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REVIEW

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Diagnostic accuracy of serological tests and kinetics of severe acute respiratory syndrome coronavirus 2 antibody: A systematic review and meta-analysis

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Summary

This study aimed to assess the diagnostic test accuracy (DTA) of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) serological test methods and the kinetics of antibody positivity. Systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. We included articles evaluating the diagnostic accuracy of serological tests and the kinetics of antibody positivity. MEDLINE through PubMed, Scopus, medRxiv and bioRxiv were sources of articles. Methodological qualities of included articles were appraised using QUADAS-2 while Metandi performs bivariate meta-analysis of DTA using a generalized linear mixed-model approach. Stata 14 and Review Manager 5.3 were used for data analysis. The summary sensitivity/specificity of chemiluminescence immunoassay (CLIA), enzyme-linked immunosorbent assay (ELISA) and lateral flow immunoassay (LFIA) were 92% (95% CI: 86%–95%)/99% (CI: 97%–99%), 86% (CI: 82%–89%)/99% (CI: 98%–100%) and 78% (CI: 71%–83%)/98% (95% CI: 96%–99%), respectively. Moreover, CLIA-based assays produced nearly 100% sensitivity within 11–15 days post-symptom onset (DPSO).

Abbreviations: BAL, Broncho alveolar lavage; CLIA, chemiluminescence immunoassay; COVID-19, coronavirus disease 2019; DOR, diagnostic odds ratio; DPSO, days post-symptom onset; DTA, diagnostic test accuracy; E, envelope protein; ELISA, enzyme-linked immunosorbent assay; HCoVs, human coronaviruses; HSROC, hierarchical summary receiver-operative characteristics; LFIA, colloidal gold lateral flow immunoassays; LIPS, luciferase immunoprecipitation assay systems; LR−, negative likelihood ratio; LR+, positive likelihood ration; MERS-CoV, Middle East respiratory syndrome coronavirus; N, NP, nucleocapsid protein; PRIMSA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBD, receptor binding domain; RdRP, RNA-dependent RNA polymerase; RT-PCR, reverse transcriptase polymerase chain reaction; S, spike protein.

Daniel Mekonnen and Hylemariam Mihiretie Mengist contributed equally to this work.

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Based on antibody type, the sensitivity of ELISA-total antibody, CLIA-IgM/G and CLIA-IgG gauged at 94%, 92% and 92%, respectively. The sensitivity of CLIA–RBD assay reached 96%, while LFIA-S demonstrated the lowest sensitivity, 71% (95% CI: 58%–80%). CLIA assays targeting antibodies against RBD considered the best DTA. The antibody positivity rate increased corresponding with DPSO, but there was some decrement when moving from acute phase to convalescent phase of infection. As immunoglobulin isotope-related DTA was heterogeneous, our data have insufficient evidence to recommend CLIA/ELISA for clinical decision-making, but likely to have comparative advantage over RT-qPCR in certain circumstances and geographic regions.

KEYWORDS
diagnostic accuracy, kinetics of antibody, SARS-CoV-2, serological tests

1 | INTRODUCTION

Since the end of 2019, there has been emergence of coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Based on worldometer (https://www.worldometers.info/coronavirus/) report, there were over 33 million infections and over a million (1,002,985) deaths as of 28 September 2020. Seven human pathogenic coronaviruses have been reported so far.[2,3] Comparatively, SARS-CoV-2 is considered as once-in-a-century pathogen.[4] Unintendedly, COVID-19 is changing the world's social, economic and political status.

Having 9-month tragedy from the first case of COVID-19 notification, there is still inadequate access to appropriate diagnostic tests for various reasons. At global level, a point-of-care test fulfilling the ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable) criteria is ultimately needed.[5] Currently, nasopharyngeal and/or oropharyngeal swabs are the scene samples for diagnosis of COVID-19 using quantitative reverse transcription polymerase chain reaction (RT-qPCR). Besides the poor quality of swab samples, the implementation of RT-qPCR by itself is resource and technical demanding, especially in resource-limited settings. Additionally, there are global stock issues with RT-qPCR primers and positive controls.[6] Moreover, due to SARS-CoV-2 evolution, periodic RT-qPCR assay and primer optimization are required.[7] These collective barriers make COVID-19 diagnostic tool as an unmet need to the global healthcare system.

Serological tests measure the amount of antibodies produced against cognate antigens of the pathogen and are important for identification of those who are immune, people with low viral dose showing false-negative RT-qPCR and late notified patients.[8]

Evidences showed that SARS-CoV-2 induce both humoral and cellular immune responses. Diagnosis of COVID-19 by targeting humoral immune response might be advantageous from several perspectives. It does not require sophisticated biosafety level 3 (BSL-3) laboratory, less infectious and robust. Three systematic review and meta-analyses had been carried out to determine the diagnostic test accuracy (DTA) of recently developed serological tests.[9,10] However, Kontou and his colleagues analysed only parts of reported data which likely introduce bias due to selective reporting.[9] Additionally, this study did not analyse the DTA of IgA-based serological tests. Although Caini et al. analysed the DTA of serological tests having information about the antigen types used, the study was limited only to quantitative assays (enzyme-linked immunosorbent assay [ELISA] and chemiluminescence immunoassay [CLIA]).[10] Recently, Bastos et al. released a better summary evidence; however, this study also lacks regressive evaluation of DTA in relation to antigen and antibody types.[11]

CLIA, which uses luminescent molecule as a label, has wide dynamic range, high signal intensity, absence of interfering emissions, high stability of reagents and ability to detect as low as 10^{-21}zmol molecular concentration.[12] ELISA, on the other hand, is fast and adaptable to automation for increased throughput, but with variable sensitivity.[13] On the other hand, lateral flow immunoassay (LFIA) is simple in design, portable, rapid and easy to interpret; however, it is qualitative and inherently lacks sensitivity.[14] Although there is an increasing interest of developing LFIA for SARS-CoV-2 diagnosis, the sensitivity of LFIA is suboptimal. On the other hand, CLIA assays targeting antibody for the receptor binding domain (RBD) of SARS-CoV-2 spike protein showed improved DTA.

