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RESEARCH ARTICLE

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Diagnostic efficacy of anti-SARS-CoV-2 IgG/IgM test for COVID-19: A meta-analysis

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Abstract

The serological testing of anti-SARS-CoV-2 immunoglobulin G (IgG) and/or IgM is widely used in the diagnosis of COVID-19. However, its diagnostic efficacy remains unclear. In this study, we searched for diagnostic studies from the Web of Science, PubMed, Embase, CNKI, and Wanfang databases to calculate the pooled diagnostic accuracy measures using bivariate random-effects model meta-analysis. As a result, 22 from a total of 1613 articles, including 2282 patients with SARS-CoV-2 and 1485 healthy persons or patients without SARS-CoV-2, were selected for a meta-analysis. Pooled sensitivity, specificity, and area under curve of the summary receiver operator curve (SROC) were: (a) 0.85 (95% confidence interval [CI]: 0.79-0.90), 0.99 (95% CI: 0.98-1.00), and 0.99 (95% CI: 0.97-0.99) for anti-SARS-CoV-2 IgG and (b) 0.74 (95% CI: 0.65-0.81), 0.99 (95% CI: 0.97-1.00), and 0.95 (95% CI: 0.93-0.97) for IgM. A subgroup analysis among detection methods indicated the sensitivity of IgG and IgM using enzyme-linked immunosorbent assay were slightly lower than those using gold immunochromatography assay (GICA) and chemiluminescence immunoassay ($P > .05$). These results showed that the detection of anti-SARS-CoV-2 IgG and IgM had high diagnostic efficiency to assist the diagnosis of SARS-CoV-2 infection. And, GICA might be used as the preferred method for its accuracy and simplicity.

KEYWORDS
antibody, COVID-2019, diagnostic efficacy, SARS-CoV-2

1 | INTRODUCTION

The coronavirus, SARS-CoV-2, is now widely spreading over the world and has infected millions of people. It causes a low respiratory infection (COVID-19) pandemic. In some patients, it may lead to acute respiratory distress syndrome that contributes to most of the COVID-19 deaths. As of 18 May 2020, nearly five million people around the world have been diagnosed with SARS-CoV-2, and more than 300 000 people have died from serve COVID-19.[1] Timely diagnosis of SARS-CoV-2 infections and isolation of infected persons and close contacts remain priorities and challenges of epidemic prevention.

The diagnosis of SARS-CoV-2 infections mainly depends on the detection of SARS-CoV-2 nucleic acid (RNA) and SARS-CoV-2 immunoglobulin antibodies (IgM and/or IgG).[2] Detection of virus RNA by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) is considered as the golden criteria of diagnosis. However, RNA molecular detection suffers from many limitations[3]: (a) It requires expensive equipment and trained technicians in a certified laboratory, (b) it usually takes more than 2 hours to generate results, and (c) it carries the risk of false-negatives due to low viral loads in clinical specimens.[4] Serological testing of anti-SARS-CoV-2 IgG/IgM (has been used to diagnose illness, but its diagnostic efficacy remains unclear.[5] This study aims to summarize the diagnostic efficacy of the anti-SARS-CoV-2 IgG/IgM test in each study, the results of which can assist in the diagnosis of SARS-CoV-2.

2 | MATERIALS AND METHODS

2.1 | Study registration

This meta-analysis was registered on PROSPERO (ID: CRD42020184771).

2.2 | Search strategy and eligibility criteria

We performed a systematic literature search in PubMed, Web of Science, Embase, CNKI (China), and Wanfang (China) databases and excluded duplicates with EndNote X9.0 software. The search terms used in PubMed were (severe acute respiratory syndrome coronavirus 2 OR Wuhan coronavirus OR Wuhan seafood market pneumonia virus OR COVID19 virus OR COVID-19 virus OR coronavirus disease 2019 virus OR SARS-CoV-2 OR SARS2 OR 2019-nCoV OR 2019 novel coronavirus) AND (antibody OR IgG OR IgM OR immunoglobulin). The searches were limited to articles published in Chinese or English in 2020. To reduce literature omissions, we checked the reference lists of the included studies.

