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Seroprevalence of Immunoglobulin M and G Antibodies against SARS-CoV-2 Virus: A Systematic Review and Meta-Analysis Study

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ABSTRACT

Background: Coronavirus disease 2019(COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a new global health threat.

Objectives: to analyze the effectiveness of the measurement of specific antibodies to SARS-CoV2 (IgM and IgG) for the diagnosis of COVID-19 and to analyze the rate of SARS-CoV2 seroprevalence in the population.

Methods: 11 relevant studies, published before June 5, 2020, were included in this meta-analysis. These studies were identified by searching the MEDLINE and Scopus databases. The final selected studies were analyzed using STATA version 14. Publication bias was examined using both Egger's test and Funnel plots. Moreover, the I^2 statistic has been used to evaluate and verify heterogeneity.

Results: The 11 relevant studies selected for the present meta-analysis cover a total of 996 infection cases. According to the results, the average rate of positive cases for IgM (AU/mL) was 2.10 (95% CI: 1.65-2.55; I^2=92.2%), and the sensitivity in individuals with positive IgM test was 63 (95% CI: 47-79; I^2=94.9%). In addition, the average rate of positive cases for IgG (AU/mL) was 67.44 (95% CI: 28.79-106.09; I^2=99.4%), and the sensitivity in individuals with positive IgG test was 79 (95% CI: 67-90; I^2=89.5%).

Conclusions: According to this analysis, detection of anti-SARS-CoV-2 IgM and IgG antibodies may assist early detection of SARS-CoV2 infection. Whether antibodies against SARS-CoV-2 confer protective immunity warrants further studies.

Keywords: Antibody, COVID-19, IgG, IgM, rRT-PCR, SARS-CoV-2, Meta-analysis

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INTRODUCTION

A novel coronavirus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been recognized as the causative virus for the coronavirus disease 2019 (COVID-19), which was first identified in Wuhan, China (1).

This viral infectious disease has spread rapidly from China to other countries, and as a result, the WHO designated COVID-19 as a pandemic in March 2020 (2, 3). By October27, 2020, a total number of 42,966,344 confirmed COVID-19 cases were globally reported,with 1,152,604 deaths in 218 countries and regions (4). Data collection confirms that the virus can be transmitted fromhuman clinical and subclinical patients to healthy individuals after close contact (5-8). In general, COVID-19 patients, especially infected adults, have symptoms including pneumonia, coughing, dyspnea, and fever (9). In a meta-analysis by R. A. Armstrong et al., the primary result assessment considered death in the ICU as a proportion of completed ICU patients, that included patients who had ended up to either death or discharge from ICU. They investigated twenty four observational studies covering 10,150 patients from centers across Europe, North America, and Asia. The in-ICU mortality rate in those studies was from about 0 to 84.6%. Moreover, only 7 papers reported the data regarding the outcomeof all patients. In other studies, the ICU discharge rate of patients varied from 24.5 to 97.2%. Among the COVID-19 patients with completed ICU admissions, the total ICU mortality rate (95%CI) was found to be 41.6% (34.0–49.7%), I^2 = 93.2%). They also performed a sub-group analysis based on individual continents, indicating that mortality was consistent globally. By the progression of the pandemic, the reported mortality rates have grown from 40% to above 50%. The results of the study show that the in-ICU mortality due to COVID-19 is higher in ICU admissions than in the other viral cases of pneumonia (10).

For example, data from Lombardy on March, 27 depicted that 30% of reported cases were in the hospital, while 4.3% of them were in the ICU, which is about 16 individuals per 100,000 (11). The population of Lombardy is about 10 million, and the rate of infection among the population since March, 21 is 0.37%, while the mortality rate in the population is 45 per 100,000 (11). According to previous studies, the mortality rate of SARS-CoV-2 is lower than MERS-CoV (~34%) and SARS-CoV (~10%), i.e., the other two main members of the *coronaviridae* family (4). However, SARS-CoV-2 has more transmission capability than MERS-CoV and SARS-CoV (12).

Accurate and rapid detection of patients with COVID-19 will be very useful in managing and monitoring this infectious disease, and it willfinally result in better control and prevention of this novel coronavirus. RT-PCR is considered an early measurement method for the diagnosis of SARS-CoV-2 (13). However, due to low viral loads in the collected samples, the molecular diagnosis carries a false negative risk (14). Serological testing, which is another common laboratory diagnostic method, can detect the disease by identifying specific antibodies. So far, serological research on COVID-19 has been limited (15). Based on the studies on the SARS-CoV-2 virus, a serological diagnosis of SARS-CoV-2 in patients with COVID-19 can be beneficial. Although the available data on the antibody response to viral infection of SARS-CoV-2 are limited, the detection value of the serological tests has been fully confirmed (16). Various serological tests, such as lateral flow rapid test, chemiluminescence immunoassay (CLIA) (17), and enzyme-linked immunosorbent assay (ELISA) (17), have already been developed to diagnose anti-SARS-CoV-2 antibodies. The Foundation for Innovative New Diagnostics (FIND (https://www.finddx.org/)) has listed more than 150 rapid antibody tests for SARS-CoV-2, which have the "Communauté Européenne" (CE) certificate (17).

