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Review

Update on Rapid Diagnostics for COVID-19: A Systematic Review

Bruna de Paula Dias [1], Ricardo Lemes Gonçalves [1], Cyntia Silva Ferreira [1], Camila Cavadas Barbosa [1], Orlando Alfredo Pineda Arrieta [1], Samara Mayra Soares Alves dos Santos [1], Wellington Carvalho Malta [1], Mariela Alves e Silva [1], Maria Laura Maximiano Dias Gomes [1], Adriana Gibara Guimarães [2], Lysandro Pinto Borges [2,*] and Breno de Mello Silva [1,*]

[1] Department of Biological Sciences, Federal University of Ouro Preto, Ouro Preto 35400-000, Brazil; bdiascmt@gmail.com (B.d.P.D.); ricardolemesg@gmail.com (R.L.G.); csf.ferreira@gmail.com (C.S.F.); camilacavadas@yahoo.com.br (C.C.B.); oapar1995@gmail.com (O.A.P.A.); samara1mayra@gmail.com (S.M.S.A.d.S.); wellington.malta@aluno.ufop.edu.br (W.C.M.); marielaaes@gmail.com (M.A.e.S.); malaudiasg@yahoo.com.br (M.L.M.D.G.)
[2] Department of Pharmacy, Federal University of Sergipe, São Cristóvão 9100-000, Brazil; adrianagibara@hotmail.com
* Correspondence: lysandro.borges@gmail.com (L.P.B.); breno@ufop.edu.br (B.d.M.S.)

Abstract: An accurate and rapid diagnosis of COVID-19 is an effective strategy for pandemic control, allowing disease screening and timely therapeutic intervention. We analyzed scientific reports about rapid tests for the diagnosis of COVID-19 to assess their reliability parameters. Medical Subject Headings terms or keywords related to point-of-care and rapid diagnostic testing for SARS-CoV-2 and COVID-19 were searched in data published from November 2020 to November 2021 in PubMed and Google Scholar databases. Notable differences were observed in sensitivity among direct tests that used different samples, and good accuracy was reported in a significant number of studies (>80%). Pediatric samples and samples with high Ct values (RT-PCR) had suboptimal sensitivity (range 45.4% to 66%). Further, a lack of sensitivity (<46.2%) was observed in point-of-care tests and in rapid diagnostic tests for antibody detection in the first days after infection, with increasing values in postinfection analysis (>60%). For serological detection of IgM or Antigen rapid diagnostic tests, no cross-reactivity was found with other coronaviruses. Therefore, although these tests are very important in facing the pandemic, they still need to be improved to test cross-reactivity against other pathogens, especially against other coronaviruses.

Keywords: SARS-CoV-2; COVID-19; point-of-care; rapid diagnostic tests

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1. Introduction

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) was discovered in November 2019 in Wuhan, China, and is the causative agent of coronavirus disease (COVID-19) [1]. A few months after its discovery, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic [2]. However, more than a year and a half into the pandemic, the number of reported cases and deaths gradually increased, reaching the mark of more than 259 million cases and more than 5 million deaths [3].

Rapid and accurate diagnosis of COVID-19 is crucial for disease screening and managing public health preparedness [4]. Real-time reverse transcription–polymerase chain reaction (rRT-PCR), a molecular test for virus nucleic-acid detection, is the most suitable method to detect SARS-CoV-2 [5]. However, rRT-PCR may yield false-negative results if there is a low amount of viral genome in the sample or a lack of an adequate window period of viral replication [6]. In addition, performing rRT-PCR requires laboratory infrastructure and can take several days to deliver results [7].

Rapid diagnostic tests (RDTs) are an alternative for fast and inexpensive diagnosis of COVID-19 because they are easy to use and results are available in a short time. Furthermore, they are easy to interpret, allowing testing to be possible in near-person, decentralized healthcare settings. In addition, antigen RDTs (Ag-RDT) have good analytical performance. Therefore, they can be used at the point of care (POC) to help increase testing and reduce the spread of infection through early self-isolation [7–13]. On the other hand, detecting antibodies produced in response to infection with SARS-CoV-2 helps identify asymptomatic patients [14,15]. Moreover, they are employed in serum-surveillance studies and investigations of the ongoing outbreak [5].

The importance of mass testing has triggered the development of numerous RDTs, which have been readily implemented during the COVID-19 pandemic [8]. However, questions about the importance of constant test selection based on its accuracy persist.

In our first review, we present an overview of studies reporting the use of POC and RDT tests to diagnose COVID-19 in the first year of the pandemic [16]. However, we observed insufficient data regarding the performance of the analyzed tests and a lack of validation of cross-reactivity with other pathogens in the tests launched in the market. Here, we carried out a new analysis of scientific data published on rapid tests available for the diagnosis of COVID-19 to verify whether the analyses of the available tests have been improved considering the discoveries about SARS-CoV-2, one-year after our first analysis.

