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Evaluation of Dynamic Changes of IgG and IgM in COVID-19 Patients by Different Detection Methods

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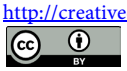

Abstract

Objective: To analyze the dynamic evaluation of chemiluminescence, colloidal gold, and immunofluorescence chromatography in detecting antibodies in COVID-19 patients within four weeks of infection, and to provide evidence for clinical application. **Method:** 74 patients with confirmed SARS-COV-2 infection in the local area were selected as the experimental group, while 231 patients with negative SARS-COV-2 results but not vaccinated with Covid19 vaccine were selected as the control group; during the first, second, third, and fourth weeks after enrollment in the experimental group, three methods were used to detect SARS-COV-2 IgG and IgM in patients' blood: chemiluminescence method, colloidal gold antibody method, and immunofluorescence chromatography. In the control group, three methods were used to detect SARS-COV-2 IgG and IgM during physical examination for SARS-COV-2 nucleic acids. The ROC curve was drawn to analyze the value of each indicator in predicting SARS-COV-2 infection, and the kappa method was used to analyze the consistency of the detection results of each indicator. **Results:** There was no significant difference in the positive rates of SARS-COV-2 IgM and IgG antibodies detected by chemiluminescence, colloidal gold, and immunofluorescence chromatography during the four-week period ($P > 0.05$). The positive rates of SARS-COV-2 IgM and IgG antibodies detected by the three methods during the first week of infection were not higher than 60%; when the three methods were used to detect SARS-COV-2 IgM and IgG *in vivo*, the AUC diagnosed by the test results was less than 0.80 at the first week, the diagnostic efficacy of the three methods was above 0.95 from the second week to the fourth week, and the diagnostic efficacy of the three methods was higher than 0.97 at the fourth week. The diagnostic efficacy of the three methods was comparable; the three methods for detecting SARS-COV-2 IgM and

IgG antibodies showed high consistency in four cycles. **Conclusion:** Chemiluminescence, colloidal gold, and immunofluorescence chromatography are highly consistent in the detection of SARS-COV-2 IgM and IgG antibodies, and can be used as an auxiliary diagnosis and efficacy observation of novel coronavirus infections according to the needs, but the positive rate of infected people in the first week is low.

Keywords

Chemiluminescence Method, Colloidal Gold Method, Immunofluorescence Chromatography, SARS-COV-2 IgM, SARS-COV-2 IgG

1. Introduction

COVID-19 is a public health event that is widely spread all over the world. In addition to the respiratory system, the virus can also involve multiple systems such as digestive, circulatory, neurological, and urinary systems [1], According to clinical and epidemic prevention practices, attention should be paid to early detection, early diagnosis, early isolation, and early treatment in the intervention of COVID-19 patients. The National Health Commission of China has included COVID-19 as a Class B infectious disease under the Law on the Prevention and Control of Infectious Diseases, but has adopted measures for the prevention and control of Class A infectious diseases, and is named NovelCoronavirus pneumonia (NPC) [2]. WHO officially named the disease caused by the virus as corona-virus disease 2019 (COVID-19), and the International Commission on Taxonomy of Viruses named the virus that caused the outbreak as SARS-COV-2 [3] [4]. 2019-nCoV has a long incubation period, strong infectivity, and the virus is constantly mutating [5], Rapid and effective laboratory testing for rapid screening and diagnosis can help improve the value of first-line epidemic prevention. China's Diagnosis and Treatment Plan for Pneumonia Infected by a novel coronavirus (Tentative Seventh Edition) includes antibody testing into the diagnostic criteria and excludes suspected cases. Positive IgM and IgG specific antibodies in the serum of suspected cases can effectively diagnose COVID-19 patients, and the exclusion criteria of suspected cases need to meet the conditions of negative SARS COV-2 nucleic acid testing and negative IgM and IgG antibodies 7 days after onset [6]. Chemiluminescence assay, colloidal gold assay, and immunofluorescence chromatography are currently the most commonly used methods for detecting antibodies *in vivo* in clinical practice, but the value of these three detection schemes in the dynamic evaluation of COVID-19 patients is still rarely reported. Therefore, this study intends to select 74 positive patients admitted to our hospital as the research object to analyze the chemiluminescence assay, colloidal gold assay, and the dynamic evaluation of immunofluorescence chromatography for detecting antibodies *in vivo* provides a basis for clinical application.

