Seropositivity rate and diagnostic accuracy of serological tests in 2019-nCoV cases: a pooled analysis of individual studies

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Abstract. – OBJECTIVE: Currently, detection of SARS-CoV-2 RNA is standard in the diagnosis of COVID-19 (2019-nCoV). However, reliable and rapid serological diagnostic methods to screen SARS-CoV-2 infected patients, including those who do not have overt symptoms, are urgently needed. Most studies have described serological tests based on the detection of SARS-CoV-2-specific IgM and IgG. Here, we attempted to systematically analyze the positive rates and comprehensive diagnostic efficacy of IgM and IgG in response to SARS-CoV-2 infection.

MATERIALS AND METHODS: By systematically searching PubMed, medRxiv, bioRxiv and other databases, studies regarding the detection of peripheral blood IgM and/or IgG related to SARS-CoV-2 were collected. The positive rate, sensitivity (SEN), specificity (SPE), area under the curve (AUC) and corresponding 95% CIs were obtained by weighted quantitative mergence, and the source of heterogeneity was explored by performing a subgroup study and sensitivity analysis.

RESULTS: A total of 30 studies were included, which were comprised of 3856 confirmed SARS-CoV-2 RNA positive cases, 368 suspected RNA negative cases, 1167 asymptomatic carriers, and 2526 RNA negative controls. The corresponding meta-analysis showed that in confirmed cases with 2019-nCoV, the positive rates of single IgM, single IgG and their joint detection related to SARS-CoV-2 were 61.2% (95% CI: 53.4%-69.0%), 58.8% (95% CI: 49.6%-68.0%) and 62.1% (52.7%-71.4%), respectively. In suspected RNA negative cases, the positive rates of single IgM, single IgG and their joint detection were 29.0% (95% CI: 14.0%-44.0%), 37.0% (95% CI: 20.0%-55.0%) and 55.0% (95% CI: 19.0%-90.0%), respectively. Interestingly, IgM/IgG detection also demonstrated a positive rate of 19% (95% CI: 10.0%-27.0%) in asymptomatic cases. Using RT-PCR test as reference, the AUCs of IgM, IgG and IgM/IgG in the diagnosis of 2019-nCoV infection were 0.9656, 0.9766, and 0.9838, respectively. The stratified analyses showed that among confirmed cases with 2019-nCoV, the positive rates of IgM and IgG were 27.3% (95%CI: 19.8%-34.8%) and 22.3% (95% CI: 11.3%-33.3%), respectively, 0-7days following the onset of symptoms, whereas the positive rate of parallel IgM/IgG testing attained 39.3% (95% CI: 24.2%-54.4%). Moreover, the efficacy of antibody testing based on CLIA (chemiluminescence enzyme immunoassays) in diagnosing 2019-nCoV infection was higher than that of LFIA (lateral flow immunoassays) and ELISA (enzyme linked immunosorbent assay).

CONCLUSIONS: IgM, IgG and their joint testing exhibited high clinical value in the diagnosis of 2019-nCoV, which may assist in making up for the deficiency of throat swab RNA tests.

Key Words:

2019-nCoV, SARS-CoV-2, Antibody test, Positive rate, Diagnosis, Meta-analysis.

Introduction

COVID-19 pneumonia is a pulmonary infection caused by novel coronavirus infection (SARS-CoV-2) and is mainly transmitted by respiratory droplets with strong infectivity and herd susceptibility[1,2]. On 12 January 2020, WHO officially named 2019 novel coronavirus as 2019-nCoV, which shares similarities with severe acute respiratory syndrome-coronavirus (SARS CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), all of which are β-coronavirus[3]. Its genetic characteristics are significantly different from those of SARS-CoV and MERS-CoV, of which homology with bat SARS-like coronavirus (bat-SL-CoVZC45) is over 85%[4]. In addition, they are enveloped, round or oval, and are often polymorphous with a diameter of 50-200 nm[4].