2. Methods

2.1. Literature Search

In this systematic review, all studies published from 01 November 2020 until 30 November 2021 were retrieved from PubMed and Google Scholar databases. We considered subject titles and headings/subtitles (when applicable) in addition to keywords and abstracts to identify the searched terms: "point of care sarscov2 diagnostic or diagnosis", "point of care COVID-19 diagnostic or diagnosis", "rapid test COVID-19 diagnostic or diagnosis" and "rapid test SARS-COV-2 diagnostic or diagnosis".

2.2. Selection Criteria

Case-control, cohort studies, and randomized clinical trials with experimental data in POC or RDT tests for SARS-CoV-2 efficiently performed analyses and provided robust data on their results were eligible for inclusion. WHO and the United Nations Children's Fund (UNICEF) point out that RDT should preferably provide results between 15 and 30 min to better deal with the COVID-19 pandemic [7,9]. Therefore, only rapid POC and RDT tests that deliver results within 30 min were included. Duplicate articles, preprints, and other articles with uncorrelated themes such as editorials, case reports, modeling studies, and studies that did not present POC or RDT data for COVID-19 were not included in the present systematic review. There were no language restrictions.

2.3. Data Extraction and Quality Assessment

One independent investigator performed a systematic search in the databases. Seven investigators independently analyzed the title, abstract, and full-text articles to apply the selection criteria following a script with the same parameters. We extracted authors, year of publication, test type, assay method, diagnostic criteria (sensitivity, specificity/accuracy), time detection, sample size, and cross-reaction analysis for each study. Two reviewers independently analyzed and resolved the methodological quality of the eligible studies.

3. Results

A total of 2135 million publications were retrieved from databases, a sample robust enough to identify all relevant articles on the addressed topic, such as our previous study of the first year of the pandemic [16]. After screening the titles, abstracts, and/or keywords, 520 studies were selected, and 52 were chosen for full-text review. Articles selected in this review were published from 01 November 2020 until 30 November 2021. Details of the

total number of articles screened, assessed for eligibility, extracted, and included in the final analyses are shown in Figure 1.

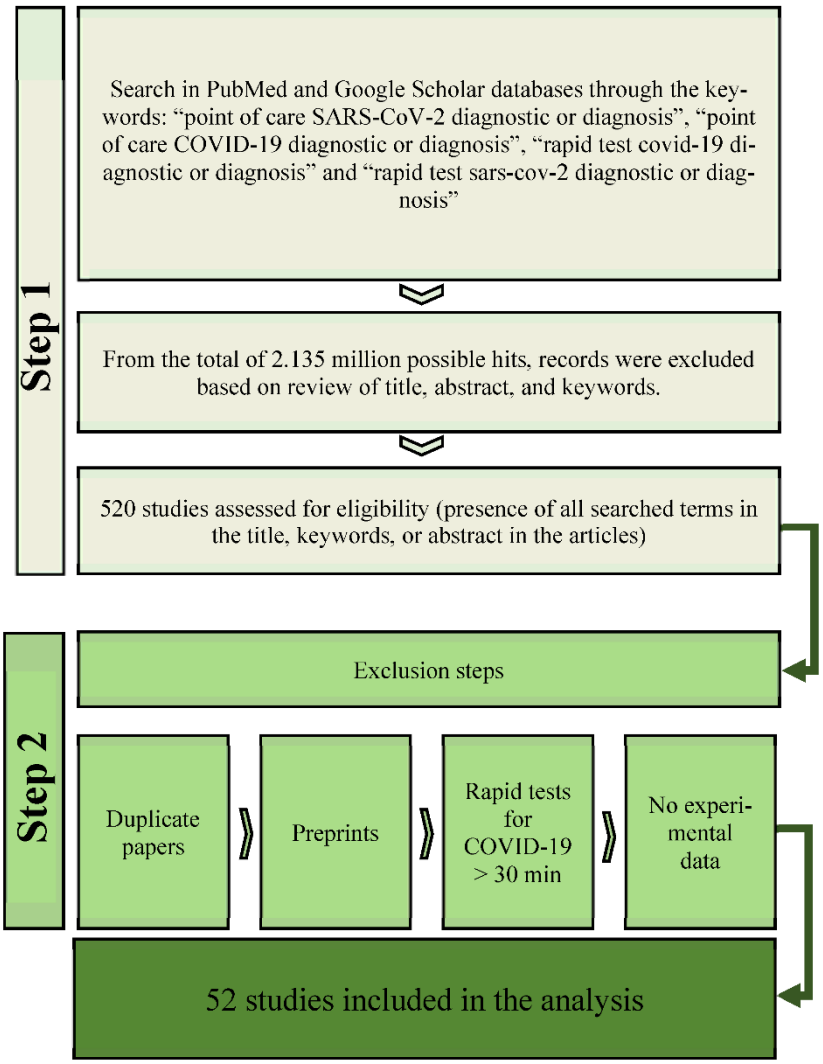

Figure 1. Outline of the methodology. Flowchart of the two main stages of the study.