2. Data and Methods

2.1. General Information

With the approval of the Ethics Committee, 74 patients with confirmed COVID-19 infection in the region were selected as the experimental group, and 231 medical workers who were not vaccinated with COVID-19 vaccine and whose nucleic acid was negative in physical examination were selected as the control group at the same time. There were 43 men and 31 women in the experimental group, aged (42.19 ± 18.12) years, and 108 men and 123 women in the control group, aged (39.87 ± 12.41) years. There was no significant difference in the general data of patients between the two groups ($P > 0.05$), the grouping is reasonable and comparable.

2.2. Methods

In the first week, the second week, the third week, and the fourth week (once every seven days after the first test) of each subject after enrollment, the control group used vacuum blood collection vessels to collect 3 - 5 ml of venous blood during the nucleic acid physical examination of a novel coronavirus, and stored, transported, and standardized the samples according to the "novel coronavirus infected pneumonia hospital infection prevention and control technology". Centrifuge at 3500 rpm for 15 min, and determine SARS-COV-2 IgM antibody, and IgG antibody according to the reagent instructions of three methods: chemiluminescence method, colloidal gold antibody method, and immunofluorescence chromatography. Collect laboratory data and statistics-related indicators, and conduct a comparative study of several detection methods. Equipment, reagents, and judgment criteria: Zhengzhou Antu SARS-COV-2 IgG IgM antibody (chemiluminescence method) reagent is positive based on the instrument result ≥1 S/CO, and the SARS-COV-2 IgG, IgM antibody (colloidal gold method) reagent provided by Guilin University of Electronic Science and Technology determines the IgG, IgM antibody results visually based on the instructions. Guangzhou Wanfu SARS-COV-2 IgG, IgM antibody (immunofluorescence chromatography) reagent detects IgG According to the IgM antibody results,All test results were divided into-, + and + +, where-was interpreted as negative, + and + + were interpreted as positive.

2.3. Statistical Methods

SPSS 26.0 was used for statistical analysis, percentage was used to represent counting data, and $\overline{X} \pm S$ was used to represent measurement data, chi-square test and Lsd-t test were used to analyze the differences between groups in counting and measurement data; Using RT PCR and imaging testing as the gold standard for diagnostic evaluation, the ROC curve was drawn to analyze the value of each index in predicting COVID-19; Kappa method was used to determine the consistency of each index. Among them, 0.8 - 1.0 was judged as strong consistency, 0.6 - 0.8 was judged as high consistency, 0.4 - 0.6 was judged as moderate

consistency, 0.2 - 0.4 was judged as weak consistency, and 0 - 0.2 was judged as weak consistency. $P < 0.05$ indicated that the results were statistically significant.

3. Results

3.1. Different Methods to Evaluate the Results of IgM Test Results

The results of this study showed that the positive rate of SARS-COV-2 IgM antibody detected by chemiluminescence, colloidal gold, and immunofluorescence chromatography after the first week of infection in patients was not higher than 60%. There was no significant difference in the positive rate of SARS-COV-2 IgM antibody detected by the three methods at the second, third, and fourth weeks of infection ($P > 0.05$), as shown in Figure 1.

3.2. Different Methods to Evaluate the Results of IgG Test Results

The results of this study showed that the positive rates of SARS-COV-2 IgG antibodies detected by chemiluminescence, colloidal gold, and immunofluorescence chromatography after the first week of infection in patients were not higher than 60%. There was no significant difference in the positive rates of SARS-COV-2 IgG antibodies detected by the three methods at the second, third, and fourth weeks of infection ($P > 0.05$), as shown in Figure 2.