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Currently, global prevention and control of COVID-19 are still not optimistic. On March 11, WHO held a regular press conference on COVID-19, announcing that the COVID-19 outbreak can be characterized as a pandemic. As of July 6, a total of 2,971,669 cases of atypical pneumonia were reported worldwide with more than 206,542 deaths. The United States, Brazil, India, the United Kingdom and Russia had the largest number of confirmed cases. Among them, the total number of confirmed cases in the United States exceeded 3,050,476 with over 133,125 deaths.

During this time, fluorescence quantitative PCR was used to detect 2019-nCoV RNA from throat swabs or other respiratory tract samples, especially for 2019-nCoV positive RNA from multiple specimens and multiple detection kits, which served as important supporting significance for its etiological diagnosis[5]. Nucleic acid detection may yield an early diagnosis, as well as high sensitivity and high specificity; however, it possesses various limitations: first, improper sampling, improper preservation of samples, the use of specimens with different types and the use of reagents from different manufacturers may cause false negatives in nucleic acid detection, thus causing missed diagnoses. Second, detection is time-consuming[6]. Antibody detection sampling, however, is relatively more convenient, and the sample is more stable; the operation is simple and fast, especially concerning the colloidal gold method, where results may be generally obtained after 15 min and observed with the naked eye[7]. However, antibody detection also has limitations. In the early stages of novel coronavirus infection, there may not be antibodies in the human body, and a window period for antibody detection is present[8]. Moreover, false negatives may occur if the sensitivity of the test kit is different; additionally, false positives may occur due to the presence of interfering substances within the sample, such as rheumatoid factor[9]. Therefore, the production and duration of SARS-CoV-2 antibodies have yet to be systematically explored. Accordingly, this study attempts to systematically evaluate the positive rate of antibody (IgM, IgG) detection in 2019-nCoV (including total positive rate, positive rate in nucleic acid negative samples, and positive rate detected in different time periods), as well as its comprehensive diagnostic efficiency through a quantitative meta-analysis in order to provide novel evidence for the clinical diagnosis and treatment of 2019-nCoV.

Materials and Methods

Data Search Strategy

The obtained online data included papers published in English on PubMed, medRxiv (https://medrxiv.org/), bioRxiv (https://medrxiv.org/), EMBASE published until July 1st, 2020. The following search words were used: "2019-nCoV OR SARS-CoV-2 OR COVID-19 OR coronavirus disease 2019" AND "IgM OR IgG OR antibody OR antibody OR rapid test OR serological test" OR "sensitivity OR specificity OR AUC OR ROC curve OR diagnosis OR diagnostic performance OR efficacy OR diagnostic value". Meanwhile, the references attached to the paper were retrieved manually so as to prevent omission in literature.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) the positive rate and/or diagnostic studies of SARS-CoV-2-related IgM and IgG detection in 2019-nCoV infected patients; (2) RT-PCR as the gold standard for case ascertainment was used in the study; (3) whole blood/serum/plasma was used as a detection matrix for antibodies(Abs) detection; and (4) true positive number (TP), false positive number (FP), false negative number (FN) and true negative number (TN) could be obtained directly or indirectly in the diagnostic study to construct a 2×2 four-fold table. Exclusion criteria: (1) the number of samples in the study was less than 10; (2) the data for statistical analysis were insufficient; and (3) the quality score of studies was low and the studies were not published in English.

Data Extraction

Two authors independently screened the related literature and extracted the following information: (1) basic information including the first author, publication year, research population, sample size, control type, SARS-CoV-2 RNA expression, Abs detection method, Abs type and combination form; and (2) the data extracted for statistical analysis including the number of antibody positive cases, total cases, TP, FP, FN, TN, SNE, SPE and 95% CI.

Quality Assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was used to evaluate the quality of literature[10]. The evaluation system included bias evaluation and applicability evaluation. Bias evaluation included four areas:

case selection, trials to be evaluated, gold standard, case process and progress. Applicability evaluation only included case selection, trials to be evaluated and gold standard. Each item corresponded to three evaluation results, namely, "low risk", "high risk" and "unknown", and the corresponding scores were "1 point", "0 point" and "0 point". When the total score was over 4 (the full score was 7), the quality of literature research was considered high.