Serological tests might be cost effective and affordable to developing countries where expertise and infrastructure are limited, and health system response is measured in days rather than in hours. Peeling and colleagues recommended serological tests for rapid triage of symptomatic individuals in community settings, surveillance and testing of all contacts of people with confirmed COVID-19. On the contrary, these authors enjoin such tests for mass screening and certification to return to work.[15] Recent report challenged some of the Peeling et al. and World Health Organization (WHO) negative recommendations on the utility of COVID-19 serological tests. For

instance, Bryant et al. promote the applicability of serological tools for addressing issues related to stay-at-home orders, business and school closures.[16]

Corresponding to resource, technical and specimen limitations of using RT-qPCR, identifying the best serological assay, antigen and antibody is of a tremendous significance at the mid of the pandemic. Hence, the aim of this study was to determine the summary DTA of serological tests and assess the kinetics of antibody production over time in COVID-19 patients.

2 | METHODS

2.1 | Eligibility criteria

Articles reporting the sensitivity and specificity of SARS-CoV-2 antibody tests (IgM, IgG and IgA, and combination of these) were included in this review. The index test was any commercial or in-house developed antibody test for the diagnosis of COVID-19. The assay formats of the index test included ELISA, LFIA, CLIA and luciferase immunoprecipitation system (LIPS). Articles published and/or pre-printed in English language in the year 2020 were eligible. Articles that did not fulfil the 2 × 2 table for the determination of sensitivity and specificity were excluded.

2.2 | Information sources and search strategy

Article search was done from MEDLINE through PubMed, Scopus, medRxiv and bioRxiv until 7 May 2020. Additionally, the reference list of some reviews was used to retrieve further literature. The search was done using medical subject heading terms and Boolean operators. Two rounds of searches were carried out at PubMed, medRxiv and bioRxiv preprints, and a single round of search was performed at Scopus. The detailed search strategy is included as a supplementary material (Table S1).

2.3 | Study selection and data collection process

All of the identified articles were exported to EndNote 9 library. After removing duplicates, screening was done by reading title followed by reading the abstract and then by reviewing the full work. Articles were independently assessed for inclusion by the first two authors of this paper (Daniel Mekonnen and Hylemariam Mihiretie Mengist). Disagreements regarding the inclusion or exclusion of articles were resolved by discussion. Similarly, data from the included articles were extracted independently by the two authors after piloting the data extraction sheet. Disagreements on the extracted data items were resolved by discussion. Despite no response was obtained, we contacted some authors of the included articles for clarity and possible sharing of their raw data.

2.4 | Data items

The extracted data included the name of the first author of the article, country of study, type of assay (ELISA, LFIA, CLIA or LIPS), manufacturer, type of antigen (spike [S], nucleoprotein [N, NP] or RBD), immunoglobulin isotypes (IgM, IgG, IgA, total antibody or a combination of them), DTA types (overall sensitivity and specificity of assay/tests, and antibody kinetics DPSO), true positive (TP), true negative (TN), false positive (FP) and false negative (FN). The TP, FP, TN and FN results of each immunoglobulin isotype (IgM, IgG, IgA, IgM and IgG, and total antibody) were reported separately and considered as a separate study.

2.5 | Definitions of data items

Index test was any commercial or in-house developed serological test kit designed in the form of CLIA, ELISA, LFIA and LIPS. RT-qPCR with or without immunoassay other than index test was used as a reference test, and samples showing positive RT-qPCR result were considered as true COVID-19 cases; otherwise considered as true negatives. Stored pre-COVID-19 blood samples collected from the blood donors and patients with different respiratory viruses were used as control. For detailed description and definition of terms related to DTA such as sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), diagnostic odds ratio (DOR) and hierarchical summary receiver-operating characteristic (HSROC) curve, readers are advised to read the Cochrane Handbook for Systematic Reviews of DTA.[17]

2.6 | Risk of bias and applicability

Methodological quality of the included articles was appraised in duplicate (by Daniel Mekonnen and Hylemariam Mihiretie Mengist) using QUADAS-2: a revised tool for the quality assessment of DTA.[17,18] The tool has four domains for risk of bias judgement and three domains for applicability judgement. If a study is judged as 'low' on all domains relating to bias or applicability, it is judged as 'low risk of bias' or 'low concern regarding applicability' for that study. If a study is judged 'high' or 'unclear' in one or more domains; it is judged as having 'high risk or unclear risk of bias/applicability'.[18]

2.7 | Diagnostic accuracy measures

The DTA summary measures were sensitivity, specificity, DOR, LR+, LR− and receiver-operating characteristic (ROC) curve. These summary measures were derived at assay level and further stratified by antibody and antigen types. The analysis was performed by using Stata 14 (StataCorp 2015. Stata Statistical Software: Release 14. College Station, TX, USA: Stata Corp LP.), and review Manager 5.3.

2.8 | Synthesis of results and meta-analysis

Metandi performs bivariate meta-analysis of DTA using a generalized linear mixed-model approach. The analysis was carried out according to Takwoing.[19] For meta-analysis, at least four experimental observations were required. The summary sensitivity, specificity, DOR, LR+ and LR− were presented using tables. Heterogeneity was assessed visually using forest plots. Due to inherent nature of heterogeneity in DTA; random-effects approach was employed. The HSROC, which plots sensitivity versus specificity, was also employed to visualize the landscape of the serological tests. Accordingly, the closer the curve to the upper left-hand corner of the plot; the better the performance of the test.

3 | RESULTS

3.1 | Study selection and study characteristics

A total of 226 articles were retrieved from the databases and through manual searching. Articles were selected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) flow chart (Figure 1). Finally, a total of 24 articles from nine countries were included in the review. These articles evaluated serological test kits developed by 47 (31 known commercial, 9 anonymous commercial and 7 in-house) companies. Majority of the studies and companies were from China followed by the United States. The profiles of included articles are summarized in Table 1.

Fifteen (62.5%) of the included articles reported the types of RT-qPCR samples used (six nasopharyngeal, four naso/oropharyngeal, four throat/oropharyngeal and one respiratory specimen). Thirteen (54%) articles used control blood sample collected in the pre-COVID-19 period (Table 2).