Tables 1 and 2 summarize the analyzes used in this study.

Table 1. POC tests and RDT for direct detection of SARS-CoV-2.

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Masiá et al. [17]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab (NPS), swab nasal and saliva samples, Panbio COVID-19 Ag RTD (Abbott).	NPS: 60.5% Saliva: 23.1% Nasal samples: 44.7%	ND	ND	100%/ND	913 patients included. 296 were asymptomatic, confirmed by RT-PCR assay.	ND
Krüger et al. [18]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, PanBio™ COVID-19 Ag Rapid Test Device (Abbott).	90.8% overall	61.5% overall	ND	0–7 days: 99.6% overall/ND 08–14 days: 100% overall/ND	1108 cases were tested in total. Information on symptom duration from the day of the test in days was available in 687 patients.	ND
Kolwijck, et al. [19]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal sample, Panbio™ COVID-19 Ag RDT (Abbott).	86.7%	ND	ND	100%/ND	433 participants, with 45 tested positive by RT-qPCR.	ND
Rubio et al. [20]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, Panbio™ COVID-19 Ag RDT (Abbott).	72%	ND	ND	100%/ND	103 nasopharyngeal swabs were evaluated, confirmed by RT-PCR.	ND
L'Huillier et al. [21]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, Panbio™ COVID-19 Ag RDT (Abbott).	66% overall	ND	ND	100%/ND	822 pediatric participants completed the study with RT-PCR positive.	ND
Villaverde et al. [22]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, Panbio™ COVID-19 Ag RDT (Abbott).	45.4%	ND	ND	99.8%/97.2%	1620 pediatric patients aged 0–16 years with symptoms compatible with severe acute respiratory SARS-CoV-2 infection.	ND
Muhi et al. [23]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, Panbio™ COVID-19 Ag RDT (Abbott).	ND	ND	ND	99.96%/ND	2413 subjects tested in hospitals (or associated screening clinics), no subjects tested positive using RT-PCR.	ND
	100%			100%/100%	26 participants with COVID-19 (as notified to the Victorian Department of Health and Human Services) with the time from symptom onset ranged from 1 to 33 days.	

Table 1. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Merino et al. [24]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, Panbio™ COVID-19 Ag RDT (Abbott).	90.5%	ND	ND	98.8%/ND	958 individuals who had at least one symptom compatible with COVID-19 (n = 830) or who had been in close contact with a diagnosed COVID-19 patient (n = 128) were included. RT-PCR was positive in 359 and negative in 599.	ND
Albert et al. [25]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, Panbio™ COVID-19 Ag RDT (Abbott).	Adults: 82.6% Pediatric: 62.5% Overall: 79.6%	ND	ND	100% overall/ND	412 patients with clinical suspicion of COVID-19, 327 were adults and 85 children. 43 were positive by RT-PCR and 358 were negative.	ND
Carbonell-Sahuquillo et al. [26]/Immunochromatographic test for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, Panbio™ COVID-19 Ag RDT (Abbott).	70.6%	ND	ND	100%/95.6%	357 patients (aged 0 to 14 years) with clinical suspicion of COVID-19 (≤5 days since symptom onset). 34 had a positive result by RT-PCR.	7 out of the 10 specimens yielding discordant results (RT-PCR+/RAD-) were run in a multiplexed PCR assay targeting common respiratory viruses. Two of the 7 specimens tested positive for *Rhinovirus/Enterovirus*
Kim et al. [27]/Immunochromatographic lateral flow assay for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swab, GenBody™ COVID-19 Ag test (COVAG025).	90%	ND	ND	98%/96.15%	130 residual NPS swabs from individuals who either visited or were hospitalized at Yeungnam University Medical Centre. 30 were confirmed positive for COVID-19 and 100 were designated negative, based on the RT-PCR assay.	ND
	94%			100%/97%	200 symptomatic and asymptomatic NPS swabs, with 100 samples positive by Real-time PCR for COVID-19.	
Singh et al. [28]/Immunochromatographic lateral flow assay for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal and oropharyngeal swab, GenBody™ COVID-19 Ag test.	35.29%	ND	ND	100%/ND	240 respiratory samples (nasopharyngeal and oropharyngeal smears) were collected from suspected cases of COVID-19. 102 samples were positive RT-PCR.	ND