We defined the eligibility criteria as follows: (a) numbers of true-positives (TP), false-positives (FP), true-negatives (TN), and false-negatives (FN) were available, (b) RT-PCR test for SARS-CoV-2 virus nucleic acids and anti-SARS-CoV-2 IgG and/or IgM test were performed. Case reports, review articles, and meta-analysis articles were excluded.

Two reviewers independently performed the literature search and screened the titles, abstracts, and full texts according to the eligibility criteria. Disagreements were resolved with a third reviewer or by consensus. All the eligibility studies were selected for meta-analysis. The steps of the literature search are shown in Figure S1.

2.3 | Quality assessment and risk of bias

Two reviewers assess the quality of studies enrolled in this study using QUADAS-2, a tool for quality assessment of diagnostic accuracy studies,[6] to assess the risk of bias. We assessed statistical heterogeneity and publication bias using the I^2 statistic, Q test, and Deeks' test, respectively. Deeks' funnel plots were drawn to evaluate the risk of publication bias.

2.4 | Data extraction and meta-analysis

The two reviewers who performed the literature search also independently extracted the data from the enrolled studies using a predefined data extraction form. The variables extracted from the selected studies included author, blood collection time from symptom onset, type of anti-SARS-CoV-2 (IgG or IgM), methods of antibody detection, TP, FP, TN, and FN.

2.5 | Statistical analysis

We performed a meta-analysis by the "meta4diag" package (version 2.0.8) in R soft (version 3.6.2) and "Midas" modules in the STATA statistical software (version 14.0). A bivariate random-effects model was employed for estimating the pooled diagnostic performance measures and a 95% confidence interval (CI).

3 | RESULTS

3.1 | Search results

A total of 1613 articles were identified from the Web of Science, PubMed, Embase, CNKI (China), Wanfang (China), and other sources. After we removed duplicates and screened all the search records, 22 studies[3,7-27] meeting the predetermined inclusion and exclusion criteria were enrolled in this study for a meta-analysis. As shown in Table 1, a total of 3767 individuals were included in this meta-analysis, including 2282 patients with SARS-CoV-2 and 1485 healthy persons or patients without SARS-CoV-2. Their age-bracket and sex ratio were not available in each included study.

3.2 | Quality assessments

We evaluated the quality of the 22 included studies according to QUADAS-2 guidelines. Bias in each study was assessed as "low risk of bias," "high risk of bias," and "unclear risk of bias." As shown in Figure 1, 95.45% (21 of 22) for patient selection, 36.36% (8 of 22) for index test, 13.64% (3 of 22) for flow and timing, and 4.55% (1 of 22) for reference standard showed a high risk of bias. Subjects in most of the included studies (95.45%, 21 of 22) were composed of patients with SARS-CoV-2 and healthy persons or patients without SARS-CoV-2 without "difficult to diagnose" patients, which did not avoid case-control design and inappropriate exclusions and contributed to the high risk of bias in terms of patient selection. For the index test, 36.36% (8 of 22) studies were classified as high risk of bias mainly because they were retrospective studies, and the IgG/IgM test results were interpreted with knowledge of the RT-PCR results not meeting the "blinding" criteria. The risk of the reference standard and flow and time bias was relatively low. Some studies did not declare aspects related to study design (ie, intervals between serologic test and RT-PCR), which limits the ability to conclude on study quality.

3.3 | Heterogeneity

The P values of the Q test were all less than .01, accompanied by $I^2 > 50\%$. The I^2 ranging from 69.85% to 93.52% in the evaluation of anti-SARS-CoV-2 IgG and/or IgM showed the heterogeneity of the statistical significance.