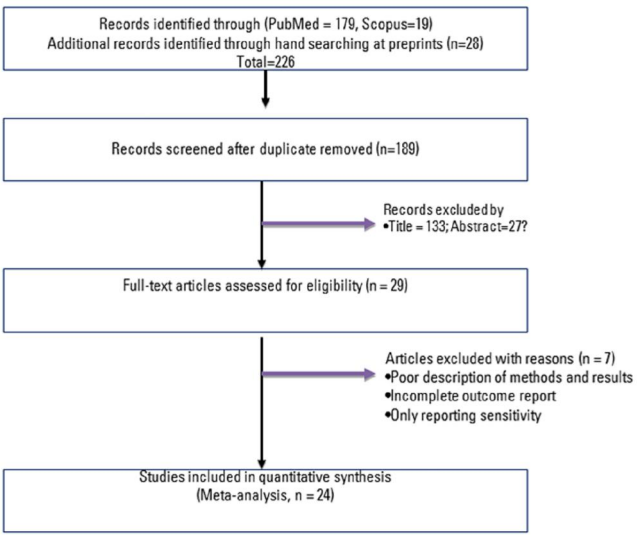

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing the strategy used for article selection

3.2 | Risk of bias and applicability

Mythological quality assessment indicated that most articles did not provide clear information about blinding when reading the index and gold standard tests. Additionally, information regarding sampling strategy (random, consecutive or case control) was not provided. Furthermore, Pan et al.[37] and Liu et al.[32] reported a score of high risk and uncertain risk in all domains. Given the main aim of the studies was selecting sensitive and specific serological test for SARS-CoV-2, applicability concern was considered as low, except for Zhang et al.[41] Figure 2 illustrates the methodological quality assessment results.

3.3 | Results of individual studies

From the 24 included studies, 316 tests were reported and each antibody test was treated as a separate study. Bryan et al.[22] evaluated IgG-N-based CLIA using 125 known SARS-CoV-2 positive samples and 1920 pre-COVID-19 controls. This study obtained 100% sensitivity and specificity of CLIA. Ma et al.[34] evaluated the diagnostic performance of an in-house developed CLIA using 216 cases and 483 controls, and reported 100% sensitivity and 99% specificity. Okba et al.[36] also reported 100% sensitivity and 99.9% specificity of serological tests in 19 COVID-19 patients. Similarly, another study from the Netherlands evaluated ELISA-based total antibody test and reported a sensitivity and specificity of 98.7% and 99%, respectively.[26] The sensitivity and specificity of each included study and antibody test were depicted using forest plot in Figure 3.

Some commercial and in-house manufactured kits revealed a sensitivity of 100% and a specificity of 95%–99% within 11 DPSO.[23,33,34,42] On the other hand, Pérez-García et al.[38] evaluated LFIA-based antibody tests and reported a sensitivity ranging from 0% to 33% and a specificity between 96% and 100%. Another ELISA-based IgG-N assay showed 19% sensitivity but with excellent specificity of 99% after 1–7 DPSO.[42] Our closer look at into the data showed that most of DTA studies used very small sample size which might hamper the results of the studies (Figure 3).

3.4 | Synthesis of results

Before splitting the data in to 'overall DTA' (studies claimed optimal sensitivity and specificity) and antibody kinetics; we pooled the whole data-set to map the serological diagnostic landscape of COVID-19 by disaggregating with assay, antibody and antigen types. The HSROC curves in Figure 4 shows that IgA-based serological tests positioned at the upper left corner of sensitivity–specificity curve (Figure 4a). Comparatively, CLIA among assays (Figure 4b) and RBD among antigens (Figure 4c) demonstrated better DTA results.

TABLE 1 Profile of articles included in the review

Reference	Country	Assay	Company	Antibody types	Antigen
Adams[20]	UK	ELISA	In-house	IgM/IgG	S
Adams[20]	UK	LFIA	9 Anonymous	IgM/IgG	S
Adams[21]	UK	ELISA	Mologic's IgG ELISA	IgG	NP+S
Bryan[22]	USA	CLIA	Abbot	IgG	NP
Burbelo[23]	USA	LIPS	Twist Biosciences	Total Ab	NP, S
Cai[24]	China	CLIA	Sangon Biotech Co	IgM, IgG, IgM/IgG	S
Freeman[25]	USA	ELISA	Thermo Fischer	IgM, IgG, total Ab	S
GeurtsvanKessel[26]	Netherlands	LFIA	Cellex Inc.	IgG	NP+S
GeurtsvanKessel[26]	Netherlands	CLIA	DiaSorin Liaison	Total Ab	S
GeurtsvanKessel[26]	Netherlands	ELISA	EUROIMMUN Medizinische	IgG, IgA	S
GeurtsvanKessel[26]	Netherlands	LFIA	InTec	IgM, IgG	NP
GeurtsvanKessel[26]	Netherlands	LFIA	Orient Gene	IgM, IgG	NP+S
GeurtsvanKessel[26]	Netherlands	ELISA	Wantai Biological Pharmacy	IgM, Total Ab	RBD
Guo[27]	China	ELISA	In-house	IgM, IgA, IgG	NP
Infantino[28]	Italy	CLIA	YHLO Biotech	IgM, IgG	No data
Lassauniere[29]	Denmark	LFIA	Acro Biotech, AllTest Biotech, Artron Laboratories, AutoBio Diagnostics, CTK Biotech, Dynamiker Biotechnology	IgM/IgG	No data
Lassauniere[29]	Denmark	ELISA	Wantai Biological Pharmacy	IgG, IgA, Total Ab	RBD
Lin[30]	China	CLIA	Darui Biotech	IgM, IgG, IgM/IgG	NP
Liu W[31]	China	ELISA	Hotgen, Beijing	IgM, IgG, IgM/IgG	S, NP
Liu R[32]	China	ELISA	YHLO Biotech	IgM	No data
Lou[33]	China	LFIA	Wantai Biological Pharmacy	IgM, IgM/IgG	RBD
Lou[33]	China	LFIA, ELISA	Wantai Biological Pharmacy	IgG	NP
Lou[33]	China	ELISA	Wantai Biological Pharmacy	IgM, IgM/IgG, total Ab	RBD
Lou[33]	China	CLIA	Xiamen InnoDx Biotech	IgM	RBD
Lou[33]	China	CLIA	Xiamen InnoDx Biotech.	IgM/IgG	NP+S
Ma[34]	China	CLIA	In-house	IgM, IgG, IgA & their combination	RBD
Meyer[35]	Switzerland	ELISA	EUROIMMUN Medizinische,	IgA, IgG	S
Okba[36]	Multi country	ELISA	In-house	IgA, IgG, IgA/IgG	S
Pan[37]	China	LFIA	Zhu Hai Liv Zon Diagnostics	IgM, IgG, IgM/IgG	No data
Perez-Garcia[38]	Spain	LFIA	AllTest Biotech, Hangzhou,	IgM, IgG, IgM/IgG	No data
Whitman[39]	USA	LFIA	BioMedomi cs	IgM, IgG, IgM/IgG	RBD
Whitman[39]	USA	LFIA	Bioperfectus, Sure	IgM, IgG, IgM/IgG	NP+S
Whitman[39]	USA	LFIA	DecomBio, DeepBlue	IgM, IgG, IgM/IgG	No data
Whitman[39]	USA	ELISA	Epitope	IgM, IgG, IgM/IgG	NP
Whitman[39]	USA	ELISA	In-house	IgM, IgG, IgM/IgG	RBD
Whitman[39]	USA	LFIA	Innovita	IgM, IgG, IgM/IgG	NP+S
Whitman[39]	USA	LFIA	Premier, UCP, VivaChek. Wondfo	IgM, IgG, IgM/IgG	No data