Table 1. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Möckel et al. [29]/Immunoassay for the rapid determination of the presence of SARS-CoV-2 antigen in human oro-nasopharingeal swabs, Roche SARS-CoV-2 rapid antigen test (Penzberg, Germany).	Adult:75.3% Pediatric:72%	ND	ND	Adult: 100%/ND Pediatric: 99.4%/ND	473 analyzed patients (n = 271 patients from the adult EDs and n = 202 from the pediatric ED).	ND
Jegerlehner et al. [30]/Immunoassay for the rapid determination of the presence of SARS-CoV-2 antigen in human nasopharyngeal swabs, Roche SARS-CoV-2 rapid antigen test (Penzberg, Germany).	65.3%	ND	ND	99.9%/ND	1465 individuals have been tested, including individuals who were referred because of exposure to infected individuals. 141 individuals tested positive according to RT-PCR.	ND
Ciotti et al. [31]/Immunochromatographic test for rapid detection of SARS CoV-2 nucleoprotein in nasopharyngeal swabs, COVID-19 Ag Respi-Strip (Coris BioConcept).	30.77%	ND	ND	100%/86.15%	50 sample have been tested, 39 confirmed by real-time RT-PCR.	ND
Kanaujia et al. [32]/Immunochromatographic test for rapid detection of SARS CoV-2 in nasopharyngeal swabs, COVID-19 Ag Respi-Strip (Coris BioConcept).	71.96%	ND	ND	99.32%/88.64%	825 symptomatic patients and their contacts were included in the study; RT-PCR and antigen detection were performed simultaneously for 484 samples to determine the sensitivity and specificity of the test.	ND
Strömer et al. [33]/Lateral flow chromatographic immunoassay for rapid detection of SARS-CoV-2 nucleoprotein in nasopharyngeal swab, ADAL® COVID-19 Ag (nal von minden GmbH).	73.1% overall	ND	ND	99.3%/ND	134 upper respiratory tract swab samples were used. 124 were positive samples, and 10 were negative samples confirmed by RT-PCR triplex of the N gene.	ND
Thakur et al. [34]/Immune-chromatographic lateral flow assay for the rapid determination of the SARS-Cov-2 antigen in nasopharyngeal swabs manufactured by PathoCatch/ACCUCARE, (Lab Care Diagnostics Private Ltd., Mumbai, India).	34.5%	ND	ND	99.8%/91.7%	677 patients have been tested include asymptomatic patients. 55 specimens that tested positive by RT-qPCR.	ND
Chaimayo et al. [35]/Chromatographic immunoassay for rapid detection of SARS-CoV-2 nucleocapsid in respiratory samples (mainly nasopharyngeal and throat swabs), Standard™ Q COVID-19 Ag kit (SD Biosensor®).	98.33%	ND	ND	98.73%/ND	454 respiratory samples suspected COVID-19 was evaluated. 60 were positive, and 394 were negative by real-time RT-PCR assay.	ND

Table 1. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Amer et al. [36]/Chromatographic immunoassay for rapid detection of SARS-CoV-2 nucleocapsid in oropharyngeal and nasopharyngeal swabs, Standard™ Q COVID-19 Ag kit (SD Biosensor®).	78.2%	ND	ND	64.2%/75.9%	83 oropharyngeal and nasopharyngeal swabs were evaluated of participants should be suspected of having COVID-19 infection. 54 were positive by RT-qPCR.	ND
Diao et al. [37]/Fluorescence immunochromatographic (FIC) assay for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swabs, manufactured by the authors.	75.6%	ND	ND	100%/80.5%	251 participants with suspected COVID-19 symptoms. The Ct value 40 is the cutoff of RT-PCR testing. 201 had a Ct value of $\leq$40.	ND
Mboumba-Bouassa et al. [38]/Chromatographic immunoassay for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swabs, Ag-RDT SIENNA™ COVID-19 Antigen Rapid Test Cassette (Nasopharyngeal Swab) (SIENNA™).	90%	ND	ND	100%/90%	100 positive and 50 negative RNA swabs from SARS-CoV-2 by reference multiplex rtRT-PCR.	ND
Tinker et al. [39]/Lateral flow immunoassay for rapid detection of SARS-CoV-2 nucleocapsid in direct anterior nasal (nares) swabs, BinaxNOW COVID-19 Ag Card (BinaxNOW; Abbott Laboratories).	20%	ND	ND	100%/ND	1540 asymptomatic cases were tested. 40 positives confirmed with RT PCR.	No specimens tested positive for Influenza A or B viruses.
Orsi et al. [40]/Qualitative fluorescence immunoassay (FIA) for rapid detection of SARS-CoV-2 nucleocapsid in nasopharyngeal swabs, FREND™ COVID-19 Ag assay (NanoEntek, South Korea).	93.3%	86.7%	ND	100%/ND	110 nasopharyngeal samples from patients with symptoms attributable to SARS-CoV-2 infection. 60of swabs tested positive by RT-qPCR.	ND
Cassuto et al. [41]/Lateral flow immunochromatographic assay for rapid detection of SARS-CoV-2 nucleocapsid in a nasal sample, COVID-VIRO® (AAZ-LMB).	96.88%	ND	ND	100%/ND	234 patients with mild to moderate symptoms lasting less than 7 days and without the need for immediate hospitalization. RT-PCR confirmed 32 positive and 202 negative samples.	ND
Rastawicki, et al. [42]/Fluorescent immunoassay (FIA), PCL COVID-19 Ag (SD BIOSENSOR, Korea).	38.9%	ND	ND	83.3%/ND	167 nasopharyngeal swabs.	ND