TABLE 1 The main features of the included studies for anti-SARS-CoV-2 IgG/IgM in the diagnosis of COVID-19

No.	Author	Number (cases/controls)	Days[a]	Study type	Cases	Controls	Method
1	Dohla et al[7]	22/27	19 (IQR: 15-24)	Prospective	PCR+	PCR−	GICA
2	Hoffman et al[8]	28/125	Range 9-29	Retrospective	PCR+	Healthy persons	GICA
3	Infantino et al[9]	30/63	12 (range 8-17)	Retrospective	PCR+	Patients without SARS-CoV-2 and healthy persons	CLIA
4	Jin et al[10]	27/33	16 (IQR: 9-20)	Retrospective	PCR+	PCR−	CLIA
5	Li et al[3]	397/128	Range 8-33	Retrospective	PCR+, clinical feathers	Patients without SARS-CoV-2	GICA
6	Liu et al[11]	214/100	15 (range 0-55)	Retrospective	PCR+	PCR−	ELISA
7	Pan et al[12]	86/22	Range 0-34	Retrospective	PCR+	PCR−	GICA
8	Qu et al[13]	41/38	Range 3-43	Retrospective	PCR+	Patients without SARS-CoV-2	CLIA
9	Shen et al[14]	97/53	Range 0-28	Retrospective	PCR+	PCR− and healthy persons	GICA
10	Spicuzza et al[15]	23/14	Range 3-34	Retrospective	PCR+	PCR−	GICA
11	Xiang et al[16]	90/60	Range 13-29	Retrospective	PCR+ and clinical feathers	Healthy persons	ELISA
12	Bao et al[17]	179/100	37 (range, 9-62)	Retrospective	PCR+	Healthy persons	GICA
13	Deng et al[18]	32/44	…	Retrospective	PCR+	PCR−	GICA
14	Li et al[19]	116/134	…	Retrospective	PCR+	PCR−	CLIA
15	Liang et al[21]	236/59	…	Retrospective	PCR+	Healthy persons	GICA
16	Li et al[20]	25/60	Convalescence	Retrospective	PCR+	PCR−	CLIA
17	Luo et al[22]	101/54	…	Retrospective	PCR+ and clinical feathers	PCR−	GICA
18	Tang et al[23]	113/27	25 (range, 3-47)	Retrospective	PCR+ and clinical feathers	Patients without SARS-CoV-2	CLIA
19	Xiong et al[24]	97/100	…	Retrospective	PCR+	PCR−	CLIA and ELISA
20	Xu et al[25]	205/79	…	Retrospective	PCR+ and clinical feathers	Patients without SARS-CoV-2	CLIA
21	Zhang et al[26]	105/138	…	Retrospective	PCR+ and clinical feathers	PCR− and healthy persons	GICA
22	Zheng et al[27]	25/20	…	Retrospective	PCR+	PCR−	CLIA and GICA

Note: Only the first author of each study is given.
Abbreviations: PCR+, PCR positive; PCR−, PCR negative; GICA, gold immunochromatography assay; CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; IgG, immunoglobulin G; IgM, immunoglobulin M.
[a]Days between the collection of blood samples and the symptom onset.

3.4 | Diagnostic performance

The result of this bivariate random-effects meta-analysis is shown in Figure 2. The sensitivity and specificity was 0.85 (95% CI: 0.79-0.90) and 0.99 (95% CI: 0.98-1.00) for anti-SARS-CoV-2 IgG, 0.74 (95% CI: 0.65-0.81) and 0.99 (95% CI: 0.97-1.00) for IgM, and 0.86 (95% CI: 0.79-0.92) and 0.99 (95% CI: 0.97-1.00) for IgG or IgM.

Summary receiver operator characteristic (SROC) curves were generated to indicate the overall diagnostic accuracy. The area under the SROC curve (AUC) was 0.99 (95% CI: 0.97-0.99) for anti-SARS-CoV-2 IgG, 0.95 (95% CI: 0.93-0.97) for IgM, and 0.98 (95% CI: 0.96-0.99) for IgG or IgM (Figure 3). Pooled diagnostic odds ratio, positive likelihood ratio, and negative likelihood ratio are shown in Table 2.