The development of immunity to the emerging zoonotic pathogen SARS-CoV-2 is a multi-stage response over 1-2 weeks. After exposure to the virus, the nonspecific response is accompanied by an adaptive response by the immune system that produces specific antibodies against the virus. Anti-SARS-CoV-2 antibodies can be found in the blood, and presumably in the respiratory system, where the virus resides and propagates. Class M immunoglobulin (i.e., IgM) usually develops after the first week of infection before the IgG, which is a longer-lasting antibody that develops 2 to 4 weeks after the onset of infection. The detection of SARS-CoV-2 specific IgG and IgM in circulating blood serves as a common method for determining whether a person has been infected recently (IgM) or earlier (IgG).

Detection of IgG and IgM antibodies against SARS-CoV-2 may be considered as a supplementary approach for diagnosis and serve an important role in the evaluation of immune responses against SARS-CoV-2 infection.

However, serological surveys alone cannot provide sufficient information on the prevalence of COVID-19, epidemiological data, and the prevalence of COVID-19-related morbidity and mortality. Indeed, SARS-CoV-2 has been isolated from seronegative individuals (18, 19). However, the diagnosis of antibodies against SARS-CoV-2 plays an important role in identifying appropriate methods for developing a vaccine and monitoring the SARS-CoV-2 pandemic (17, 20-24). Serological assays have been considered as efficient and accurate methods for detecting many pathogens since specific IgG and IgM antibodies can be identified with an enzyme-linked immunosorbent assay (ELISA), which has less stringent specimen requirements and higher capacity than RNA-based assays (25). Recently, several commercial IC assays have become available for clinical applicationto identify IgM or IgG antibodies against SARS-CoV-2. However, their clinical efficiency remains to be assessed (26).

In addition to ELISA, methods based on immunochromatography (IC) for the detection of IgM and IgG antibodies against SARS-CoV-2 can be useful in the diagnosis of infection. It is quick and easy to perform; however, its sensitivity is low in the early phase of infection. Nonetheless, this technique may be used in settings where COVID-19 RT-qPCR is not available. The main goalof this systematic review is to investigatethe diagnostic value of the serological laboratory tests of SARS-CoV-2antibodiesin COVID-19 patients.

MATERIALS AND METHODS

Search Strategy and Study Selection

We have searched Scopus and PubMed databases to identify eligible articles doneon COVID-19 before June 5, 2020. Keywords used in thesearch included: antibody, COVID, immunoassay, IgG, IgM, and ELISA. Moreover, the reference lists of the identified papers were also searched to find more articles related to the topic.

Inclusion and Exclusion Criteria

All studies measuring IgG and IgM using ELISA in cases with COVID-19 infection have been reviewed. To perform the first analysis, the chosen papers should represent data on the immunoassays for detecting IgG and IgM, and the comparison of these factors with each other. Some of the included articles have compared these two antibodies in different groups; however, some of these articles have not done this. All the selected studies present data on their cases in different periods. Only human papers were chosen to be included in this meta-analysis. The authors have assessed the full texts of the related papers based on the inclusion and exclusion criteria. After evaluating all the qualified studies, those with inadequate data, duplicate publications, non-English publications, and non-human papershad been excluded.

Data Extraction

All chosen studies were screened and evaluated by one of the authors, and the outcomes were checked by another one. After performing all these steps, the following data were extracted by the authors for the final analysis: number of patients with a positive IgG test, number of patients with a positive IgM test, IgG level (AU/mL), IgM level (AU/mL), the sensitivity and specificity of IgG, and the sensitivity and specificity of IgM. Since COVID-19 is a novel disease and investigations are still ongoing, more studies should be performed on this topic.

Statistical Analysis

Since the effect size of our meta-analysis was based on a proportion (the number of patients with positive IgG test, the number of patients with positive IgM test, IgG (AU/mL), IgM (AU/mL), the sensitivity and specificity of IgG, and the sensitivity and specificity of IgM), we used a normal and binomial distribution to calculate the variance for each data point. The outbreak rates in different papers were combined employing the average weight. An inverse association was observed between the weight and the variance of the research. Heterogeneity was evaluated by applying the I^2 index. If a heterogeneous article was observed, the random-effects model was used. Version 14 of STATA was employed for data analysis. If p is close to 0 or 1, the Metaprop (Meta-analysis for Proportionin) in STATA will be used. For stabilization of the variances, the Freeman-Tukey Double Arcsine Transformation was applied (27). This work was conducted under the surveillance and approval of the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1399.086).