Table 1. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Bianco et al. [43]/Microfluidic immunofluorescence assay for detection of the nucleocapsid protein of SARS-CoV-2 in nasal, LumiraDx™ (LumiraDx GmbH, Colônia, Alemanha).	90.3% overall	ND	ND	92.1% overall/ND	907 patients were evaluated, including participants asymptomatic. As a result, 298 participants were positive for SARS-CoV-2 confirmed by RT-PCR.	ND
Krüger et al. [44]/Microfluidic immunofluorescence assay to detect the nucleocapsid protein of SARS-CoV-2 in nasal mid-turbinate (NMT) self-swab manufactured by LumiraDx™ (LumiraDx™, London, UK).	82.2%	ND	ND	99.3%/ND	761 samples were evaluated, of which 146 were RT-PCR positive and 615 negatives.	The respiratory swab samples contained four seasonal coronaviruses, *Adenovirus*, *Bocavirus*, *Influenza virus*, *Metapneumovirus*, *Parainfluenza virus*, *Respiratory syncytial virus*, *Rhinovirus* or *Mycoplasma pneumoniae*, *Staphylococcus aureus* and *Streptococcus sp*. No cross-reactivity was detected.
Drain et al. [45]/Microfluidic immunofluorescence assay to detect the nucleocapsid protein of SARS-CoV-2 in nasal and nasopharyngeal (NP) swab manufactured by LumiraDx™ (LumiraDx™, Reino Unido).	ND	Up to 12 days: 97.6% (nasal swab) 97.5% (NP swab)	ND	96.6% (nasal swab)/ND 97.7% (NP swab)/ND	512 participants, aged 0–90 years.	ND
Liu et al. [46]/Nanozyme chemiluminescence paper test for rapid and sensitive detection of SARS-CoV-2 antigen, manufactured by the authors.	ND	ND	ND	ND/ND	Viral samples were recombinant peak proteins (2×10^4 TCID50/mL titer) and 98% purity confirmed by SDS-PAGE.	Other human coronaviruses (SARS-CoV, MERS-CoV, HCoV-HKU1 and HCoV-OC43) were tested to validate the specificity. There was no cross-reaction with other coronaviruses or Influenza A subtypes.

Table 1. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Egerer et al. [47]/Reverse transcriptase-loop-mediated isothermal amplification (RT-LAMP) for rapid detection of SARS-CoV-2 N and ORF8 genes in oropharyngeal, eazyplex® SARS-CoV-2 (Amplex Diagnostics, Gars Bahnhof, Germany).	Ct $\leq$ 28: 97.4%	ND	ND	100%/ND	150 oropharyngeal and nasal swabs were evaluated and confirmed by RT-PCR.	ND
Wang et al. [48]/Multiplexed RT-LAMP microwell biochip for rapid detection of SARS-CoV-2 ORF1ab gene in throat swab, manufactured by the authors.	95.4%	ND	ND	95.35%/ND	87 samples from PCR-positive and 43 PCR-negative patients.	ND
Xun et al. [49]/Scalable and Portable Testing (SPOT) assay comprise a one-pot RT-LAMP followed by PfAgo-based target sequence detection (detecting the N gene and E gene in a multiplexed reaction) in clinical saliva samples.	93.3%	ND	ND	98.6%/ND	104 in total saliva samples, confirmed by qRT-PCR.	Samples of saliva were spiked with or without SARS-CoV-2, three other genomic RNA from human coronaviruses (OC43, 229E, and NL63), SARS, and MERS viruses (γ-irradiated), and Influenza. Among these samples, SARS-CoV-2 genes were only detected in the positive control.
de Oliveira Coelho et al. [50]/Reverse Transcription Loop-mediated Isothermal Amplification (RT-LAMP) for the rapid determination of SARS-CoV-2 copies in nasal and oral rayon-swabs samples, manufactured by the authors.	93.8%	ND	ND	90.4%/ND	466 samples were evaluated. 250 were negative, and 216 were positive by RT-qPCR.	ND
Wei et al. [51]/High-Performance Loop-mediated isothermal Amplification (HP-LAMP) for the rapid determination of SARS-CoV-2 copies in saliva samples.	>96%	ND	ND	>96%/ND	120 samples were evaluated.	Wet testing was performed to evaluate potential cross-reactivity of the assay with other organisms using ZeptoMetrix Corporation NATtrol Respiratory Verification Panel (ZeptoMetrix, NATRVP-IDI), including 19 respiratory pathogens, NATtrol Coronavirus-SARS Stock, NATtrol MERS-CoV Stock, and NATtrol SARS-Related Coronavirus 2 External Run Control. No cross-reactivity was detected.