(Continues)

TABLE 1 (Continued)

Reference	Country	Assay	Company	Antibody types	Antigen
Xiang[40]	China	LFIA	Zhu Hai Liv Zon Diagnostics	IgM, IgG, IgM/IgG, total Ab	No data
Zhang[41]	Multi country	LFIA	In-house	IgM/IgG	RBD
Zhao J[42]	China	ELISA	Wantai Biological Pharmacy	IgM, total Ab	RBD
Zhao J[42]	China	ELISA	Wantai Biological Pharmacy	IgG	NP
Zhao R[43]	China	ELISA	In-house	IgM/IgG	S

Abbreviations: Ab, antibody; CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent immunoassay; LFIA, lateral flow immunoassay; NP, nucleocapsid protein; RBD, receptor-binding domain; S, Spike protein.

TABLE 2 Reference test with types of samples and clinical profile of controls

Article	Reference	Specimen	Types of controls used
Adams[20]	RT-PCR	Nasopharyngeal	564 pre-COVID-19 from people with other respiratory condition
Adams[21]	RT-PCR	Nasopharyngeal/throat	50 pre-COVID-19 donors and healthy people
Bryan[22]	RT-PCR	Nasopharyngeal	1020 pre-COVID samples
Burbelo[23]	RT-PCR	Naso/oropharyngeal	32 pre-COVID blood bank donors, 6 non covid-19 patients
Cai[24]	RT-PCR	Nasopharyngeal	200 pre-COVID-19 healthy and 167 individuals with different viral & bacterial infection
Freeman[25]	RT-PCR	No information	377 pre-COVID healthy, 101 Hanta virus suspected, 21 HIV infected, 10 HBV infected and 10 HCV positive people
Geurtsvan Kessel[26]	PRNT50 + PCR	No information	147 people with non-COVID-19 coronavirus and other RTI cases
Guo[27]	RT-PCR	Throat	135 with LRTI & 150 with pre-COVID-19 health people
Infantino[28]	RT-PCR	Naso/oropharyngeal	31 rheumatic cases in Pre-COVID era, 13 pre-COVID-19 and 20 blood bank sera taken during COVID-19 outbreak
Lassaunière[29]	RT-PCR	No information	10 healthy, 5 non-COVID-19 coronaviruses positive, 45 other RTI, 9 dengu virus, 10 EBV, 2 CMV and 1 CMV+EBV infected
Lin[30]	RT-PCR	No information	29 healthy and 51 tuberculosis patients
Liu W[31]	RT-PCR	Nasopharyngeal	100 healthy blood donors
Liu R[32]	RT-PCR	No information	42 COVID-19 suspects but negative by RT-qPCR test
Lou[33]	RT-PCR	No information	300 healthy people from the community
Ma[34]	RT-PCR	Throat	330 health people, 15 COVID-19 suspected pneumonia and 138 individuals with other health conditions
Meyer[35]	RT-PCR+rIFA	No information	176 pre-COVID-19 samples stored in the laboratory
Okba[36]	PRNT+PCR	No information	45 healthy blood donors, 31 non-COVID-19 coronavirus positive patients
Pan[37]	RT-PCR	Throat	No information provided
Pérez-García[38]	RT-PCR	Nasopharyngeal	55 pre-COVID-19 healthy controls and 63 persons with pneumonia of unknown aetiology
Whitman[39]	RT-PCR	Naso/oropharyngeal	108 pre-COVID-19 blood bank samples, 50 people with RTI and 32 with non-COVID RTI
Xiang[40]	RT-PCR	Throat	35 Healthy controls
Zhang[41]	RT-PCR	Nasopharyngeal	7 Healthy sera
Zhao J[42]	RT-PCR	Respiratory tract	213 Pre-COVID healthy people
Zhao R[43]	RT-PCR	No information	257 pre-COVID-19 and 155 controls during COVID-19

Abbreviations: LRTI, lower respiratory tract infection; PRNT 50, plague-reduction neutralization test 50; rIFA, recombinant immunofluorescence assay; RTI, respiratory tract infection.