Quality Assessment

To evaluate the quality Level of each study, the Newcastle-Ottawa Scale (NOS) was used (28). 8 assessment items were included for the evaluation of these studies. These items could be classified into 3 main sections including 'outcome', 'comparability', and 'selection' (based on the Ottawa checklist for Cross-Sectional Studies). Based on the NOS score that each study has been given, the studies were classified into 3 groups: high-quality studies (scores ≥7), moderate-quality studies (scores of 5–6), and low-quality studies (scores of 0–4) (Table 1).

Specificity

Maglumi CLIA IgM test demonstrates the specificity of 100%, as shown by Montesinos Isabel et al. (11).

Kazuo Imai et al. (29) calculated the specificity of 98.0 % for the IC assay.

By testing the specimens from healthy patients before the prevalence of SARS-CoV-2 in their study, Juanjuan Zhao et al. (30) have mentioned that the specificityof the assays for IgM, IgG, and Ab was 98.6% (210/213), 99.0% (195/197), and 99.1% (211/213), respectively.

Raymond T. Suhandynata et al. (31) reported that the specificity of the assay showed excellent outcomes for IgG, IgM/IgG, and IgM panel with 99.1%, 98.7%, and 99.6%, respectively.

Yujiao Jin et al. (21) reported that compared to the molecular diagnosis, the specificities of serum IgG and IgM antibodies for the detection of COVID-19 were 90.9% and 100%, respectively.

Table 1. Baseline characteristics of studies included in this meta-analysis.

Study	Date	Time	Patients (No.)	Patients with positive IgM test (No.)	Patients with positive IgM test (%)	Patients with positive IgG test (No.)	Patients with positive IgG test (%)
(2)	April 2020	≤5 days	4.00	0	0	0	0
(2)	April 2020	6–7 days	6.00	3	0.50	4	0.667

(2)	April 2020	8–9 days	12.00	7	0.583	9	0.75
(2)	April 2020	10–11 days	14.00	5	0.357	10	0.714
(2)	April 2020	12–13 days	9.00	7	0.778	9	1
(2)	April 2020	>13 days	25.00	22	0.88	25	1
(34)	April 2020	≤5 days	30.00				
(34)	April 2020	>5–10 days	13.00				
(34)	April 2020	>10–21 days	5.00				
(42)	March 2020		80.00	74.0			
(42)	March 2020		80.00			71.0	
(42)	March 2020	0-7 days	39.00	13.0		13.0	
(42)	March 2020	8-14 days	75.00	65.0		57.0	
(42)	March 2020	15-29 days	60.00	58.0		56.0	
(21)	March 2020	Before conversion to virus-negative	20.00	10	0.5	18	0.9
(21)	March 2020	After conversion to virus-negative	20.00	10	0.5	19	0.95
(11)	April 2020		79.00				
(22)	April 2020	≤5 days	8.00	0	0		
(22)	April 2020	6–7 days	8.00	2	0.25		
(22)	April 2020	8–9 days	18.00	9	0.5		
(22)	April 2020	10–11 days	17.00	9	0.529		
(22)	April 2020	12–13 days	14.00	11	0.786		
(22)	April 2020	14–15 days	17.00	13	0.765		
(22)	April 2020	16–17 days	18.00	16	0.889		
(22)	April 2020	18–19 days	17.00	16	0.941		
(22)	April 2020	20–21 days	12.00	10	0.833		
(22)	April 2020	22–23 days	22.00	15	0.682		
(9)	March 2020	1–7 days	9.00	2		4	
(9)	March 2020	8–14 days	6.00	2		4	
(9)	March 2020	≥15 days	7.00	4		5	
(9)	March 2020	In total	22.00	8		13	
(29)	April 2020	<1 week	53.00	9	0.17	2	0.038
(29)	April 2020	1–2 weeks	12.00	4	0.333	1	0.083
(29)	April 2020	>2 weeks	9.00	9	1	4	0.444
(29)	April 2020	Total	74.00	22	0.297	7	0.095
(30)	March 2020	0-7 days		27		74	
(30)	March 2020	8-14 days		99		131	
(30)	March 2020	15-39 days		83		90	
(30)	March 2020	Total		143		172	
(31)	May 2020	≤ 7 days					
(31)	May 2020	8 - 14 days					
(31)	May 2020	≥ 15 days					
(33)	May 2020	Week1 (non-ICU patients)	14.00				
(33)	May 2020	Week1 (ICU patients)	6.00				
(33)	May 2020	Week2 (non-ICU patients)	19.00				
(33)	May 2020	Week2 (ICU patients)	15.00				
(33)	May 2020	Week3 (non-ICU patients)	20.00				
(33)	May 2020	Week3 ICU	25.00	0	0	0	0

*Abbreviations: No=Number.