Statistical Analysis

Stata 12.0 and MetaDiSc 1.4 software were used for the statistical analysis. The combined effect measures included the positive rate, SEN, SPE, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), AUC and 95% confidence interval (CI). The Spearman correlation coefficient of Meta-DiSc 1.4 software was used to evaluate the threshold effect, and $p < 0.05$ was considered to be statistically significant. The Cochran' Q test and I^2 test in Stata 12.0 were used to evaluate the non-threshold effect, and the statistical difference was set as $p < 0.01$ or $I^2 > 50\%$. When no heterogeneity existed among studies, the statistics were combined using the fixed effect model. When heterogeneity was present, the statistics were combined using the random effect model. The sources of heterogeneity were further explored by a sensitivity analysis and regression analysis. Publication bias was evaluated by Deek's quantitative funnel plot and visual funnel plot, and the difference level was set as $p < 0.05$.

Results

Literature Inclusion and Data Characteristics

By searching the online database according to the search strategy, 5118 related studies were obtained. According to the inclusion and exclusion criteria, 30 literatures (including 122 that were independent inter-group) were finally included for the subsequent meta-analysis[11-40]. The process detailing the literature inclusion and exclusion is shown in Figure 1, and the basic characteristics of the included literatures are shown in Table I. Accordingly, there were 3856 confirmed SARS-CoV-2 RNA positive patients, 368 suspected RNA negative cases, 1167 asymptomatic individuals and 2526 RNA negative controls. RT-PCR was used as reference for the diagnosis of 2019-nCoV infection. The study population was comprised of Asian and European populations, and the detection methods of Abs included CLIA, ELISA, LIFA and IFA (fluorescence immunoassays).

Research Heterogeneity and Bias Risk Assessment

The Spearman correlation coefficient analysis demonstrated no heterogeneity caused by the threshold effect among all analyses. Cochran's Q test and I^2 test were used to analyze the heterogeneity caused by the non-threshold effect, and the results are given in Tables II and III.

Risk and bias among the diagnostic study were assessed using the QUADAS-2 tool, which demonstrated that the QUADAS scores of all 8 studies were higher than 4 points, indicating that the quality of the included studies was acceptable (Table I).

Positive Rate of Expression

An influence analysis was initially conducted in order to assess the homogeneity of all included studies, and all identified outliers were excluded prior to data combination. The combined results showed that in confirmed cases with 2019-nCoV, the positive rates of single IgM, single IgG and

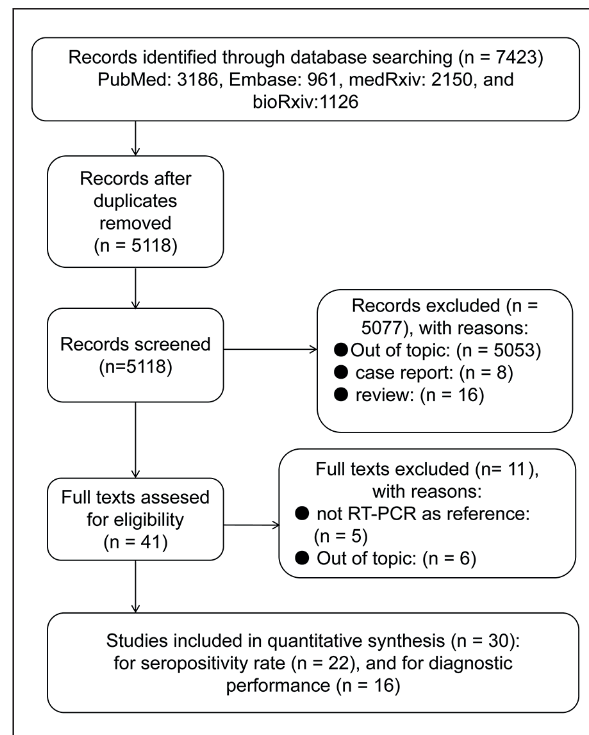

Figure 1. The process of inclusion and exclusion of related studies.

Table I. Clinicopathological features of the included studies.