3.5 | Subgroup analyses

In the selected studies, the detection methods of anti-SARS-CoV-2 IgG and IgM included gold immunochromatography assay (GICA), chemiluminescence immunoassay (CLIA), enzyme-linked

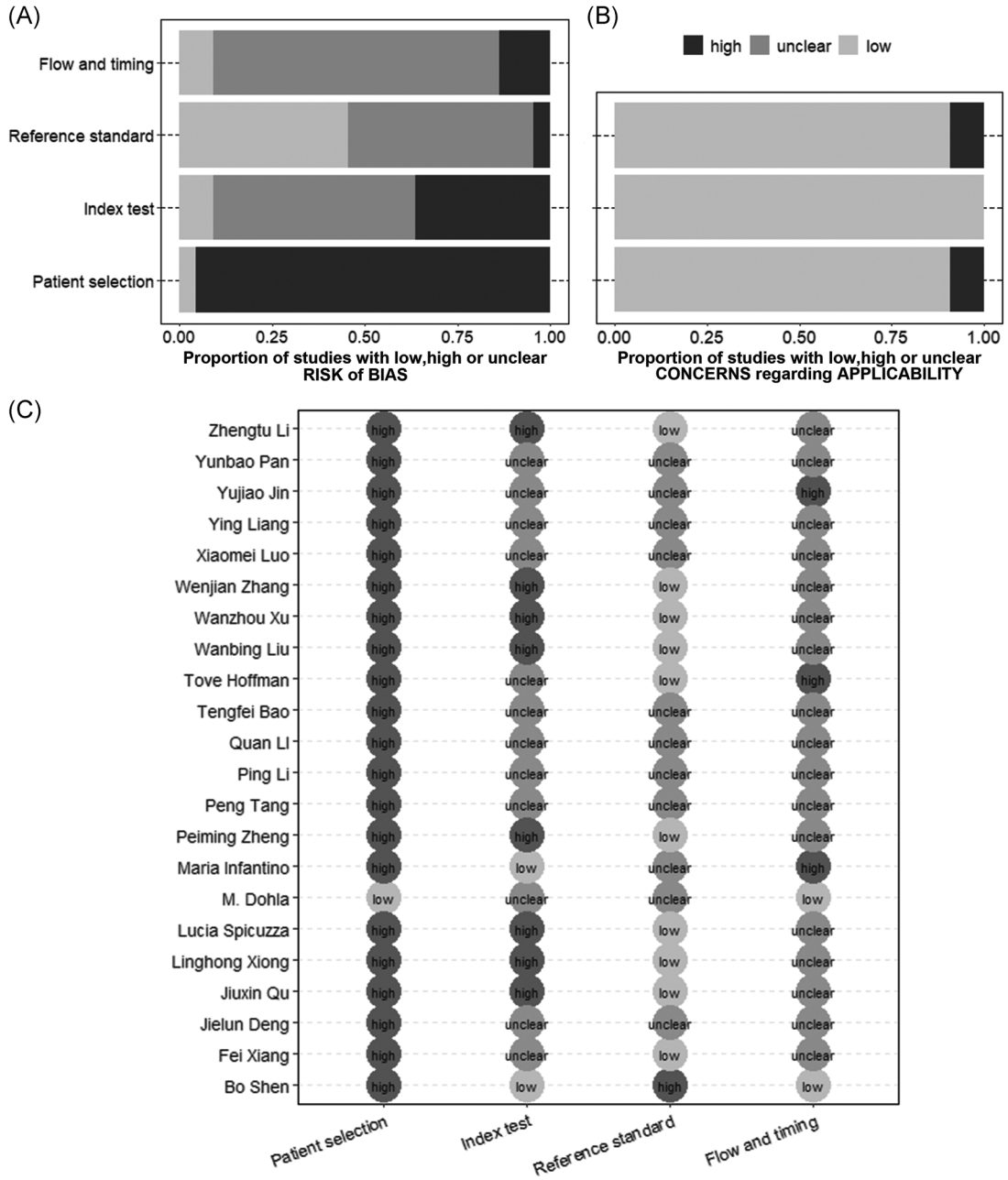

FIGURE 1 Study quality assessment using modified QUADAS-2. (a) Risk of bias. (b) Concerns regarding applicability. (c) Details of quality assessment