3.3. IgM Results of Different Detection Methods at Different Time Points

The research results of this group show that when using the chemiluminescence method, colloidal gold method, and immunofluorescence chromatography to detect SARS-COV-2 IgM *in vivo*, the AUC diagnosed by the test results at the first week was lower than 0.80, and its diagnostic efficacy was relatively low. At the fourth week, the diagnostic efficacy of the three methods was higher than 0.97, with comparable diagnostic efficacy. See Table 1 and Figure 3 for details.

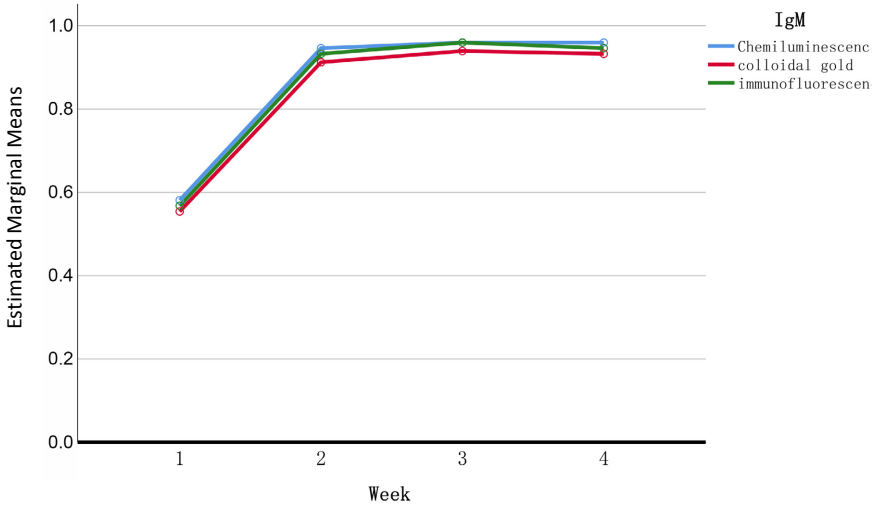

Figure 1. Test results of different methods for evaluating SARS-COV-2 IgM.

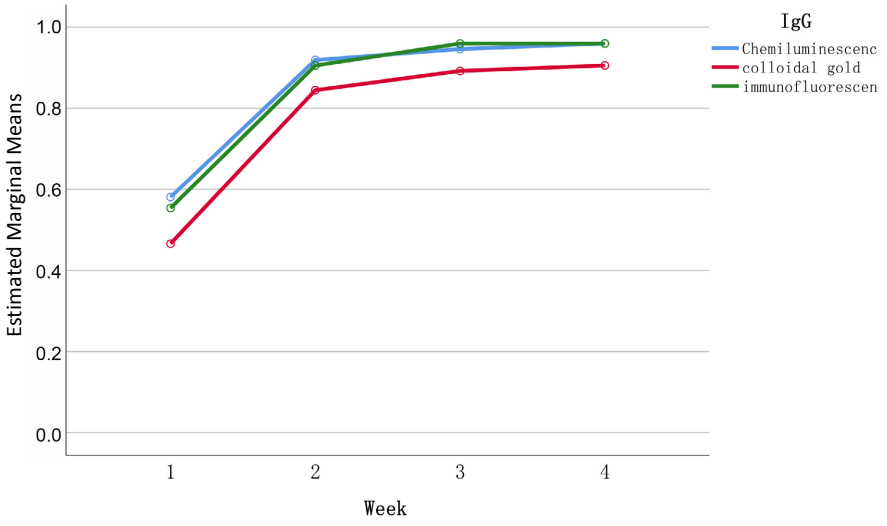

Figure 2. Test results of different methods for evaluating SARS-COV-2 IgG.