Table 1. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Lee et al. [52]/CRISPR Optical Detection of Anisotropy for rapid detection of SARS-CoV-2 copies in a nasopharyngeal or oropharyngeal swabs or sputum, manufactured by the authors.	ND	ND	ND	ND/ND	20 clinical specimens of nasopharyngeal and oropharyngeal smears and sputum from individuals suspected of COVID-19. 10 COVID-19 positive samples and 10 negative samples were confirmed by qRT-PCR.	ND
Li et al. [53]/reverse transcription recombinase-aided amplification (RT-RAA) for rapid detection of SARS-CoV-2 in throat swab.	Ct (22.1 to 32.8): 98% Ct (33.2 to 36.4): 33%	ND	ND	100%/ND	80 throat swab specimens were collected from the suspected SARS-CoV-2 infectious patients, confirmed by qRT-PCR.	Were tested 8 respiratory RNA viruses, including Influenza A viruses (H3N2, H7N9, H5N1, H1N1) and Influenza B viruses (Victoria and Yamagata lineages), which were isolated from humans or birds and adenoviruses (AdV3 of strain IVCAS16(A).00027 and AdV7 of strain IVCAS 16(A).00028). The non-targeted RNA genomes generated similar baselines as the negative control (water).
Margulis et al. [54]/Magnetic modulation biosensing (MMB) for rapid detection of SARS-CoV-2 in nasopharyngeal swabs.	97.8%	ND	ND	100%/ND	Were tested 309 clinical samples from SARS-CoV-2–positive and SARS-CoV-2–negative patients with a wide range of initial viral loads ($C_T \leq 42$).	30 nasopharyngeal swab samples collected in 2019 from patients with different viral respiratory diseases, such as influenza A (13 samples), influenza B (10 samples), and respiratory syncytial virus (7 samples), were tested to evaluate the specificity of the assay further. All SARS-CoV-2 samples were identified as negative.

Table 1. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Torres et al. [55]/RAPID 1.0 (real-time accurate portable impedimetric detection prototype 1.0) in saliva, nasopharyngeal and oropharyngeal swabs, manufactured by the authors.	NP/OP: 83.5% Saliva: 100%	ND	ND	NP/OP: 100%/87.1% Saliva: 86.5%/90%	A total of 151 saliva and (NP/OP) swabs were evaluated, confirmed by RT-PCR	It performed specificity assays with three coronaviruses (MHV-*Murine hepatitis virus*, HCoV-OC43–human coronavirus OC43 and human coronavirus 229E) and four non-coronavirus viral strains (H1N1-A/California/2009, H3N2-A/Nicaragua, Influenza B-B/Colorado, HSV2-*Herpes simplex virus*-2). No cross-reactivity was detected.

Table 2. Serological POC tests and RDT for detection of antibodies against SARS-CoV-2.

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Kumar et al. [56]/Electrochemical ELISA platform detects both IgM and IgG antibodies against the SARS-CoV-2 Spike Glycoprotein (S1) in clinical whole blood and serum samples. anuPath™ Electrochemical ELISA Analyzer.	ND	ND	100%	100%/100%	450 samples were evaluated, of which 252 were EDTA whole blood samples and 198 were sera samples.	ND
Munck et al. [57]/COVID-19 IgG/IgM Duo is a fluorescent lateral flow immunoassay detecting both IgM and IgG antibodies against the SARS-CoV-2 nucleocapsid (N) protein separately in serum samples. NanoEntec.	46.2%	93.8%	100%	IgM: 87.5% IgG: 91.7% IgG/IgM: 95.8%/ND	105 serum samples were evaluated, confirmed by PCR.	False-positive results were found in two samples with antibodies to other coronaviruses (NL63 and HKU1) and one sample with Epstein Barr viral capsid IgG.