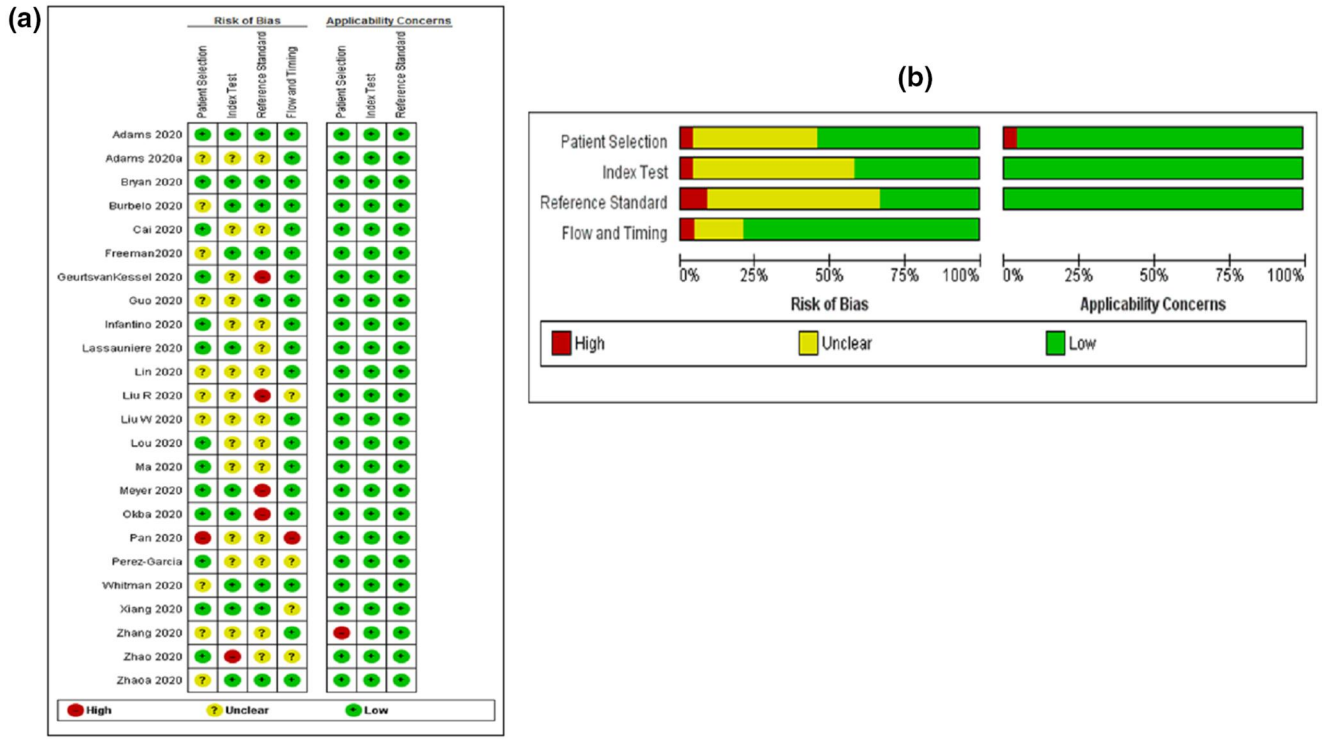

FIGURE 2 (a) Risk of bias and applicability concerns summary (b) Percentages across included studies: QUADAS-2 tool review authors' judgements about each domain for each included study

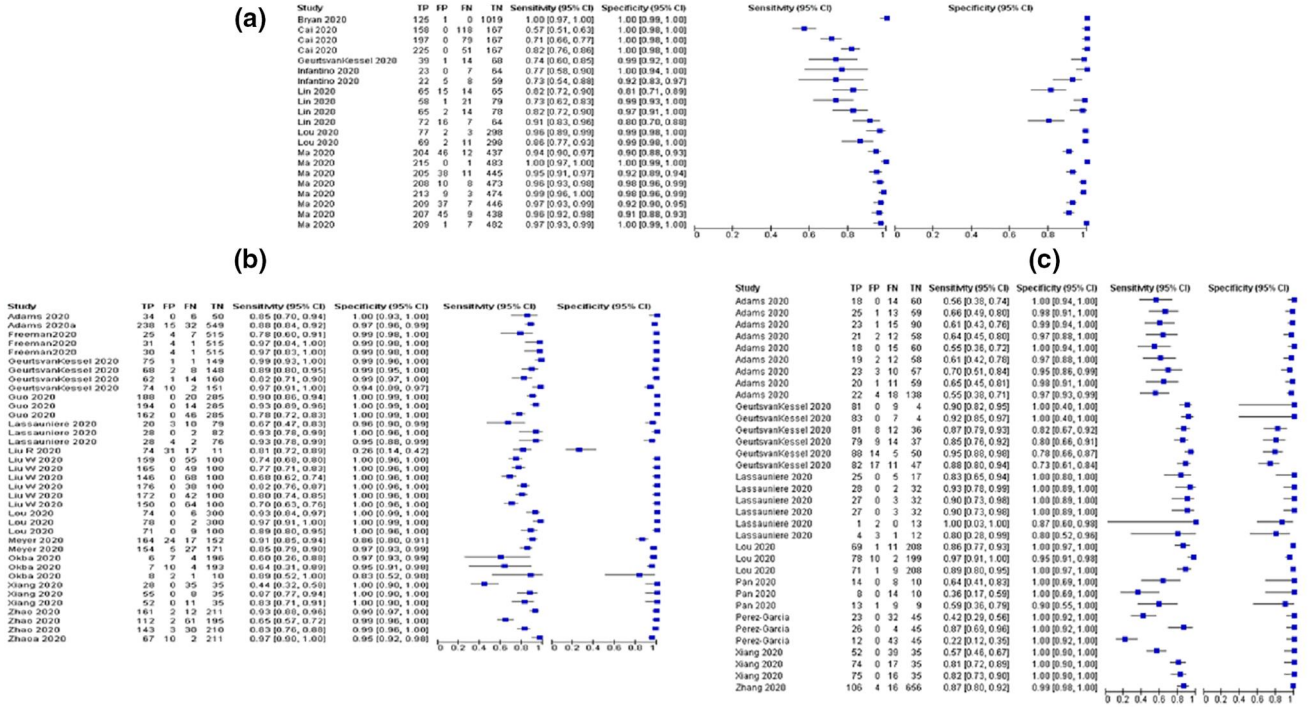

FIGURE 3 Summary forest plot for (a) chemiluminescence immunoassay (b) enzyme-linked immunosorbent assay and (c) lateral fluorescent immunoassay showing heterogeneity

Meta-analysis for an 'overall DTA' was performed by stratifying with types of assay (CLIA, ELISA and LFIA), antibody and antigen. As such, the summary sensitivity and specificity of CLIA were gauged at 92% (95% CI: 86%–95%) and 99% (97%–99%), respectively. Again, CLIA-assay-based antibodies exhibited better sensitivity and specificity compared to ELISA and LFIA. Similarly, the summary sensitivity