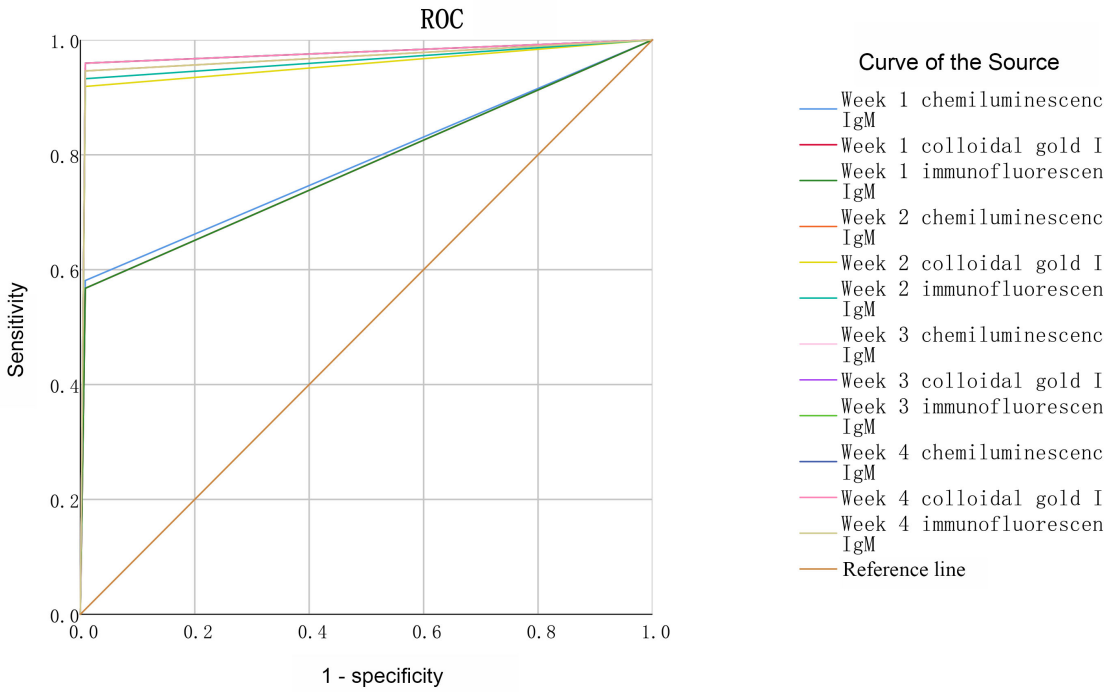

Figure 3. Test results of SARS-COV-2 IgM antibodies by various methods.

3.4. IgG Detection Results of Different Detection Methods at Different Time Points

The research results of this group showed that when using the chemiluminescence method, colloidal gold method, and immunofluorescence chromatography to detect SARS-COV-2 IgG *in vivo*, the AUC diagnosed by the test results at the first week was lower than 0.80, with a relatively low diagnostic efficiency. At the fourth week, the diagnostic efficiency of the three methods was higher than 0.97, with comparable diagnostic efficiency. See **Table 2** and **Figure 4** for details.

Table 1. Results of SARS-COV-2 IgM detection at different time points using different detection methods.

Time	Methodology	AUC	SE	P	95% CI	
					lower limit	upper limit
Week 1	chemiluminescence	0.786	0.037	<0.001	0.714	0.859
	colloidal gold	0.779	0.037	<0.001	0.706	0.852
	immunofluorescence	0.779	0.037	<0.001	0.706	0.852
Week 2	chemiluminescence	0.969	0.016	<0.001	0.938	0.999
	colloidal gold	0.955	0.019	<0.001	0.918	0.992
	immunofluorescence	0.962	0.017	<0.001	0.928	0.996
Week 3	chemiluminescence	0.975	0.014	<0.001	0.948	1.000
	colloidal gold	0.975	0.014	<0.001	0.948	1.000
	immunofluorescence	0.975	0.014	<0.001	0.948	1.000
Week 4	chemiluminescence	0.975	0.014	<0.001	0.948	1.000
	colloidal gold	0.975	0.014	<0.001	0.948	1.000
	immunofluorescence	0.969	0.016	<0.001	0.938	0.999