RESULTS

The current study has been performed based on the PRISMA checklist (32). As the first step, 80 papers had been identified through the initial search on PubMed database and Google Scholar. Additionally, 22 more studies were obtained from Scopus. However, 42 of those 102 studies were excluded due to duplication. We excluded 29 more papers after screening the abstracts and titles of all the selected studies. The full texts of the 31 remaining studies were assessed by the authors, resulting in the exclusion of 20 studies because of several reasons, including insufficient data, short reports, case reports, inappropriate employed methods, and review articles. Eventually, 11 studies, published from April 2019 to May 2020, were chosen for this meta-analysis (Figure 1).

Based on the evaluation of all the collected data, the total number of cases covered by this meta-analysis was 996, including 787 patients with a positive IgM test and 798 patients with a positive IgG test (Table 2). According to the results, the average rate of positive cases for

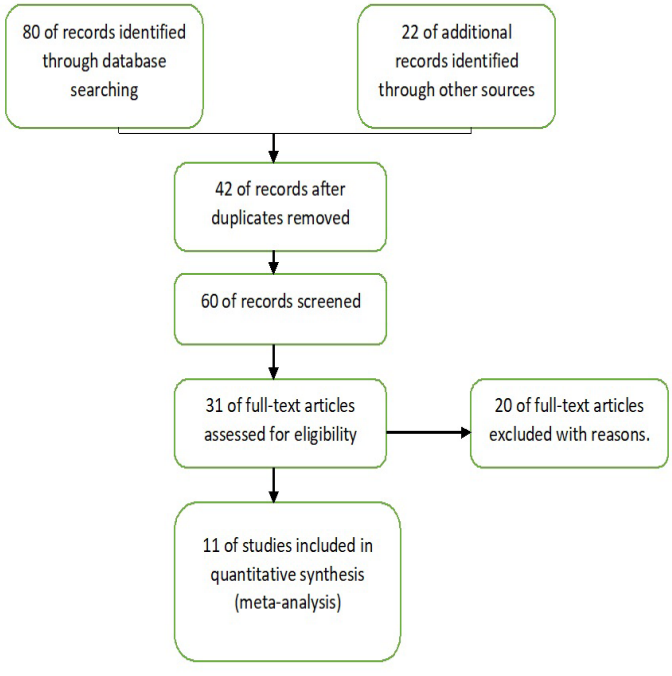

Figure 1. Study flow diagram

Table 2. NEWCASTLE-OTTAWA quality assessment scale for cross sectional studies

Author(references)	Selection				Comparability	Outcome	
	1	2	3	4	1	1	2
Andrea Padoan(2)	*	*	*	**	*	**	
Giuseppe Lippi(34)	*	*		**	*	**	*
Bin Lou(42)	*	*	*	**	**	**	*
Yujiao Jin(21)	*	*	*	**	*	**	*
Montesinos Isabel(11)	*	*	*	**	*	**	*
Andrea Padoan(22)	*	*	*	**	*	**	
Yunbao Pan(9)	*	*	*	**	*	**	*
Kazuo Imai(29)	*	*		**	*	**	
Juanjuan Zhao(30)	*	*	*	**	**	**	
Raymond T. Suhandynata(31)	*	*	*	**	**	**	
Baoqing Sun(33)	*	*	*	**	*	**	*