Study	Country	Covid19 cases	Control	Covid19 diagnosis	Days from onset	Abs testing	Method	SEN	SPE	QUADAS-Score
He J 2020[11]	China	169	NA	RT-PCR	Unknown	IgM, IgG	LFIA, CLIA	NA	NA	NA
Li H 2020[12]	China	75	139	RT-PCR	Unknown	IgM, IgG, IgM/IgG	LFIA	0.9067	0.6933	6
Li Z 2020[13]	China	397	128	RT-PCR	Unknown	IgM/IgG	LFIA	0.8866	0.9063	6
Choe JY 2020[14]	Republic of Korea	70	79	RT-PCR	Unknown	IgM/IgG	LFIA, ELISA	0.929	0.962	6
Kohmer N 2020[15]	Germany	17	24	RT-PCR	5-9 days, 10-18 days	IgG	LFIA, ELISA, IFA	0.588-1	0.833-1	6
Pan Y 2020[16]	China	105	NA	RT-PCR	1-7 days, 8-14 days, ≥ 15 days	IgM, IgG, IgM/IgG	LFIA	NA	NA	NA
Ma H 2020[17]	China	87	330	RT-PCR	4-10 d, 11- 15d, 16-20d, 21-25d, 26-30d	IgM, IgG	CLIA	NA	NA	NA
Hoffman T 2020[18]	Vietnam	29	124	RT-PCR	9-17d, 18-29d	IgM, IgG	ELISA	NA	NA	NA
Sun B 2020[19]	China	38	NA	RT-PCR	NA	IgM, IgG, IgM/IgG	ELISA	NA	NA	NA
Zhao J 2020[20]	China	173	NA	RT-PCR	1-7 days, 8-14 days, 15-39 days	IgM, IgG, IgM/IgG	ELISA	NA	NA	NA
Xiang F 2020[21]	China	Confirmed: 85; suspected: 24	60	RT-PCR	0-29d, ≥ 30d	IgM, IgG	ELISA	Extracted indirectly	Extracted indirectly	5
Suhandynata RT 2020[22]	USA	289	235	RT-PCR	0-7 days,	IgM, IgG, 8-14 days, ≥ 15 days	CLIA IgM/IgG	0.583-1	0.987-	6 0.996
Lou B 2020[23]	China	80	300	RT-PCR	NA	IgM, IgG, IgM/IgG	LFIA, ELISA, CLIA	0.863-	0.971-1 0.988	5
Whitman JD 2020[24]	USA	128	NA	RT-PCR	1-5, 6-10, 11-15, 16-20, and > 20 days	IgM, IgG, IgM/IgG	LFIA, ELISA	NA	NA	NA
Shen B 2020[25]	China	Suspected:150	53	RT-PCR	NA	IgM/IgG	LFIA	Extracted indirectly	Extracted indirectly	5
Cai XF 2020[26]	China	276	200	RT-PCR	NA	IgM/IgG	CLIA	NA	NA	NA
Imai K 2020[27]	Japan	Asymptomatic: 38, Symptomatic: 74	NA	RT-PCR	0-7 days, 8-14 days, ≥ 15 days	IgM, IgG, IgM/IgG	LFIA	NA	NA	NA
Van Elslande J 2020[28]	Belgium	153	103	RT-PCR	0-6 s, 7-13, 14-25 days	IgM, IgG, IgM/IgG	LFIA, ELISA	0.392-0.791	0.854-0.990	5
Dellière S 2020[29]	France	102	42	RT-PCR	NA	IgM, IgG	LFIA	0.905, 0.958	1.0	6
Pingping Zhang 2020[30]	China	Asymptomatic: 32	NA	NA	NA	IgM/IgG	LFIA	NA	NA	NA
Rui Liu 2020[31]	China	Total: 238; Asymptomatic: 91	120	RT-PCR	NA	IgM	ELISA	0.8132	0.7381	5
Quan-xin Long 2020[32]	China	Total: 262 Asymptomatic: 162	148	RT-PCR	NA	IgM/IgG	CLIA	0.67-0.80	0.95	4

Tabla Continued

Table I *(Contiued).* Clinicopathological features of the included studies.