Table 2. Results of SARS-COV-2 IgG detection at different time points using different detection methods.

time	Methodology	AUC	SE	P	95% CI	
					lower limit	upper limit
Week 1	chemiluminescence	0.784	0.037	<0.001	0.712	0.856
	colloidal gold	0.764	0.038	<0.001	0.689	0.838
	immunofluorescence	0.773	0.038	<0.001	0.699	0.846
Week 2	chemiluminescence	0.953	0.019	<0.001	0.916	0.990
	colloidal gold	0.946	0.020	<0.001	0.906	0.986
	immunofluorescence	0.948	0.020	<0.001	0.909	0.988
Week 3	chemiluminescence	0.966	0.016	<0.001	0.935	0.998
	colloidal gold	0.960	0.018	<0.001	0.925	0.994
	immunofluorescence	0.975	0.014	<0.001	0.948	1.000
Week 4	chemiluminescence	0.973	0.014	<0.001	0.946	1.000
	colloidal gold	0.966	0.016	<0.001	0.935	0.998
	immunofluorescence	0.975	0.014	<0.001	0.948	1.000

3.5. Consistency Analysis of IgM and IgG Detected by Three Methods

The results of this group of studies show that the chemiluminescence method, immunofluorescence chromatography, and colloidal gold antibody methods showed high consistency when detecting SARS-COV-2 IgM and IgG in the first, second, third, and fourth weeks. See Table 3 and Table 4 for details.

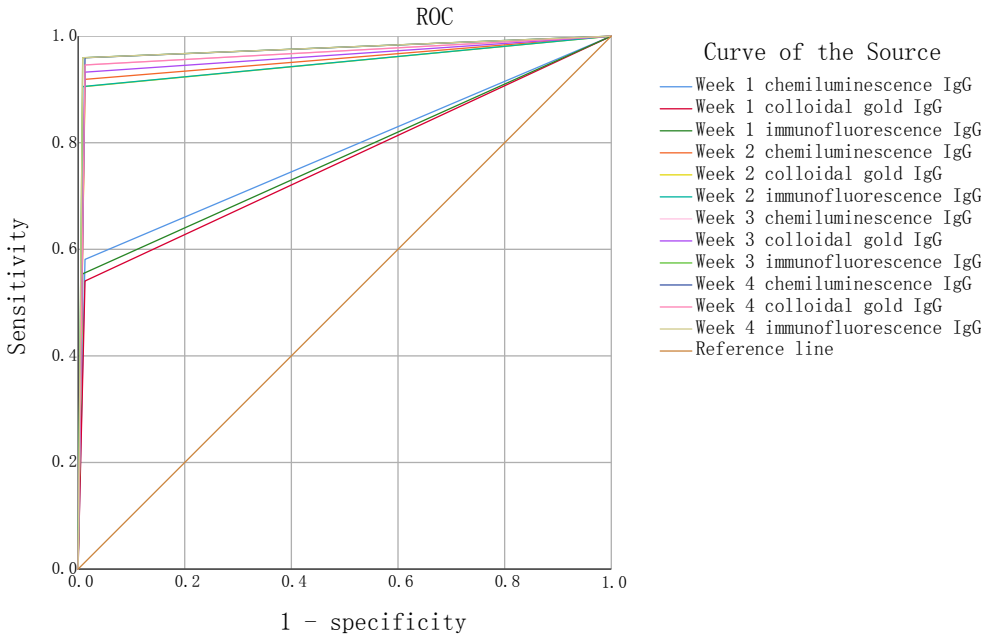

Figure 4. Detection results of SARS-COV-2 IgG antibodies by various methods.