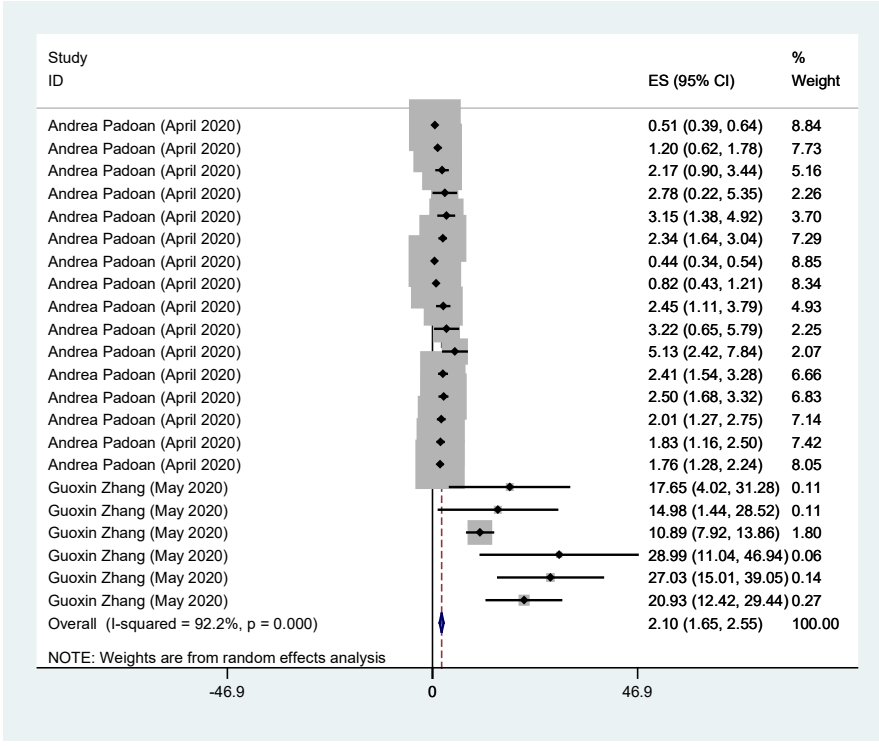

Figure 2. Forest Plot of the average rate of positive COVID-19 cases for IgM.
Each square demonstrates the effect estimate of each study with their 95% CI Size of squares is proportional to the weight of each individual article in the meta-analysis. In this plot investigations are shown in the order of first publication date and also author's names (based on a random effects model).

Table 3. Statistical analysis of reviewed articles

	Number of studies	Prevalence (%)	95% CI	I^2(%)
Mean of IgM(AU/mL)	3	2.10	(1.65-2.55)	92.2
Patients with positive IgM test (No.)	6	60.49	(47.23-73.09)	90.51
Sensitivity in positive IgM test (%)	3	63	(47-79)	94.9
Mean of IgG(AU/mL)	2	67.44	(28.79-106.09)	99.4
Patients with positive IgG test (No.)	5	65.18	(44.43-83.58)	95.2
Sensitivity in positive IgG test (%)	2	79	(67-90)	89.5

*Abbreviations: No=Number.

IgM (AU/mL) was 2.10 (95% CI: 1.65-2.55; I^2=92.2%) (Figure 2, Table 3). Moreover, the percentage of sensitivity in individuals with positive IgM test was 63 (95% CI: 47-79; I^2=94.9%) (Figure 3, Table 3), the average rate of positive cases for IgG (AU/mL) was 67.44 (95% CI: 28.79-106.09; I^2=99.4%) (Table 3), and the percentage of sensitivity in individuals with positive IgG test was 79 (95% CI: 67-90; I^2=89.5%) (Figure 4, Table 3). It is important to note that the measurement of antibodies (i.e., IgG and IgM) had been performed in different periods, and since the periods were completely different in various papers, it was not possible to compare IgG and IgM at every single period.

Summary of Data from the Studies Included in the Meta-Analysis

Baoqing Sun et al. (33) investigated IgG and IgM responses against SARS-CoV-2 proteins (including: spike (S) and nucleocapsid (N)) after the onset of symptoms in ICU and non-ICU patients. Besides, 130 blood

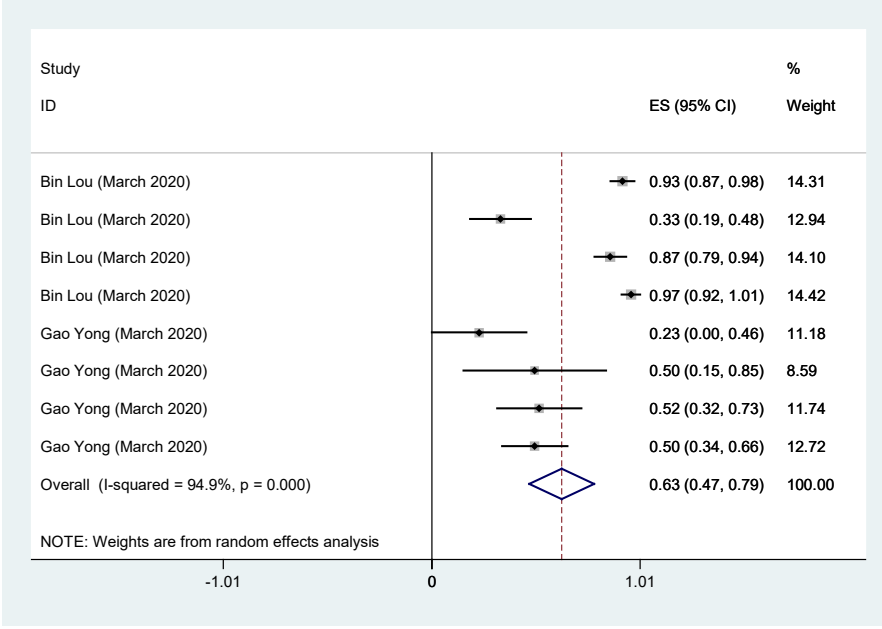

Figure 3. Forest Plot of the sensitivity in COVID-19 infected patients with positive IgM test result. Each square demonstrates the effect estimate of each study with their 95% CI Size of squares is proportional to the weight of each individual article in the meta-analysis. In this plot investigations are shown in the order of first publication date and also author's names (based on a random effects model).