immunosorbent assay (ELISA). We performed subgroup analyses among these three groups. The results showed that the sensitivity of IgG and IgM using ELISA were lower than those using GICA or CLIA. However, the meta-regression analysis results showed that no significant differences in sensitivity and specificity were observed among these groups ($P > .05$) (Table 3). Additionally, the I^2 for the sensitivity of IgG, IgM, and IgG/IgM in the subgroup analyses were more than 50%. And the I^2 for the specificity of IgG using CLIA (0%) and IgG or IgM using GICA (23.78%) declined significantly.

3.6 | Influence analysis

As shown in Figure S2, we generated crosshair plots and performed influence analysis to identify outliers. Two study[3,11] in the meta-analysis of IgG were identified as outliers. After excluding the outliers, the overall pooled sensitivity of IgG slightly increased from 0.85 to 0.87, specificity and AUC did not change. Moreover, the I^2 for sensitivity and specificity slightly declined from 93.52% and 69.85% to 90.53% and 66.63%, respectively. These results suggested that the outliers contributed a little heterogeneity in this meta-analysis.

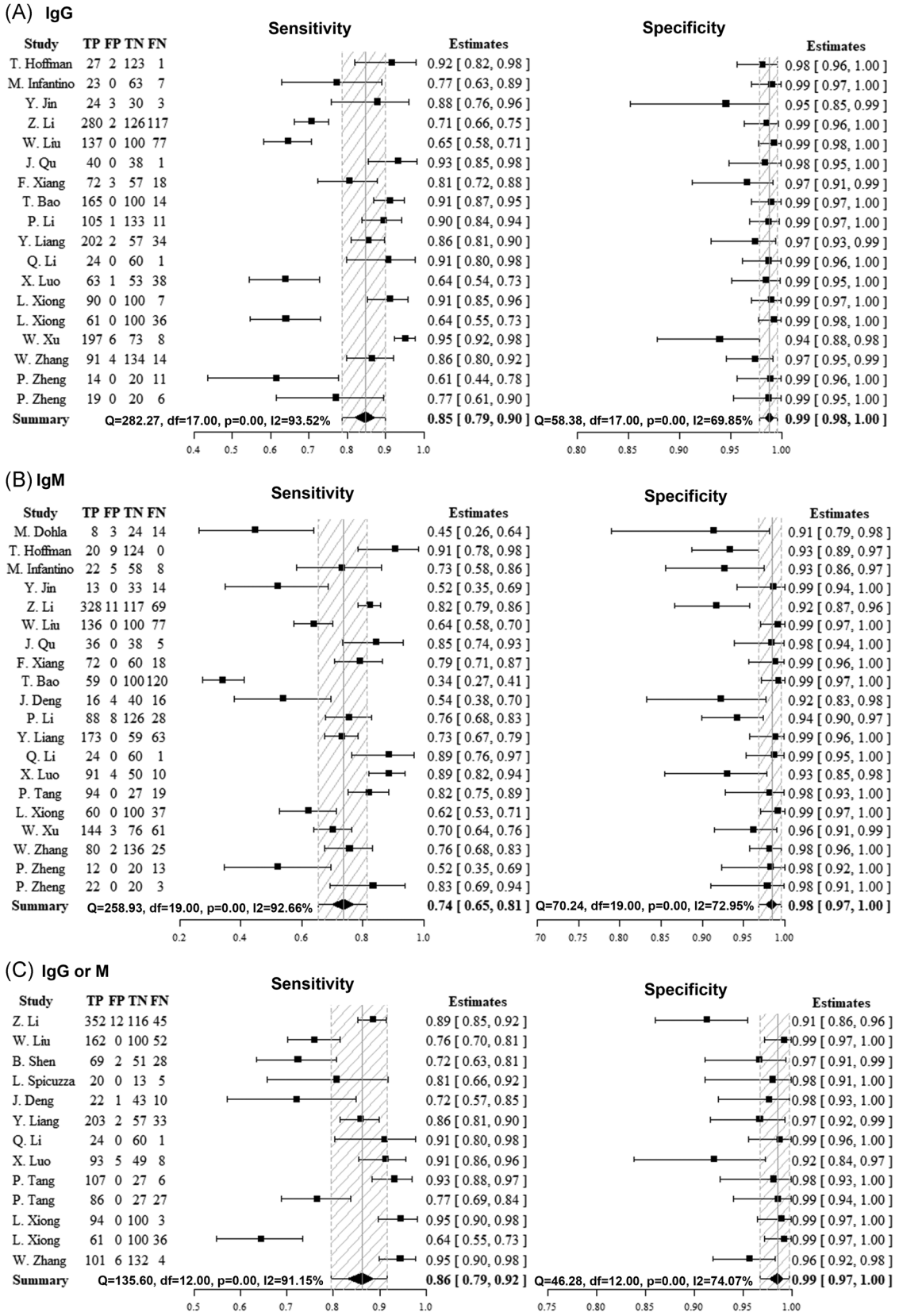

FIGURE 2 Forest plots of the pooled sensitivity and specificity for anti-SARS-CoV-2 immunoglobulin G (IgG), IgM, and IgG or IgM in diagnosis of COVID-19. (a) IgG. (b) IgM. (c) IgG or IgM. Only the first author of each study is given. Sensitivity and specificity were given with confidence intervals (CI)

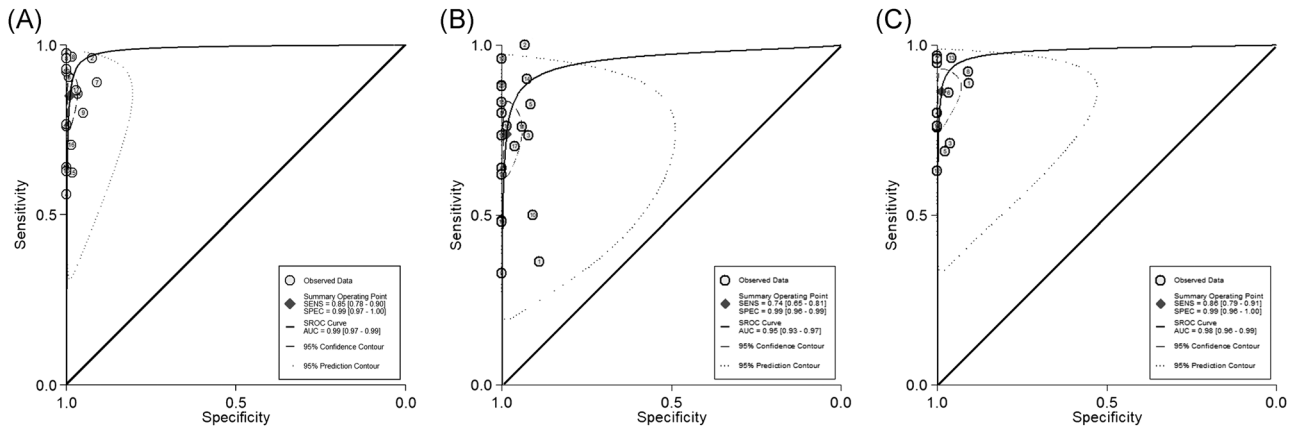

FIGURE 3 The SROC curves of the serological testing of anti-SARS-CoV-2 antibodies. The regression SROC curve indicates the overall diagnostic accuracy. (a) IgG, (b) IgM, (c) IgG or IgM. AUC, area under the curve; IgG, immunoglobulin G; IgM, immunoglobulin M; SENS, sensitivity; SPEC, specificity; SROC, summary receiver operator curve

3.7 | Publication bias

Deeks' funnel plot asymmetry test was used to evaluate the publication bias of the included studies. The results indicated that there was no obvious publication bias in this meta-analysis ($P > .05$) (Figure S3).