Table 3. Consistency analysis of three methods for detecting SARS-COV-2 IgM at different time points.

time	Methodology	Kappa	P
Week 1	chemiluminescencevs immunofluorescence	0.685	<0.05
	chemiluminescencevscolloidal gold	0.662	<0.05
	immunofluorescencevscolloidal gold	0.674	<0.05
Week 2	chemiluminescencevs immunofluorescence	0.623	<0.05
	chemiluminescencevscolloidal gold	0.685	<0.05
	immunofluorescencevscolloidal gold	0.663	<0.05
Week 3	chemiluminescencevs immunofluorescence	0.643	<0.05
	chemiluminescencevscolloidal gold	0.654	<0.05
	immunofluorescencevscolloidal gold	0.617	<0.05
Week 4	chemiluminescencevs immunofluorescence	0.602	<0.05
	chemiluminescencevscolloidal gold	0.697	<0.05
	immunofluorescencevscolloidal gold	0.615	<0.05

4. Discussions

COVID-19 is a disease caused by SARS-COV-2 infection that is generally susceptible to infection in the population, with respiratory symptoms, fever, dry cough, and fatigue as the main clinical manifestations [7]. The gold standard for clinical diagnosis of COVID-19 is the RT-PCR method for detecting viral nucleic acids. However, due to factors such as sampling quality, sample type, storage and submission method, nucleic acid detection window period, and reasons inherent in the technology itself, the detection method may have false negatives or

Table 4. Consistency analysis of three methods for detecting SARS-COV-2 IgG at different time points.

time	Methodology	Kappa	P
Week 1	chemiluminescencevs immunofluorescence	0.692	<0.05
	chemiluminescencevscolloidal gold	0.711	<0.05
	immunofluorescencevscolloidal gold	0.684	<0.05
Week 2	chemiluminescencevs immunofluorescence	0.689	<0.05
	chemiluminescencevscolloidal gold	0.691	<0.05
	immunofluorescencevscolloidal gold	0.677	<0.05
Week 3	chemiluminescencevs immunofluorescence	0.609	<0.05
	chemiluminescencevscolloidal gold	0.637	<0.05
	immunofluorescencevscolloidal gold	0.628	<0.05
Week 4	chemiluminescencevs immunofluorescence	0.667	<0.05
	chemiluminescencevscolloidal gold	0.616	<0.05
	immunofluorescencevscolloidal gold	0.664	<0.05

false positives [8], leading to misdiagnosis of COVID-19 infection, which has an impact on the disease diagnosis, prevention, and control. There is an urgent need for other detection methods that can compensate for the misdiagnosis of nucleic acids in clinical practice, therefore, various institutions are exploring new methods to diagnose COVID-19 infection [9]. In the Diagnosis and Treatment Plan for Pneumonia Infected by novel coronavirus (Tentative Seventh Edition), the importance of antibody detection was pointed out. Some studies also pointed out that SARS-COV-2 antibody detection can effectively compensate for the risk of nucleic acid detection omission, and it has a certain complement or synergy as the basis for the diagnosis, clinical diagnosis and treatment of suspected and positive patients, and the discharge of patients [10].

Samples for antigen-antibody serological testing are derived from peripheral blood, serum, or plasma samples. Their collection and preservation are simple and easy, and the stability of antibodies in serum samples is good, making them a good detection indicator. Currently, SARS-COV-2 antibodies are mainly detected using colloidal gold antibody detection technology, chemiluminescence assay, immunofluorescence chromatography, and other detection methods. The principle is to mainly detect SARS-COV-2 specific antibodies, IgM, IgG antibodies, or total antibodies produced after the virus enters the body. Most of them target S and/or N proteins as antigens [11]. Although the colloidal gold antibody detection technology has the characteristics of simple operation, no need for special instruments, no need for special training operations, intuitive detection results, and convenient for grassroots units and on-site use, there are significant differences between colloidal gold batches, low sensitivity, unstable markers, easy to misjudge by naked eye observation, and sample factors can lead to more false positives and false negatives [12]. Chemiluminescence method has lower re-