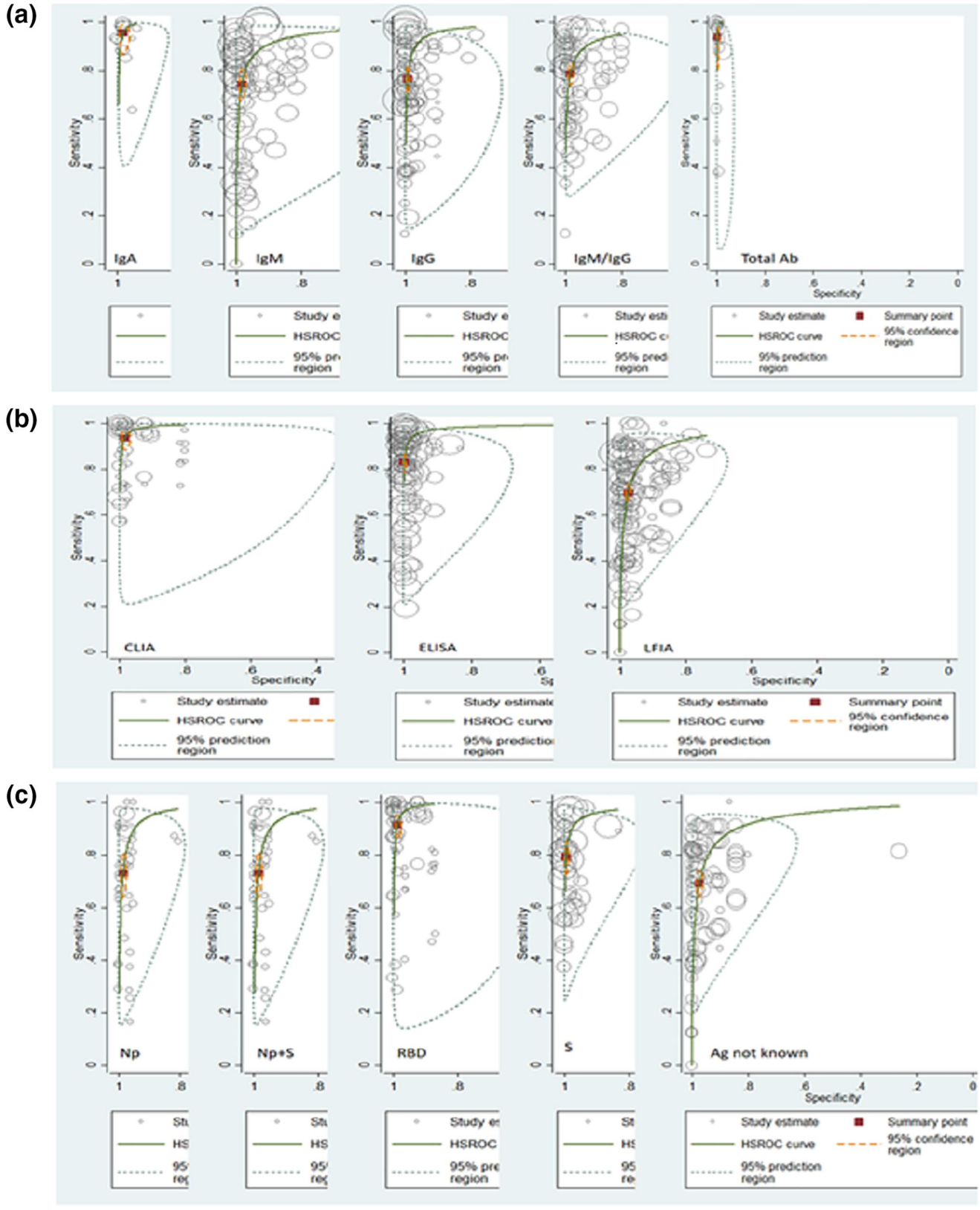

FIGURE 4 Comparison of the hierarchical summary receiver-operating characteristic curve of (a) antibodies, (b) assay types and (c) antigen types of severe acute respiratory syndrome coronavirus 2 serological tests

TABLE 3 Overall diagnostic accuracy profile of serological assays included in the review

Assay	#Tests	Sn% (95% CI)	Sp% (95% CI)	DOR% (95% CI)	LR+% (95% CI)	LR-% (95% CI)
CLIA	21	92 (86–95)	99 (97–99)	856 (278–2630)	71 (28–181)	0.08 (0.05–0.1)
ELISA	37	86 (82–89)	99 (98–100)	980 (391–2455)	136 (57–326)	0.1 (0.1–0.2)
LFIA	34	78 (71–83)	98 (96–99)	216 (101–463)	49 (23–103)	0.2 (0.2–0.3)
CLIA-IgG	5	92 (71–98)	99.7 (99–100)	3845 (344–42962)	289 (80–1040)	0.8 (0.02–0.3)
CLIA-IgM	5	84 (67–93)	97 (86–99.5)	180 (37–877)	30 (6–157)	0.2 (0.08–0.3)
CLIA-IgM/IgG	4	92 (85–96)	98 (78–99.9)	670 (55–8145)	56 (4–843)	0.08 (0.05–0.15)
CLIA-N	5	91 (70–98)	97 (83–99.6)	366 (17–7918)	32 (4–232)	0.1 (0.02–0.4)
CLIA-S	4	72 (61–80)	99 (93–99.9)	1821 (37–90442)	516 (10–25342)	0.3 (0.2–0.4)
CLIA-RBD	9	96 (94–98)	98 (94–99)	1335 (321–5549)	48 (15–148)	0.03 (0.02–0.06)
ELISA-IgM	9	81 (73–88)	99.8 (95–100)	1841 (75–45431)	356 (15–8609)	0.2 (0.1–0.3)
ELISA-IgA	5	91 (81–96)	97 (93–99)	354 (93–1346)	34 (12–92)	0.1 (0.04–0.2)
ELISA-IgG	11	79 (73–85)	99 (97–100)	840 (148–1968)	111 (31–402)	0.2 (0.15–0.3)
ELISA-IgM/G	4	85 (77–93)	100 (92–100)	2626 (94–73188)	339 (11–10737)	0.15 (0.07–0.23)
ELISA-tAb	7	94 (90–97)	99 (98–100)	2174 (573–8248)	127 (48–335)	0.06 (0.03–0.1)
ELISA-RBD	9	92 (86–96)	99 (98–100)	1455 (345–6144)	120 (44–325)	0.08 (0.04–0.2)
ELISA-S	15	87 (81–91)	98 (97–99)	403 (186–871)	55 (26–117)	0.14 (0.1–0.2)
ELISA-NP	8	81 (72–88)	100 (63–100)	112014 (2–2 × 10^9)	21150 (1–3 × 10^8)	0.2 (0.1–0.3)
ELISA-uAg	4	76 (58–88)	100 (0.4–100)	-	-	-
LFIA-IgM	7	82 (67–91)	98 (85–99.6)	184 (32–1052)	34 (5.5–211)	0.2 (0.1–0.3)
LFIA-IgG	7	72 (50–88)	100 (46–100)	796 (3–196457)	221 (0.7–69210)	0.3 (0.1–0.6)
LFIA-IgM/G	20	77 (69–84)	98 (97–99)	201 (92–437)	46 (24–91)	0.2 (0.2–0.3)
LFIA-S	9	71 (58–80)	98 (97–99)	122 (61–244)	36 (21–63)	0.3 (0.2–0.44)
LFIA-(S+N)	4	88 (85–91)	96 (78–99.5)	199 (23–1693)	24 (3–179)	0.12 (0.09–0.16)