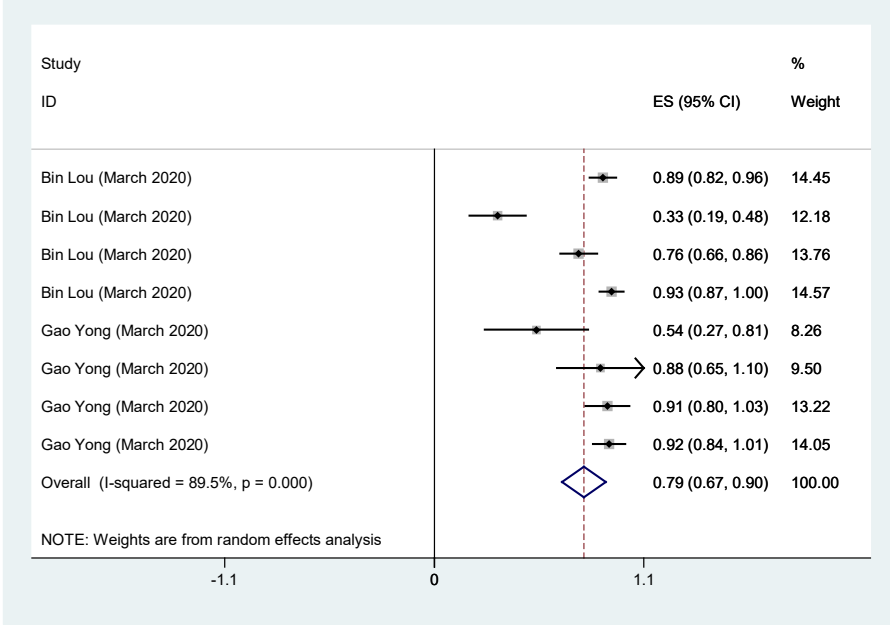

Figure 4. Forest Plot of the sensitivity in COVID-19 infected patients with positive IgG test result. Each square demonstrates the effect estimate of each study with their 95% CI Size of squares is proportional to the weight of each individual article in the meta-analysis. In this plot investigations are shown in the order of first publication date and also author's names (based on a random effects model).

specimens from 38 patients suffering from COVID-19 were gathered. ELISA diagnosed the serologic levels of IgG and IgM against S and N proteins. S and N-specific IgG and IgM (S-IgM, S-IgG, N-IgG, N-IgM) in non-ICU cases increased after the onset of the symptoms. In some non-ICU patients, N-IgM and S-IgM indicated a high number in the second week; however, S-IgG and also N-IgG increased in the third week.

Andrea Padoan et al. (2) stated that the analytical validation of the assay, performed

base on the CLSI EP15-A3 guidelines, showed that repeatability and precisionhave been accepted (<6% and <4% for IgG and IgM, respectively). Immunoglobulin time kinetics have been assessed employing a series of serum specimens gathered from positive COVID-19 patients at various times from less than 5 days up to 26–30 days. Intermediate imprecision was less than 6%. Additionally, the outcomes of recovery and dilution studies were showing positive outcomes. Kinetics of the COVID-19 antibodies proved the previous data, indicating rapid growth in both IgG and IgM after 6–7 days from the onset of the symptoms. IgG showed a sensitivity of 100% on the 12th day, while the higher positive statistics for IgM after the same period was 88%.

In a study by Giuseppe Lippi et al. (34), the antibodies employed in the assessments were against both e CoV-N (nucleocapside) and CoV-S (spike). The outcomes of MAGLUMI 2019-nCoV have been compared with the results through automated Anti-SARS-CoV-2 IgG and IgA ELISAs (Euroimmun AG, Luebeck, Germany), which are considered CE marked tests available for researchers. PCR and automated RNA extraction setup have been performed by using Seegene NIMBUS (i.e., a liquid handling workstation). RT-PCR was performed on a CFX96TMDx platform (Bio-Rad Laboratories Inc., CA, the USA), and it was then explained by Seegene's Viewer software. A test with the result ≥1.10 AU/mL was considered reactive, while the total reproducibility specified by the manufacturer had resulting values between 6.8% and 8.7%. In cases with the onset of the symptoms in ≤5 days, the positive rate of antibodies had been shown very low, i.e., always <5%, while in those with the onset of the symptomsin 5 to 10 days, the positive rate of antibodies was from 15.4% to 53.8%. Specifically, in patients with the onset of symptoms from >10 to 21 days, the positive rate of antibodies was observed to always be over 100%, except for MAGLUMI IgM, which was positive in 60% of the cases.