4 | DISCUSSION

Serological testing of anti-SARS-CoV-2 IgG/IgM has been widely used to diagnose SARS-CoV-2 infection. However, the diagnostic efficacy of the serum antibody test reported in the earlier studies confused the clinician. The sensitivities of IgG and IgM ranged from 0.61[27] and 0.34[17] to 0.93[13] and 0.91,[8] respectively. And, there was no significant difference in the specificities of IgG and IgM among the studies. Therefore, a broad summary analysis of the diagnostic efficacy of anti-SARS-CoV-2 IgG and IgM is significantly necessary to assist in the diagnosis of SARS-CoV-2. As of 10 May 2020, 22 studies published in Chinese or English were selected in this study. A total of 2282 patients with SARS-CoV-2 and 1485 controls were included in our meta-analysis. In this unusual and urgent situation, most of the included studies were retrospective and did not meet the QUADAS guidelines well, but a summary meta-analysis from the studies still had significantly reference value for the diagnosis of SARS-CoV-2.[28]

This meta-analysis results showed promising accuracy for IgG detection in diagnosing SARS-CoV-2, in which the pooled sensitivity was 0.85 and specificity was 0.99, with an AUC of 0.99. The pooled diagnostic performance of IgM was slightly lower than those of IgG, with a sensitivity of 0.74 and an AUC of 0.95. Additionally, combining the IgG and IgM test did not obtain a higher diagnostic accuracy than single IgG. Subgroup analysis among groups with different detection methods demonstrated that the diagnostic efficacy of the antibody test by ELISA was slightly lower than that by CLIA and GICA ($P > .05$). Taking the principles of accuracy and simplicity into consideration, we commented that GICA was the preferred method. A meta-analysis of diagnostic test accuracy of the anti-SARS-CoV-2 IgG/IgM test was performed in Brazil,[29] in which the pooled sensitivity of IgG and IgM (0.97 and 0.82) were all higher than those in our meta-analysis (0.85 and 0.74). As our analysis contained more studies (22 vs 11) and patients, it is more accurate than the previous report.

Researchers have demonstrated the longitudinal change of anti-SARS-CoV-2 IgG/IgM in patients with SARS-CoV-2. Anti-SARS-CoV-2 IgM appeared in the blood and could be initially detected after 5 days (interquartile range [IQR]: 3-6) of symptom onset,[30] and lasted for 1 month and gradually decreased.[31] And the median duration of IgG antibody detection was 14 days (IQR: 10-18)[30] and lasted for a longer time.[31] These results suggested that the test of the serum antibodies was exceedingly helpful for the diagnosis of SARS-CoV-2 after the corresponding window periods. In particular, the detection

TABLE 2 Summary table of the diagnostic accuracy of IgG, IgM, and IgG/IgM for SARS-CoV-2 infection

	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	LRpos (95% CI)	LRneg (95% CI)	AUC (95% CI)
IgG	0.85 (0.79-0.90)	0.99 (0.98-1.00)	592.62 (226.79-1634.34)	88.32 (38.48-229.57)	0.15 (0.10-0.22	0.99 (0.97-0.99)
IgM	0.74 (0.65-0.81)	0.99 (0.97-1.00)	278.12 (76.02-1029.37)	71.41 (22.09-259.48)	0.27 (0.18-0.36)	0.95 (0.93-0.97)
IgG/IgM	0.86 (0.79-0.92)	0.99 (0.97-1.00)	777.53 (161.26-3478.47)	104.14 (24.99-456.71)	0.14 (0.08-0.22)	0.98 (0.96-0.99)

Abbreviations: AUC, area under the curve; CI, confidence interval; DOR, diagnostic odds ratio; IgG, immunoglobulin G; IgM, immunoglobulin M; LRpos, positive likelihood ratio; LRneg, negative-positive likelihood ratio.

