19 epidemic. The analysis targets the unique genetic sequence of the virus by adopting real-time quantitative PCR, which is an established and easy-to-carry-out test. Therefore, nucleic acid detection plays an important role in early diagnosis, isolation and treatment. Patients test positive when the dual target is positive in nucleic acid detection; however, some individuals have a single-target—positive result in nucleic acid detection, thus receiving a negative test result, although they may be infected—in these circumstances, multiple detections should be conducted. However, it needs to be emphasised that nucleic acid detection cannot be used as the golden standard for the diagnosis of COVID-19 and that the possibility of SARS-CoV-2 infection cannot be ruled out by negative test results, which may be due to factors such as poor sample quality, inappropriate sampling time, incorrect storage, transportation and handling, virus mutation or limitations of nucleic acid detection kits. Many suspected cases have daily negative nucleic acid detection results for 3–4 consecutive days, or many cases after having a weakly positive result on the first day can then have negative results for the following 3 days. Thus, a conclusion cannot be drawn from the results of nucleic acid detection. In this study, only 43.7% of the 71 suspected cases who underwent nucleic acid detection were tested positive. In addition, many remote areas currently do not have the facilities for nucleic acid detection, leading to a number of missed diagnoses.

Therefore, it is essential to find more effective diagnostic indicators or auxiliary examination for comprehensive judgement to confirm suspected cases as soon as possible. Tens of thousands of suspected cases have seriously impacted the assessment of the epidemic trend and affected the decision-making and implementation of prevention and control measures.

As a helpful complement to the nucleic acid detection of SARS-CoV-2, CT of the chest that typically manifests as multiple ground-glass opacity, patch opacity and consolidation opacity and the combination of CT of the chest and nucleic acid detection in nasopharyngeal swabs can effectively improve the diagnosis rate of SARS-CoV-2 infection. A previous report showed that the positive detection rate of 19 suspected cases via nucleic acid detection was only 47.4%, while CT of the chest can improve the diagnosis rate of SARS-CoV-2 infection. In addition, another study showed that of 1014 patients, only 59% tested positive in nucleic acid detection, whereas 88% were tested positive in CT of the chest, and 308 patients were tested negative in nucleic acid detection, but positive in CT of the chest. This indicates that CT of the chest has a significant sensitivity for the diagnosis of SARS-CoV-2 infection compared with nucleic acid detection in nasopharyngeal swabs. The CT results of 71 suspected cases in the present study showed that 23.94% of patients had typical changes in both lungs, and these changes needed to be differentiated from other virus pneumonia, such as influenza A, influenza B and adenovirus pneumonia. It was speculated that all of our clinical cases had mild or common symptoms rather than severe disease. Therefore, the CT results can be used to assist judgements but are not recommended as the diagnostic standard. Laboratory biochemical examination showed that the routine blood results such as transaminase, creatine kinase, myoglobin, C-reactive protein, erythrocyte sedimentation rate and interleukin 6 levels were increased; lymphocyte count and albumin levels were decreased; procalcitonin levels were normal, which were helpful to determine whether the disease contained bacterial infection, oxidative disorder, and prognosis and outcome. However, it was shown in this study that most indicators were normal at the early stage (69.01%); however, a few patients had lymphopenia and leucopenia (4.23% and 12.68%, respectively) and leucocytosis and neutrophilic leucocytosis (14.08% and 14.08%, respectively), which were not diagnostic.