In a study by Bin Lou et al. (10), the seroconversion rate for IgG, IgM, and Ab in COVID-19 patients was 93.8% (75/80), 93.8% (75/80), and 98.8% (79/80), respectively. The total antibody, as the first detectable marker, has been evaluated by IgG and IgM (median seroconversion time= 20, 18, and 15 days after exposure or 12, 10, and 9 days after onset), respectively. Antibody levels raised quickly 6 days after the exposure. For patients with COVID-19 in the early stages of the disorder (0 to 7 days after exposure), Ab demonstrated the highest sensitivity about (64.1%) in comparison to the IgG and IgM (33.3% for both, $p<0.001$). Two weeks later, the sensitivities of Ab, IgG, and IgM detection increased to 100%, 93.3%, and 96.7%, respectively.

In Yujiao Jin et al. (21), the sensitivities of serum IgG and IgM antibodies for the diagnosis of COVID-19 were 88.9% and 48.1%, respectively, while the specificities were 90.9% and 100%, respectively. Due to the results, in the COVID-19 patients, the IgM-positive rate raised slowly at first, and then it reduced gradually; however, the IgG-positive rate raised to 100% (higher than IgM). IgM-positive titer and rate did not show a significant difference after and before conversion to virus-negative. Likewise, the detected IgG-positive rate was measured up to 90%, and it did not show a significant difference after and before conversion to virus-negative. Nevertheless, the IgG titer after conversion to virus-negative was doubled in comparison to the value before the conversion, and the difference was significant.

In a study by Montesinos Isabel et al. (11), the Euroimmun IgG/IgA (64.3%) test demonstrated higher sensitivity than the Maglumi™ IgG/IgM test (84.4%). However, the tests demonstrated similar specificities for IgG at 100% and 99%, respectively. The sensitivity of the serological quantitative assays and the three lateral flow assays enhanced during the 2nd week after the onset of the symptoms, while all the assays obtained similar values (i.e., 91% to 94%) after 14 days.

In a study by Andrea Padoan et al. (22), the authors assessed the kinetics of IgG, IgA, and IgM SARS-CoV-2 antibodies in the cases with COVID-19 with confirmed rRT-PCR. They realized that the IgA response emerges and increases early, with a peak at the 3rd week, and it is also stronger than the IgM response.

Yunbao Pan et al. (9) performed the colloidal gold-based immunochromatographic (ICG) strip assay, which targets viral IgG or IgM antibodies. They also compared the assay with the real-time RT-PCR. The sensitivity of the ICG assay in terms of IgG and IgM combinatorial detection in the nucleic acid of the confirmed patients was 11.1%, 92.9%, and 96.8% at the early phase (1–7 days after the onset), the intermediate phase (8–14 days after onset), and the late phase (> 15 days), respectively.

Kazuo Imai et al. (29) evaluated 139 COVID-19 serum samples. IgM was detected in 95.8 %, 27.8 %, and 48.0 % of the samples more than 2 weeks, within 1 week, and 1–2 weeks after the onset of the symptoms, respectively. Moreover, IgG was also detected in 3.3 %, 8.0 %, and 62.5 % of the samples, respectively.

In a study by Juanjuan Zhao et al. (30) on 173 patients, the seroconversion rate for IgM, IgG, and Ab was 82.7%, 64.7%, and 93.1%, respectively. The median day seroconversion for IgG, IgM, and Ab was 14, 12, and 11, respectively. The rate of antibody presence was less than 40% among the cases within one week after the onset; however, it rapidly increased to 79.8% (IgG), 94.3% (IgM), and 100.0% (Ab) from the 15th day after the onset.

In a study by Raymond T. Suhandynata et al. (31), thespecificity and sensitivity for the diagnosis of the seropositivity at more than 15 days following a positive SARS-CoV-2 PCR outcome were 98.7% and 100.0% when evaluating for IgG and IgM. The median time to seropositivity, obtained for a reactive IgG and IgM outcome, from the date of a positive PCR was 4 days (IQR: 2.75-6.75 days) and 5 days (IQR: 2.75-9 days), respectively.

DISCUSSION

Since the detection of COVID-19 is so complicated due to the imaging and laboratory outcomes, as well as the variety of symptoms, especially in patients without symptoms or with mild symptoms, serological and molecular detection devices are developing rapidly. According to the high specificity of real-time RT-PCR, positive results of this test are known as the gold standard for the detection of COVID-19. However, serological investigations for antibodies against SARS-CoV-2 could be considered as a valuable approach to check the immune status following infection and as a supplementary modality for the diagnosis of past infection. Serological approaches are especially remarkably valuable in populations with a higher rate of infection (21).