Study	Country	Covid19 cases	Control	Covid19 diagnosis	Days from onset	Abs testing	Method	SEN	SPE	QUADAS-Score
Xingwang Jia 2020[33]	China	33	242	NR-NAT/ clinical features	NA	IgM, IgG, IgM/IgG	FIA	0.45–0.72	0.95	6
Ying Liu 2020[34]	China	95	84	RT-PCR	NA	IgM/IgG	LFIA	0.37-0.86	0.93–0.94	5
Yang Xu 2020[35]	China	10	NA	NAT/sequencing	NA	IgM, IgG, IgM/IgG	LFIA	0.3-0.9	NA	NA
Jie Xiang 2020[36]	China	154 (ELISA: 63; LFIA; 91)	35	RT-PCR	NA	IgM, IgG, IgM/IgG	LFIA, ELISA	0.44-0.87	1	6
Dachuan Lin 2020[37]	China	79	80	RT-PCR	NA	IgM, IgG	ELISA, CLIA	0.23-0.91	0.78–1.0	6
Zheng Zhang 2020[38]	China	Asymptomatic: 22	NA	RT-PCR	NA	IgM	CLIA	NA	NA	NA
Shue Xiong 2020[39]	China	Asymptomatic: 797	NA	RT-PCR	NA	IgG	ELISA	NA	NA	N
Etienne Brochot 2020[40]	France	Asymptomatic: 25	NA	RT-PCR	NA	IgG	ELISA	NA	NA	NA

CLIA: chemiluminescence enzyme immunoassays; LFIA: lateral flow immunoassays; ELISA: enzyme linked immunosorbent assay; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2; IFA: fluorescence immunoassays; RT-PCR: reverse transcription-polymerase chain reaction; NA: not applicable.

Table II. The positive rates of single IgM, single IgG and their joint detection in PCR positive and negative cases related to SARS-CoV-2.

Test	PCR negative (-)			PCR positive (+)			Asymptomatic cases		
	Included individual studies (n)	Sensitivity analysis of outliers	Positive rate (95% CI)	Included individual studies (n)	Sensitivity analysis of outliers	Positive rate (95% CI)	Included individual studies (n)	Sensitivity analysis of outliers	Positive rate (95%CI)
IgM	8	1	29.0% (14.0%-44.0%)	59	5	61.2% (53.4%-69.0%)	/	/	
IgG	8	1	37.0% (20.0%-55.0%)	60	11	58.8% (49.6%-68.0%)	/	/	
IgM/IgG	7	1	55.0% (19.0%-90.0%)	33	1	62.1% (52.7%-71.4%)	5	0	19.0% (10.0%-27.0%)

CLIA: chemiluminescence enzyme immunoassays; LFIA: lateral flow immunoassays; ELISA: enzyme linked immunosorbent assay; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2; IFA: fluorescence immunoassays; RT-PCR: reverse transcription-polymerase chain reaction; NA: not applicable.

Table III. The positive rates of single IgM, single IgG and their joint detection in PCR positive cases based on testing method and period.