TABLE 3 The pooled sensitivity and specificity of subgroup meta-analyses and meta-regression

Antidody	Test method (*n*)	I^2 (%)	Sensitivity (95% CI)	*P* value	I^2 (%)	Specificity (95% CI)	*P* value
IgG	GICA (7)	87.09	0.83 (0.73, 0.90)	.07	77.27	0.99 (0.96, 1.00)	.71
	CLIA (8)	93.16	0.90 (0.84, 0.95)		0	0.99 (0.97, 1.00)	
	ELISA (3)	…	0.69 (0.48, 0.85)		…	0.99 (0.96, 1.00)	
IgM	GICA (9)	96.54	0.74 (0.60, 0.85)	.93	76.97	0.97 (0.93, 0.99)	1.00
	CLIA (9)	81.24	0.74 (0.60, 0.85)		63.67	0.99 (0.97, 1.00)	
	ELISA (2)	…	0.71 (0.40, 0.91)		…	1.00 (1.00, 1.00)	
IgG/IgM	GICA (8)	85.30	0.84 (0.78, 0.90)	.06	23.78	0.95 (0.93, 0.98)	1.00
	CLIA (3)	…	0.96 (0.91, 0.98)		…	1.00 (1.00, 1.00)	
	ELISA (2)	…	0.69 (0.50, 0.85)		…	1.00 (1.00, 1.00)	

Note: The *P* value was obtained comparing ELISA with GILA and CLIA.
Abbreviations: CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; GICA, gold immunochromatography assay; IgG, immunoglobulin G; IgM, immunoglobulin M.

efficiency of IgM was considered higher than that of the RT-PCR method after 5.5 days of symptom onset.[30] Moreover, another study showed that a higher titer of the antibody was highly associated with a worse clinical classification.[32]

However, the detection of anti-SARS-CoV-2 IgG/IgM for patients in window periods had low-diagnostic efficiency. And, the diagnostic efficiency of the serological antibody test in asymptomatic carriers was unclear. An earlier study showed that anti-SARS-CoV-2 IgG was positive in only 20% (1 of 5) asymptomatic carriers, and IgM was negative in all the five carriers.[33] And, a positive IgG was detected after 18 days of diagnosis with SARS-CoV-2 by RT-PCR. The sample size was relatively small, but it still indicated that the antibody test was not applicable to asymptomatic populations. Furthermore, there is no evidence for cases of SARS-CoV-2 reinfections in literature, but only patients with positive PCR test and IgM seroconversion several weeks after negative RT-PCR tests.[34] As the acquired immunity and the presence of anti-SARS-CoV-2 antibodies were thought to protect upon further exposure to SARS-CoV-2, the negative RT-PCR test was considered as a false-negative, which may result from reduced viral loads in convalescence, sampling errors during collection or transport.[35] And IgM seroconversion was considered deriving from an expansion of IgM+ memory B cells. There is currently no evidence to support the use of a specific antibody test to diagnose the reinfection of SARS-CoV-2. So, if any, I think that the diagnosis of reinfection may be based on symptoms, radiological imaging, leukocytes count, and inflammatory indexes alterations.[36]

4.1 | Limitations

This review has several limitations. First, none of the persons with cover, cough, and runny nose of unknown origin was enrolled in the studies. Controls in all the included studies were proven without SARS-CoV-2, leading to an exaggerated specificity. Second, this meta-analysis had high heterogeneity. The bivariate random-effects model was applied to weaken influences by heterogeneity. And also, we performed subgroup and sensitivity analysis to explore the source of heterogeneity. Finally, all the patients included in this analysis were first infected with SARS-CoV-2, and the diagnostic efficiency of the specific immunoglobulin for reinfection of SARS-CoV-2 is unclear.

5 | CONCLUSIONS

This meta-analysis showed that the detection of anti-SARS-CoV-2 IgG and IgM had high diagnostic efficiency to assist the diagnosis of SARS-CoV-2. It was suitable for patients with symptoms for at least 5 days.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Z-LZ and Y-LH formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript. F-ZL and D-TL refined the search strategy, searched, collected the articles, and then conducted quality assessment. All authors have read and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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