IgG and IgM are diagnostic indicators of infection owing to their high concentration and strong affinity. IgM of SARS-CoV-2 can be detected on day 4 after infection and peaks on day 20, and the level is significantly decreased after 28 days. However, IgG can be detected on day 7 after infection and peaks on day 25, and the level remains high for several months. In addition, it was also reported that during days 0–40 after infection, IgG and IgM are simultaneously detected and share the same peak times, as well as the decreasing trend. Specific double-positive antibody (IgM and IgG) can diagnose SARS-CoV-2 infection according to the novel coronavirus pneumonia diagnosis and treatment plan (seventh trial edition). Antibody detection is used to detect antibodies in peripheral blood samples collected in a controllable way, via automatic chemiluminescence immunoassay with high flux and high speed, which can be carried out in all hospitals without the need for specially trained professionals. At the critical stage of epidemic prevention and control, antibody detection can not only decrease the number of patients misdiagnosed as a result of false-negative nucleic acid detection and improve the diagnosis rate of SARS-CoV-2 infection, but can also avoid the spread of infection by repeated collection of nasopharyngeal swab samples. A previous study showed that on the day of the first blood sampling from 16 patients with COVID-19, the rate of IgM and IgG detection were 50% and 81%, respectively. Moreover, the positive rates of IgM and IgG detection were 81% and 100% on the fifth day, respectively. Among 139 patients with confirmed COVID-19, the positive rates of IgM detection during week 1, weeks 1–2 and >2 weeks were 27.8%, 48.0% and 95.0%, respectively; whereas those of IgG detection were 3.3%, 8.0% and 62.5%, respectively. The detection of antibodies on days 17–23 for 41 patients with COVID-19 demonstrated that the positive detection rates of IgG and IgM were 97.6% and 87.8%, respectively. The fast detection kit of Orient Gene Biotech was used to detect 102 patients with COVID-19 within 3–4 weeks. It was found that both positive detection rates of IgG and IgM reached higher than 95%, indicating high consistency of positive IgM and IgG results. In addition, another report of 68 patients with suspected COVID-19 showed that 22 cases were tested positive in nucleic acid detection and 31 were tested positive for both IgM and IgG testing, which indicated that detection of specific antibodies for COVID-19 is more advantageous. In this study, specific antibody (IgG and IgM) detection for 71 suspected cases illustrated that the double-positive rate was 42.25% 3–4 weeks after infection; in addition, among 33 patients who tested positive in nucleic acid detection, 18 were double positive in antibody detection, and the other 15 were single positive in IgG (n = 10) or IgM (n = 5) antibody detection. This may be a result of individual differences in the immune response, which can also vary by age; thus, dynamic monitoring is recommended. In addition, according to the test instructions of the IgM/IgG kit, a high titre of IgM may lead to negative results of IgG detection; similarly, a high titre of IgG can also result in negative IgM results. In this study, 3 cases exhibited this situation. Moreover, negative test results can also be seen when IgG or IgM levels in the blood are lower than the bottom threshold of the test kit (specificity, sensitivity and judgement criteria). In addition, blood sample contamination, different detection units, different operation experience and instruments may also contribute to a difference in the results. Furthermore, a false-positive result may occur when the detection result is susceptible to some interfering substances (e.g., other interferons, rheumatoid factor or non-specific IgM) and cross-recognition reactions (e.g., SARS-CoV, NL63, OC43, 229 E and HKU1) in the blood samples. The false-positive rates were 0.5% for IgM and 1.0% for IgG in healthy blood samples. It was also reported that the IgM and IgG combined assay has better utility and sensitivity than a single IgM or IgG test as a diagnostic criterion. Further analysis...
showed that the positive rate of SARS-CoV-2 detection in combined nucleic acid detection and antibody kit detection reached 63.38%, which greatly increases the diagnosis rate.

Conclusion

In suspected COVID-19 cases, nucleic acid detection and specific antibody (IgG and IgM) detection showed a similar positive rate, and their combination could greatly improve the positive rate of diagnosis, which is of great significance for diagnosis and epidemic control.

Author statements

Ethical approval

This study was approved by the Ethics Committee of Shenzhen Hospital, Southern Medical University (NYSZYYEC20200009).

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Competing interests

None declared.

Author contributions

J.W. contributed to study design. H.Z., Z.Z., X.Q., X.J., Z.L., J.W., H.D., L.T. and J.W. contributed to data collection. H.Z., S.D. and J.W. contributed to data analysis and writing. All authors read and approved the final manuscript.

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