Analysis	Included individual studies (*n*)	Positive rate (95% CI)	Sensitivity analysis of outliers	I^2 (%); *p*-value of Cochran'*Q* test
IgM testing				
0-4 days	3	21.5% (6.2%-36.9%)	0	65.0%; $p = 0.057$
5-9 days	3	55.1% (33.1%-77.1%)	0	88.8%; $p = 0.000$
10-14 days	3	87.5% (79.1%-95.9%)	0	72.7%; $p = 0.012$
15-19 days	3	93.6% (90.1%-97.1%)	0	10.4%; $p = 0.328$
20-24 days	3	73.2% (63.2%-83.2%)	0	0.0%; $p = 0.448$
25-19 days	3	81.4% (72.2%-90.6%)	0	44.2%; $p = 0.181$
0-7 days	7	27.3% (19.8%-34.8%)	0	30.5%; $p = 0.195$
8-14 days	9	56.4% (29.7%-83.1%)	0	91.2%; $p = 0.000$
> 14 days	6	72.4% (32.5%-100.0%)	0	93.8%; $p = 0.000$
IgG testing				
0-4 days	3	16.6% (5.2%-28.1%)	0	78.3%; ; $p = 0.010$
5-9 days	4	52.0% (31.4%-72.5%)	0	87.3%; $p = 0.000$
10-14 days	4	78.5% (61.3%-95.7%)	0	88.1%; $p = 0.000$
15-19 days	4	98.5% (96.7%-100.0%)	0	44.3%; $p = 0.166$
20-24 Days	3	91.9% (75.2%-100.0%)	0	66.5%; $p = 0.084$
0-7 days	8	22.3% (11.3%-33.3%)	0	93.6%; $p = 0.000$
8-14 days	10	51.6% (23.8%-79.3%)	0	97.8%; $p = 0.000$
> 14 days	5	62.3% (33.1%-91.6%)	0	7.7%; $p = 0.000$
Combined IgM/IgG testing				
0-7 days	8	39.3% (24.2%-54.4%)	0	92.0%; $p = 0.000$
8-14 days	8	72.5% (59.6%-85.4%)	0	87.0%; $p = 0.000$
> 14 days	7	68.6% (41.5%-95.7%)	0	97.3%; $p = 0.000$
Different method based Abs testing				
LFIA-IgM	24	49.3% (34.8%-63.8%)	1	95.2%; $p = 0.000$
CLIA-IgM	12	66.6% (41.7%-91.5%)	0	99.0%; $p = 0.000$
ELISA-IgM	23	65.8% (52.9%-78.7%)	1	93.3%; $p = 0.000$
LFIA-IgG	24	35.3% (18.9%-51.7%)	2	99.0%; $p = 0.000$
CLIA-IgG	12	76.4% (64.4%-88.3%)	0	98.2%; $p = 0.000$
ELISA-IgG	23	64.1% (48.4%-79.8%)	2	98.0%; $p = 0.000$
LFIA-IgM/IgG	16	47.9% (31.9%-63.9%)	1	96.0%; $p = 0.000$
CLIA-IgM/IgG	3	82.6% (73.9%-91.3%)	0	81.0%; $p = 0.005$
ELISA-IgM/IgG	13	72.2% (55.5%-88.8%)	1	98.0%; $p = 0.000$

their joint detection related to SARS-CoV-2 were 61.2% (95% CI: 53.4%-69.0%), 58.8% (95% CI: 49.6%-68.0%) and 62.1% (52.7%-71.4%), respectively. In highly suspected COVID-19 infection cases with negative RNA results, the positive rates of single IgM, single IgG and their joint testing were 29.0% (95% CI: 14.0%-44.0%), 37.0% (95% CI: 20.0%-55.0%) and 55.0% (95% CI: 19.0%-90.0%), respectively. Abs testing also yielded high values in the identification of asymptomatic infections among close contacts. The present analysis showed that IgM/IgG testing exhibited a positive rate of 19% (95% CI: 10.0%-27.0%) in asymptomatic infection cases.

A subgroup analysis was also conducted based on the time of symptom onset and method of measurement (Table III), which illustrated that among confirmed cases with 2019-nCoV, the positive rate of single IgM testing was higher than that of IgG (27.3% *vs.* 22.3%) 0-7days after patients reported onset of symptoms, whereas the positive rate of parallel IgM/IgG testing attained 39.3%. IgG testing reached a peak positive rate of 98.5% 15-19 days after symptom onset, which was higher than that of IgM (93.6%). When stratified according to the testing method, the positive rate of Abs detection (single IgM, IgG, and combined IgM/IgG) based on CLIA was found to be higher than that based on CLIA and ELISA (Table III).

Diagnostic Value

Using RT-PCR test as reference, the SEN, SPE and AUC of IgM in the diagnosis of 2019-nCoV were 0.71 (95% CI: 0.69-0.73), 0.97 (95% CI:

0.96-0.97), and 0.9656, respectively, while the SEN, SPE and AUC of single IgG diagnosis were 0.76 (95% CI: 0.75-0.78), 0.97 (95% CI: 0.96-0.97), and 0.9766, respectively, and the SEN, SPE and AUC of IgM/IgG joint diagnosis were 0.82 (95% CI: 0.81-0.84), 0.97 (95% CI: 0.96-0.97), and 0.9838, respectively. The subgroup analysis showed that Abs testing based on CLIA showed a SEN, SPE, and AUC higher than LFIA and ELISA (Table IV). Moreover, Abs testing also revealed high SEN and AUC in Asians compared to Caucasians (SEN: 0.87 *vs*. 0.73).