Abbreviations: CI, confidence interval; DOR, diagnostics odds ratio; LR+, positive likelihood ratio; LR−, negative likelihood ratio; Sn, sensitivity; Sp, specificity; tAb, total antibody; uAg, unknown antigen.

of ELISA tests was gauged at 86% (95% CI: 82%–89%). ELISA, having no information about the type of antigen, demonstrated the lowest DTA, 76% (95% CI: 58%–88%), but it is noted that IgA- and total-antibody-based ELISA assays gave improved summary sensitivity (Table 3).

LFIA-assay-based studies demonstrated the lowest summary test accuracy with 78% (95% CI: 71%–83%) sensitivity. Moreover, the sensitivity of LFIA could not be improved at various antibody and antigen combinations. The use of both S and N antigens increased the sensitivity of LFIA to 88% at the cost of decreasing specificity (Table 3). Subgroup analysis was executed to arbitrate the summary DTA of assays disaggregated by antigen and antibody types. Only RBD consistently showed superior DTA compared with other types of antigens (S, N and unknown Ag). The DTA subgroup analysis by the type of antibody and antigens other than RBD produced heterogeneous results and were inconclusive. For instance, CLIA-IgG is better in terms of sensitivity (92%, 95% CI: 91%–98%) than CLIA-IgM (84%, 95% CI: 67%–93%). On the contrary, the DTA of ELISA-IgM and LFIA-IgM becomes superior over ELISA-IgG and LFIA-IgG, respectively. Taken together, only assay types consistently showed significant influence on DTA (Table 3).

The specificity of the assays and tests ranged from 96% to 100%. The higher specificity implies that there is relatively low cross-reactivity. It should be noted that, due to small number of tests in each summary DTA; the pooled results must be interpreted with caution.

Different studies classified DPSO differently. Some studies classified DPSO into <14 and >14,[23] while others classified it into 1–7, 8–14 and ≥15.[20,27,30,33,37,38,42] Some studies classified DPSO into 1–10, 11–15, 16–20 and ≥21.[22,31,34,39] Among these classifications, the one which classified DPSO into 1–10, 11–15, 16–20 and ≥21 has relatively more kinetics data so that this study determined the antibody kinetics based on this DPSO interval. Based on this, there were trends of increasing antibody positivity among included cases. However, there was a slight decrease in the antibody positivity when moving from the second phase (11–15 DPSO) to the third phase (16–20 DPSO) of follow-up period. The fluctuation on the trends might be due to the small number of studies, small sample size or waning of IgM antibodies (Figure 5). Most importantly, it is

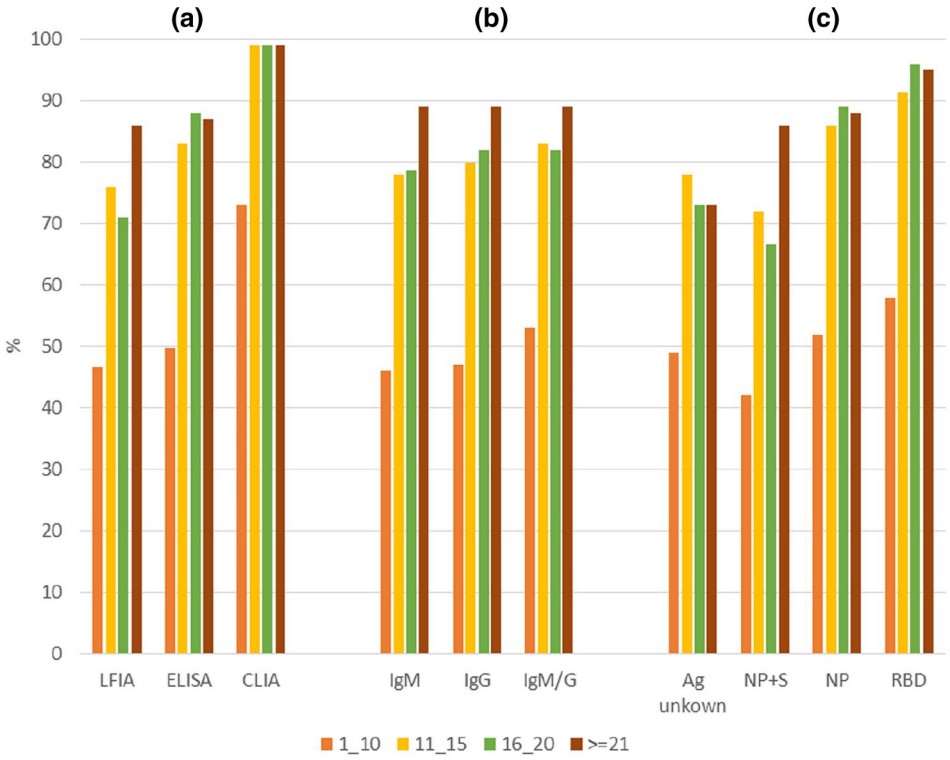

FIGURE 5 The kinetics of antibody positivity based on (a) assay type, (b) antibody type and (c) antigen type disaggregated by days post-symptom onset

recognized now that SARS-CoV-2 infections generate two waves of antibodies: early short-lived plasma cells followed by longer lived plasma cells that provide long-lived immunity.[44]

Surprisingly, IgG positivity was seen similarly and even slightly earlier than IgM positivity at any interval of DPSO (Figure 5) among COVID-19 patients. It is generally known that seroconversion of IgM appears earlier than that of IgG and IgA. This apparent contradiction may arise from two reasons: the first one is the long incubation time of COVID-19 (ranging between 1 and 14 days) and the other is the higher specificity of IgG antibodies in general, which increases detection sensitivity. If this scenario is true and reproducible, IgG-based assays would be preferable over IgM-based assays, as it is more sensitive and detects both early and past histories of infection. Indeed, it was also reported that seroconversion of IgG occurred at the same time or one day earlier than IgM and IgA in a cohort of 20 SARS patients.[45]

CLIA-based assays attained nearly 100% sensitivity within 11–15 DPSO (Figure 5) which might be due to the analytical sensitivity of the assays that are able to detect as low as 10^{-21} zmol molecule.[12] Relatively, antibody positivity rate was higher for anti-RBD antibody followed by anti-N antibodies in the early period of infection (1–10 DPSO; Figure 5), which indicates the higher potential immunogenicity of RBD over other antigens.