Table 2. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Peng et al. [58]/Lateral Flow Immunoassay test for rapidly detecting of specific IgM and IgG antibodies against the nucleocapsid and S-RBD protein recombinant of SARS-CoV-2 in serum samples, manufactured by the authors.	Anti-N IgG: 96.6% Anti-N igM: 96.6% Anti-S-RBD-IgG: 95.9% Anti-S-RBD-IgM: 96.6%	ND	ND	Anti-N IgG: 94.1%/ND Anti-N igM: 100%/ND Anti-S-RBD-IgG: 96.1%/ND Anti-S-RBD-IgM: 100%/ND	108 serum samples were tested, 82 positives of 83 confirmed with CLIA	ND
Kiziloglu et al. [59]/Gold Immunochromatography for the rapid detection of anti-SARS-CoV-2-IgG and IgM manufactured by Bioeasy COVID-19 Coronavirus IgG/IgM GICA Rapid Test Kit ©.	57.5%	ND	ND	85.5%/ND	181 cases were tested: 71 positives were clinically confirmed (RT-PCR test).	ND
Plebani et al. [60]/Immunochromatographic assay that detects IgM and IgG antibodies against the spike protein SARS-CoV-2 (S1), and the nucleocapsid protein in a serum or plasma sample. COVID19SEROSpeed-IgM-IgG (BioSpeedia).	ND	ND	92.5%	98.1%/ND	710 samples. For specificity analysis, 215 pre-pandemic serum samples were analyzed. For sensitivity analysis, the samples were positive by qRT-PCR.	Four false-positive samples tested positive for IgG in three of them and IgM in one of them; two of these four patients exhibited IgM targeted to *Mycoplasma pneumoniae* and *Toxoplasma gondii*, respectively.
Villarreal et al. [61]/Gold Immunochromatography for the rapid detection of specific IgM and IgG antibodies against SARS-CoV-2 nucleocapsid (N) protein in serum samples, manufactured by the group of Dr. Chong Li of the Institute of Biophysics of the Chinese Academy of Sciences.	36.4% for IgM and IgG	76.2% (IgM) and 71.4% (IgG)	87.0% for IgM and IgG	95.0%/ND	810 serum samples, confirmed by qRT-PCR and a set of pre-pandemic panel samples.	Cross-reaction was tested on pre-pandemic samples from patients with Dengue, pulmonary tuberculosis, and latent tuberculosis infection. Only one patient who tested positive for Dengue showed a positive IgM.
Scotta et al. [62]/Lateral flow for the rapid detection of specific IgM and IgG antibodies against the spike protein SARS-CoV-2 in the blood sample, manufactured by Wondfo Biotech.	ND	60.0%	73.2%	96.8% overall/ND	175 whole blood samples of pediatric patients were evaluated, confirmed by qRT-PCR	ND
Fauziah et al. [63]/Lateral flow qualitative immunoassay for rapidly detecting specific IgM and IgG antibodies against SARS-CoV-2 in serum and capillary blood samples, manufactured by Guangzhou Wondfo Biotech Co., Ltd., Guangzhou, China	Serum: 63%. Capillary blood: 41.2%	ND	ND	Serum: 95 %/78.7% Capillary blood: 100%/50%	47 sample, 27 patients had a positive rRT-PCR result.	Cross-reaction was tested on serum samples from a patient with Dengue or typhoid fever. No cross-reactivity was observed.

Table 2. *Cont.*

Autor/Methods Used	Sensitivity			Specificity/Accuracy	N	Cross-Reaction
	Day after Symptom Onset					
	01–07	08–14	15–39			
Pallett et al. [64]/Lateral flow immunoassay for the rapidly detecting specific IgM and IgG antibodies against SARS-CoV-2 in blood samples, OrientGene COVID-19 split IgG/IgM (OrientGene).	74%	86%	100%	96%/ND	200 samples, 50 negatives and 130 positives of the 150 positives were confirmed with RT PCR.	ND
Prendecki et al. [65]/Lateral flow immunoassay for rapidly detecting specific IgG antibodies against the spike protein SARS-CoV-2 in blood, serum, and plasma sample, manufactured by Biomedomics Inc.	ND	ND	96.6%	97.7%/97.3%	Sixty samples were collected from maintenance hemodialysis patients and kidney transplant recipients. All patients had undergone RT-PCR testing. And 88 plasma samples were pre-pandemic.	ND
Zhang et al. [66]/Magnetofluidic immuno-PCR platform assay for anti-SARS-CoV-2 Immunoglobulin G (IgG) detection using a magnetofluidic instrument, manufactured by the authors.	ND	ND	93.8% overall	98.3%/ND	Were tested 108 samples, 34 of which were 34 convalescent plasma samples from patients with SARS-CoV-2 confirmed with the Roche ECLIA test (Elecsys® Anti-SARS-CoV-2), 14 convalescent serum samples confirmed by a custom serological test based on beads and 40 serum samples and 20 plasma samples as negative controls.	ND
Elledge et al. [67]/Split luciferase (spLUC) antibody sensor for the rapid detection of specific antibodies against the nucleocapsid and S-RBD protein recombinant of SARS-CoV-2 in serum, plasma, whole blood, and saliva samples, manufactured by the authors.	ND	ND	anti-S protein antibodies: 89% anti-N protein antibodies: 98%	anti-S protein antibodies: 100% anti-N protein antibodies: 99%/ND	Testing of over 150 patient serum/plasma samples.	They were tested for seasonal coronavirus patient samples and 20 pre- and post-vaccination influenza vaccine samples. These controls generated significantly lower luminescent signals than the COVID-19 patient sera samples.
Li et al. [68]/Lateral flow assay test for the rapid detection of specific IgA, IgM and IgG antibodies against the recombinant N protein and recombinant S1 protein of SARS-CoV-2 in serum and plasma samples manufactured by the authors.	ND	ND	88.56%	88.56%/ND	The kit was used to test the serum from 43 suspected COVID-19 patients, 97 COVID-19 patients, and 88 with general fever or pulmonary infection patients.	Cross-reactivity in patients infected with *M. pneumoniae* and respiratory tract infection.