quirements in terms of acquisition difficulty, detection operation, detection time, and experimental requirements compared to nucleic acid detection, and have better repeatability and sensitivity than the serum colloidal gold antibody method. However, it is suitable for units that already have a detectable antibody chemiluminescence instrument. If there is no equipment, it requires a large amount of investment to purchase [13]. Using small detection equipment, immunofluorescence chromatography can achieve daily bedside detection. Its repeatability and sensitivity are better than the colloidal gold antibody method, but lower than the chemiluminescence method. Its performance is between the colloidal gold method and chemiluminescence method [14] [15]. Compared to nucleic acid testing, antibody testing has significant advantages, breaking through the limitations of nucleic acid testing technology on the site and operators. As a good complement or collaboration for nucleic acid testing, medical and health institutions at all levels can purchase legal reagents from various parties according to their own conditions, achieving rapid and accurate screening of suspected patients and the forward and downward movement of diagnosis, providing a favorable basis for disease prevention and control, disease screening, and clinical diagnosis, Effectively reducing economic and social burdens [16] [17].

The results of this study show that the three detection methods of SARS-COV-2 IgM and IgG using chemiluminescence, immunofluorescence chromatography, and colloidal gold antibody detection and evaluation have high consistency. The positive rate in the first week of infection is not high. Considering that after the body is infected with the virus, the immune tissue of the body performs the defense, and the production of antibodies in the peripheral blood requires a period of time, that is, a window period. At the same time, due to the regularity of antibody production, the earliest generation of IgM antibodies can be used for early infection diagnosis, while the later occurrence of IgG indicates mid to late infection or previous infection, with slight differences. Therefore, there is a slight difference in missed detection and the positive rate of the two antibodies [18]. Although the positive coincidence rate is not high, it still has a certain effect in screening patients with latent infection or patients with low viral content. The positive rate of the infected person increases within the second week, considering that the content of antibody increases sharply, the positive rate will increase accordingly; the positive coincidence rate of the infected person in the third week is high, but it does not reach 100% diagnosis, due to differences in individual bias, reagent sensitivity, and antigen specificity; The positive rate of infected persons decreased in the fourth week. Considering that some patients were cured and the virus cleared, the antibody began to decrease, which also indicates that antibody detection is of great significance for infection monitoring [19]. Among the 231 cases of nucleic acid negative medical staff in our hospital who were not vaccinated with a novel coronavirus vaccine, there were 3 cases of false positives. Among them, one person was vaccinated with hepatitis B immunoglobulin, one person was vaccinated with rabies virus vaccine, and one person was vaccinated with influenza vaccine. Whether it was the vaccine effect

that caused the false positive [20], or the presence of autoantibodies, heterophilic antibodies, or special substances that could easily lead to the occurrence of false positive detection [21].

This study is subject to various limitations of research conditions, which are difficult to avoid. Firstly, the number of samples is limited, and the number of cases may have an impact on the accuracy of the analysis results; secondly, this study is a cross-sectional study without tracking the antibody data of patients. When analyzing the dynamic changes of antibody levels in patients at different onset times, it may be inaccurate; thirdly, the healthy population failed to conduct accurate epidemiological surveys, and the issue of false positives could not be fully explained without detailed research; finally, only one reagent were used for each methodology, making it necessary to further conduct carefully designed large-scale validation tests. The spread of SARS-COV-2 has had a significant impact. The results of this study may provide useful information for the diagnosis, treatment, and control of COVID-19, which needs further research and analysis.

5. Conclusion

In summary, using chemiluminescence, immunofluorescence chromatography, and colloidal gold antibody methods to detect SARS-COV-2 IgM and IgG antibodies in different patients has no significant difference in the detection rate of the three detection methods, and there is no significant difference in the auxiliary diagnosis of SARS-COV-2 nucleic acid detection. In the initial stage of infection, it is advisable to use multiple methods to screen patients. After two weeks of infection, the three reagents are used for auxiliary diagnosis and curative effect observation of the course of disease, all of which have good significance.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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