4 | DISCUSSION

COVID-19 continues to ravage the world and is reported in almost every country. The global population is looking for point-of-care tests, vaccines and drugs to combate the pandemic. Majority of research works are focussing on COVID-19 infection and immunity. Ongoing efforts are now uncovering many mysteries regarding immune responses in COVID-19 patients.[15,32,44,46–48]

Currently, different companies and research laboratories are developing serological tests to be used for research and clinical decision-making. However, WHO reserves to recommend serological tests for clinical decision-making due to limited evidence on the accuracy of these diagnostics technologies. On the other hand, a recent perspective by Weinstein et al. challenged the WHO through withholding decision of serological tests. Weinstein and colleagues stated that demanding incontrovertible evidence at this time of pandemic might have a profound costs and health consequences.[49] Similarly, Bryant et al. promoted the applicability of serological tools for addressing issues related to stay-at-home orders, business and school closures.[16]

In the current study, IgM/IgA/IgG-based CLIA gained a sensitivity of 92% (95% CI: 86%–95%), a specificity of 99 (97%–99%), and DOR of 865 (278–2630). The higher DOR value of CLIA over ELISA and LFIA indicated the better discriminatory power of CLIA. Long et al.[50]

assessed the application of CLIA in surveillance of a cluster of 164 close contacts of COVID-19 patients in which all of the 16 RT-qPCR-confirmed cases were positive for virus-specific IgG/IgM. Interestingly, CLIA also detected additional seven cases missed by RT-qPCR which indicates the usefulness of the assay to rule out COVID-19.

This review noticed that assays without a known information on the coated antigen suffered from low sensitivity and specificity than S- and RBD-based serological assays. A recent *Lancet* report[6] called these groups of developers 'cagey' to mean 'reserved from giving too many details about their antigen type'.

Nucleocapsid and S antigen-based assays showed heterogeneous DTA information. Although proteins including S, S1, S2, RBD and N are able to elicit antibody response, S2 and S2-containing full-length S proteins performed better in the ELISAs,[46] which is in line with our summary where S-based ELISA showed improved DTA than the N-based assay. A recent review by Kontou et al.[9] described that tests using the S antigen are more sensitive than N-antigen-based tests. SARS-CoV-2 showed antibody cross-reactivity with SARS-CoV N and S proteins but not in patients with MERS.[46]

Due to small number of studies and tests, IgA antibody kinetics was not evaluated in this review. The IgG positivity rate was equal and even slightly higher than IgM positivity at any time interval of DPSO (Figure 5) showing a comparable DTA in acute phase of COVID-19 infection. This condition is in line with Bastos et al. (2020) who concluded the absence of DTA difference by the type of immunoglobulin (IgM, IgG or both).[11] Additionally, Long et al.[50] stated apparent absence of chronological order and general rule for IgM and IgG seroconversion for a specific patient.

Previous studies reported a possible waning of humoral immunity and apparent absence of antibody among asymptomatic patients, which hampered the speed of diagnostic and vaccine development activities. But recent reports challenged this scenario, and now a high titre and stable antibody production for at least 4 months are reported among COVID-19 patients.[44,47,48] It is recognized now that SARS-CoV-2 infection and vaccines generate two waves of antibodies: early short-lived followed by longer lived plasma cells. Between these two phases, there is a transient antibody waning.[44,51,52] Therefore, studying antibody kinetics should be accompanied with several serial samplings or there must be enough time between the period of acute disease stage and convalescent sera.[44]

Serological tests have several clinical and epidemiological applications; however, poor regulatory status might open a door for introduction of poorly designed serological test methods into the market. Poorly designed serological tests will shield the true-positive rate and fuel the transmission of the virus in the community. Hence, urgent scientific direction and tight regulation should be in place.

This review has limitations including absence of unequivocal search term which might cause missing of relevant articles. Small number of observations in the subgroup summary DTA data preclude us from giving strong recommendations. Summary DTA of assays and tests was drawn regardless of thresholds and majority of included articles were non-peer-reviewed preprints. Despite these limitations, our study provides a glimpse into choosing the best serological tests and help policy-makers revise the test algorithms for COVID-19 diagnosis either for clinical decision-making or epidemiological survey.

5 | CONCLUSION

We found significant differences in the DTA among serological assays used for SARS-CoV-2 diagnosis. Selection of serological tests to rule out COVID-19 must be evaluated in the context of diagnostic accuracy. Relatively, our findings support that IgA- and/or IgG-based CLIA assays against viral RBD demonstrated better test accuracy followed by ELISA-(IgA + IgM) against RBD. This review does not recommend the use of LFIA assays. The quality of our evidence is low to support the use of serological tests for clinical decision-making tool but might be applicable in certain conditions. The comparative advantage of IgM versus IgG and N versus S protein shall be investigated further. The immunoglobulin concentrations were significantly higher in severe cases than mild and moderate cases.[22,34] Whether this condition affects the DTA of testing methods and vaccine efficacy should be the subject of further scrutiny. Due to small number of studies included in the review, our summary DTA must be interpreted with caution, and further similar studies comprising a significant number of articles are warranted in the future.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHORS' CONTRIBUTION

Daniel Mekonnen and Hylemariam Mihiretie Mengist: Drafting the protocol and methodology, data collection, formal analysis, writing original draft, writing review and editing manuscript. Awoke Derbie, Hongliang He and Abaineh Munshea, Endalkachew Nibret: Assisted with drafting the protocol and methodology, writing the draft and reviewing the final manuscript. Tengchuan Jin and Bofeng Li: Conceived the review topic, reviewed the protocol, supervised the review process, reviewed, investigated and validated the final manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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