Sensitivity Analysis and Publication Bias

Results of the sensitivity analysis and publication bias among all individual analyses are summarized in Table III. All outlier studies were excluded prior to the effects combination to make the results more homogenous. Deek's funnel plot showed that no clear publication bias existed in the overall pooled diagnostic studies (IgM testing: p=0.096; IgG testing: p=0.231; IgM/IgG testing: p=0.154).

Discussion

The pathogen of COVID-19 is SARS-CoV-2, which is a single strand plus RNA virus that exhibits strong infectivity[1,2]. The population generally lacks immunity to it, and a specific therapy does not yet exist. In regard to disease prognosis and epidemic prevention and control, early detection, diagnosis, isolation, and treatment is of great significance. Serological testing is a mainly used in its diagnosis, which may detect virus specific antibodies and antigens *via* pathogen specific antigens or antibodies[41]. Currently, ELISA, LIFA, CLIA and FIA are used to detect IgM and IgG of SARS-CoV-2[42]. This study initially reported the positive rates of IgM and IgG in confirmed and suspected patients with SARS-CoV-2 infection. Moreover, the positive rates of Abs expression in different periods after patient-reported symptom onset, as well as asymptomatic cases were discussed. In addition, the comprehensive diagnostic efficacy of IgM and IgG in SARS-CoV-2 was also evaluated.

By conducting a quantitative meta-analysis, among confirmed cases with 2019-nCoV, the positive rates of single IgM, single IgG and their joint detection of SARS-CoV-2 were found to be 61.2%, 58.8% and 62.1%, respectively. Accordingly, their combination was found to be beneficial in improving the positive rates of screening. Moreover, due to the hysteresis of RT-PCR detection as well as the quality of detection, many false negative suspected infected patients were present during 2019-nCoV infection[43]. Here, Abs detection was also found to possess a certain positive rate in RNA negative suspected infected patients, where the positive rates of IgM, IgG and their joint detections were 29%, 37% and 55%, respectively. Accordingly, Abs detection was noted to be helpful in making up for the lack of missed diagnosis due to RNA detection. Importantly, IgM/IgG combined testing had a positive rate of 19% in the identification of asymptomatic infections. The obtained data suggest that serological testing may be helpful in the diagnosis of suspected patients with negative RT-PCR results and asymptomatic infections.

Evidently, IgM peaks between days 5 and 12 and drops slowly thereafter[44]. IgG reaches peak concentrations after around day 20 as IgM antibodies disappear[44]. Therefore, joint detection of IgM and IgG can improve the sensitivity of COVID-19. However, most COVID-19 patients in this study were in the middle or later stages of infection, and IgG was produced in large quantities in the later stages of viral infection[45]. Therefore, the positive rate of IgG may be higher than that of IgM in this study. Through the subgroup analysis, among confirmed cases with 2019-nCoV, the IgM positive rate was found to be higher than that of IgG 0-7 days after patient-reported symptom onset, however, combined IgM/IgG testing could increase the detection of the positive rate. Moreover, the positive rate of Abs detection (single IgM, IgG, and combined IgM/IgG) based on CLIA was higher than that based on CLIA and ELISA. Notably, CLIA was observed to be superior to ELISA and LFIA in detecting total antibodies, which is suitable for all stages of disease.

Currently, pathogen genome sequencing is the most accurate detection method, which is also of great significance in monitoring virus mutations[5,42,43]. The results showed that the AUC of single IgM, IgG and IgM/IgG combination testing in the diagnosis of 2019-nCoV infection were 0.9656, 0.9766, and 0.9838, respectively, while the SEN and AUC of IgM/IgG were higher than those of single detection. It can be seen that the joint detection of IgM and IgG can improve the accuracy of diagnosis. In addition, the diagnostic value of different Abs detection methods for 2019-nCoV infection was also compared, in which the diagnostic efficiency of CLIA was

Table IV. Subgroup analyses of the diagnostic efficacy of Abs against SARS-CoV-2.