Serological testing can be considered as a diagnostic test for COVID-19, and as a strategic technique for the second phase of the COVID-19 pandemic, essential for epidemiological research, as well as COVID-19 eradication programs.

Serological assays developed for the diagnosis of virus-neutralizing antibodies and antibodies against nucleocapsid protein (N) and various spike domains (S) include the S1 subunit and the receptor-binding domain (RBD) of SARS-CoV-2 in ELISA format. These assays take a wide range of formats; however, they essentially consist of an antigen or antibody, immobilized on a surface (most often a title plate or paper strip), which binds to the virus-specific antigens or antibodies in a patient's sample (e.g., blood sera). By adding additional reporter protein, a virus-specific immune signal can then be detected to confirm the presence of an ongoing or past viral infection. To have a better insight into immune responses during COVID-19 infection, we have focused onIgG and IgM antibodies against SARS-CoV-2, and we have collected data from all studies that have measured the amount of IgG and IgM using ELISA in individuals. It should be noted that

some of these studies have only performed antibody tests on either symptomatic or asymptomatic patients. Besides, the results of the serological test provide important epidemiological data. Yongchen et al. has highlighted the supplementary importance of immunoassay in COVID-19 diagnosis especially in the critical cases that have shown a negative RT-qPCR result (37).

The results of our meta-analysis demonstrate thatthe average rate of positive cases for IgG (AU/mL) was 67.44 (95% CI: 28.79-106.09; I^2=99.4%) was much higher than the average rate of positive cases for IgM (AU/mL) was 2.10 (95% CI: 1.65-2.55; I^2=92.2%); however, the sensitivity in patients with a positive test result did not show any significant difference (percentage of sensitivity in individuals with a positive IgM test was 63 (95% CI: 47-79; I^2=94.9%), and the percentage of sensitivity in individuals with a positive IgM test was 79 (95% CI: 67-90; I^2=89.5%).

As noted earlier, there are various serological tests, such as ELISA, accessible on the market, which can be used in the current challenge the world is facing. While we are still waiting for the outcomes of the studies evaluating the high prevalence rate of this disease in the world, Wu et al. reported the diagnosis of about 10% of SARS-CoV-2 IgG in asymptomatic individuals from a single-center study (38).

Diagnosis of specific antibodies, such as IgG and IgM, against SARS-CoV-2 spike protein, may be helpful to confirm the infection with SARS-CoV-2 virus in cases with PCR-positive COVID-19 infection. This is necessary in infected but asymptomatic individuals, in COVID-19 cases who were tested many weeks after the onset of the disease, or in patients who have a low viral load. These evaluations can also be employed to screen the convalescent plasma for transfusion to patients suffering from severe COVID-19 infection (40).

The studies also demonstrated that the IgG-positive rate (88.9%) in COVID-19 patientswas much higher than the IgM-positive rate (48.1%). In another related study, Zhang *et al*. showedthat the IgG and IgM positive rates were 81% and 50%, respectively, on day zero, while they increased to 100% and 81%, respectively, on the fifth day (41). Consequently, no COVID-19 patients have been identified among individuals with negative serological (IgM and IgG) tests (21). We aimed to assess the rate of seropositivity in patients with SARS-CoV-2 infection compared with healthy subjects to assess the efficacy of serologic tests as a supplementary approach in the diagnosis of COVID-19. Due to the results, neutralizing antibody tests are not extensively accessible, and outcomes from the accessible serologic assays are not well-known to be associated with the neutralizing antibody titers. Further research studies are also being done to specify whether semi-quantitative outcomes from SARS-CoV-2 IgG ELISAs display any relationship to neutralizing antibody levels.

CONCLUSIONS

In conclusion, the IgM antibody appears earlier than the IgG antibody during the COVID-19 infection. Moreover, based on our findings, there is a higher level of IgG in the plasma of patients with COVID-19, compared to IgM. Further studies regarding protective immunity against this novel coronavirus, as well as the immune system efficacy in reinfection, are required, and their results will be important for understanding the proper treatment and control of COVID-19 patients, such as monoclonal antibodies and vaccination. According to the findingsof our study, the alterations of specific antibodies (IgG and IgM) against SARS-CoV-2 can be a marker for COVID-19 infection, and thus therapeutic methods including convalescent plasma therapy can be considered for future treatment.

Limitations

First of all, the studies that did not have

sufficient data, those not relevant to our subject matter, and those that were not in English were excluded. The heterogeneity can also be considered as a limiting factor for our meta-analysis. Moreover, there were some variations among the papers regarding the exclusion and inclusion criteria, such as the assessed factors and the diagnostic methods for the detection of the immunoglobulins. Another limitation of the current study involved the quality of the trials.

Conflicts of Interest: None declared.

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