	SEN (95% CI)	SPE (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC	I^2; Cochran'Q test *p*-value	Spearman coefficient *p*-value)
Abs testing								
IgM	0.71 (0.69-0.73)	0.97 (0.96-0.97)	24.16 (12.78-45.66)	0.22 (0.16-0.31)	144.28 (61.70-337.39)	0.966	88.6%; $p = 0.000$	0.804
IgG	0.76 (0.75-0.78)	0.97 (0.96-0.97)	27.04 (15.78-46.36)	0.20 (0.16-0.26)	185.45 (98.85-347.91)	0.977	72.7%; $p = 0.000$	0.783
IgM/IgG	0.82 (0.81-0.84)	0.97 (0.96-0.97)	23.09 (14.70-36.27)	0.15 (0.11-0.21)	206.33 (99.87-426.30)	0.984	88.0%; $p = 0.000$	0.322
Methods								
LFIA	0.71 (0.70-0.72)	0.96 (0.95-0.96)	17.42 (12.77-23.75)	0.25 (0.21-0.31)	93.13 (58.59-148.03)	0.962	82.0%; $p = 0.000$	0.679
ELISA	0.80 (0.78-0.83)	0.95 (0.94-0.96)	15.47 (7.84-30.54)	0.16 (0.10-0.27)	144.78 (56.29-372.38)	0.964	76.8%; $p = 0.000$	0.931
CLIA	0.85 (0.84-0.86)	0.99(0.99-0.99)	92.82 (60.32-142.83)	0.09 (0.05-0.18)	1275.31 (522.03-3115.55)	0.999	65.7%; $p = 0.0019$	0.338
Ethnicity								
Asians	0.87 (0.85-0.88)	0.97 (0.96-0.97)	27.86 (17.40-44.60)	0.12 (0.08-0.17)	336.61 (180.29-628.46)	0.98	80.0%; $p = 0.000$	0.265
Caucasians	0.73 (0.71-0.74)	0.97 (0.96-0.97)	21.98 (14.74-32.78)	0.26 (0.21-0.32)	106.25 (62.40-180.92)	0.971	85.2%; $p = 0.000$	0.952

AUC: area under the curve; CLIA: chemiluminescence enzyme immunoassays; LFIA: lateral flow immunoassays; ELISA: enzyme linked immunosorbent assay; SEN: sensitivity; SPE: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio.

found to be higher than that of LFIA and ELISA. Additionally, de Ory F et al[46] compared the efficacy of CLIA with ELISA and found that CLIA demonstrated excellent sensitivity and specificity in detecting measles IgG and IgM antibodies. Kontou et al[44] showed that the overall diagnostic efficacy of CLIA in the diagnosis of 2019-nCoV infection was higher than that of ELISA, LFIA and FIA. Intriguingly, Abs testing in Asians was observed to be higher than in Caucasians in this analysis, which has yet to be reported. However, due to the application of different testing methods among studies, more evidence is necessary to understand this finding.

Conclusions

Overall, antibody diagnosis is specific and rapid and may be used as an auxiliary diagnostic method for SARS-CoV-2 infection. Compared to specific antibody serological detection, RNA testing can detect patients in the window period and detect infected individuals as soon as possible. When RNA detection is negative, supplementation with IgM and IgG antibody detection can make up for the lack of missed diagnoses caused by nucleic acid detection. Therefore, during actual detection, it is suggested that the joint detection of Abs be carried out in order to improve the positive detection rate of virus carriers and reduce the risk of social transmission. Furthermore, the benefits pertaining to IgM and IgG detection in the diagnosis of asymptomatic RNA-positive patients should be further studied.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

CCG designed the study; JQM and HN collected the literature and conducted the analysis of pooled data and helped to draft the manuscript; CCG wrote the manuscript; CCG and JQM proofread, revised and final approved the manuscript; all authors have approved the version to be published.

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