3.1. Direct Detection Tests

We identified 30 rapid tests that detected antigenic structures [17–46] and 9 that detected SARS-CoV-2 RNA [47–55]. Among the assay methods, 26 were performed by lateral flow assays (considering assays with gold and fluorescence) [17–42]; 5 by Isothermal Amplification Mediated by Reverse Transcriptase (RT-LAMP) [47–51]; 1 by Fluorescent-Transcription probe-based real-time reverse (RT-RAA) [53]; 1 by clustered regular-spaced short palindromic repeats (CRISPR) [52]; 1 by real-time accurate portable impedimetric detection 1.0 prototype (RAPID 1.0) [55]; and 3 by microfluidic immunofluorescence (LumiraDx™) [43–45]. Furthermore, two other studies developed new diagnostic methodologies, which are the magnetic modulation biosensor (MMB) [54] and the nanozyme chemiluminescent paper test [46].

In the studies reporting direct detection, 37 reported the sensitivity and specificity of the test [17–45,47–51,53–55], 11 studies provided information about diagnostic accuracy [22,23,26,27,31,32,34,36–38,54], and 2 studies did not reveal any of these parameters, mentioning only the limit of detection [46,52] (Table 1). All studies that reported sensitivity used RT-PCR variations as reference standards to determine SARS-CoV-2 infection.

Most analyzed studies were lateral-flow-based assays for viral antigen detection [17–42]. Among the 26 studies that reported Ag-RDTs, only 10 met the WHO recommended minimum performance requirements of $\geq$80% sensitivity and $\geq$97% specificity [8,18,19,23–25,27,35,38,40,41].

Overall, Ag-RDT studies used nasopharyngeal swabs samples (NPS). However, two of them used nasal swabs [39,41]; one used NPS/throat swabs [35]; one used both swabs' NPs, such as nasal and saliva swabs [17]; and three used NPS/oropharyngeal swabs (OP) [28,29,36].

Notable differences were observed in sensitivity values among studies that used nasal swab samples (20% [39], 44.7% [17], and >96% [41]). Likewise, NPS/OP swab samples [28,29,36] showed suboptimal values of sensitivity between studies (35.29%, 75%, and 78.2%). In saliva samples, the sensitivity was lower compared with that of NPS/throat swab samples (23.1% [17] versus >98% [35]).

Suboptimal sensitivity was also observed in samples with low viral loads (high Ct value in RT-PCR) [17–19,24,26–28,30–34,36,38,39,42] and in pediatric samples, when compared with samples from adult patients [22,24,25,28]. Only two studies showed values of specificity lower than 98% (64.2% and 83.3%) [36,42].

Relative to other direct-detection methods, the RT-RAA [53], RT-LAMP [47–51], and MMB [54] assays reported sensitivity and specificity >90%. In studies using the LumiraDx™ SARS-CoV-2 antigen test [43–45], the specificity was >92%, and only in the assay performed by Krüger et al. [44] the sensitivity was less than 90% (82.2%). In the method proposed by Torres et al. [55], sensitivity was higher in saliva samples (100%) than in NPS/OP swabs (83.5%). The opposite was verified for specificity values, with higher values in NPS/OP samples (100%) than in saliva samples (86.5%).

Diagnostic accuracy was reported in only 11 studies [22,23,26,27,31,32,34,36–38,55], with values greater than 80% except for one study that reported 75.9% [36], demonstrating that the developed tests had a good performance in detecting SARS-CoV-2. Otherwise, cross-reaction analyses were verified in only nine studies, showing the need to improve the diagnostic performance and the information provided about them.

Different pathogens were considered, such as *Rhinovirus* [26,44], *Enterovirus* [26], *Adenovirus* [44,53], *Bocavirus* [44], *Influenza A* [39,44,46,49,53–55], *Influenza B* [39,44,53–55], *Metapneumovirus* [44], *Parainfluenza virus* [44], *Respiratory syncytial virus* [44,54], *Herpes simplex virus-2* [55], *Mycoplasma pneumoniae* [44], *Staphylococcus aureus* [44], and *Streptococcus sp.* [44].

Among these studies, five evaluated cross-reactivity with other coronaviruses: HCoV-OC43 [46,49,55], HCoV-229E [49,55], HCoV-HKU1 [46] and HCoV-NL63 [49], Murine hepatitis virus [55], SARS-CoV [46,49,51], and MERS-CoV [46,49,51]. Only one study reported cross-reaction [26].

This report analyzed seven samples with discordant results between RT-PCR (positive results) and Ag-RDT (negative results) by a multiplexed PCR assay targeting common respiratory viruses. Interestingly, two showed a positive result for *Rhinovirus/Enterovirus* [26].

The sensitivity and specificity of these tests are shown in Figure 2.

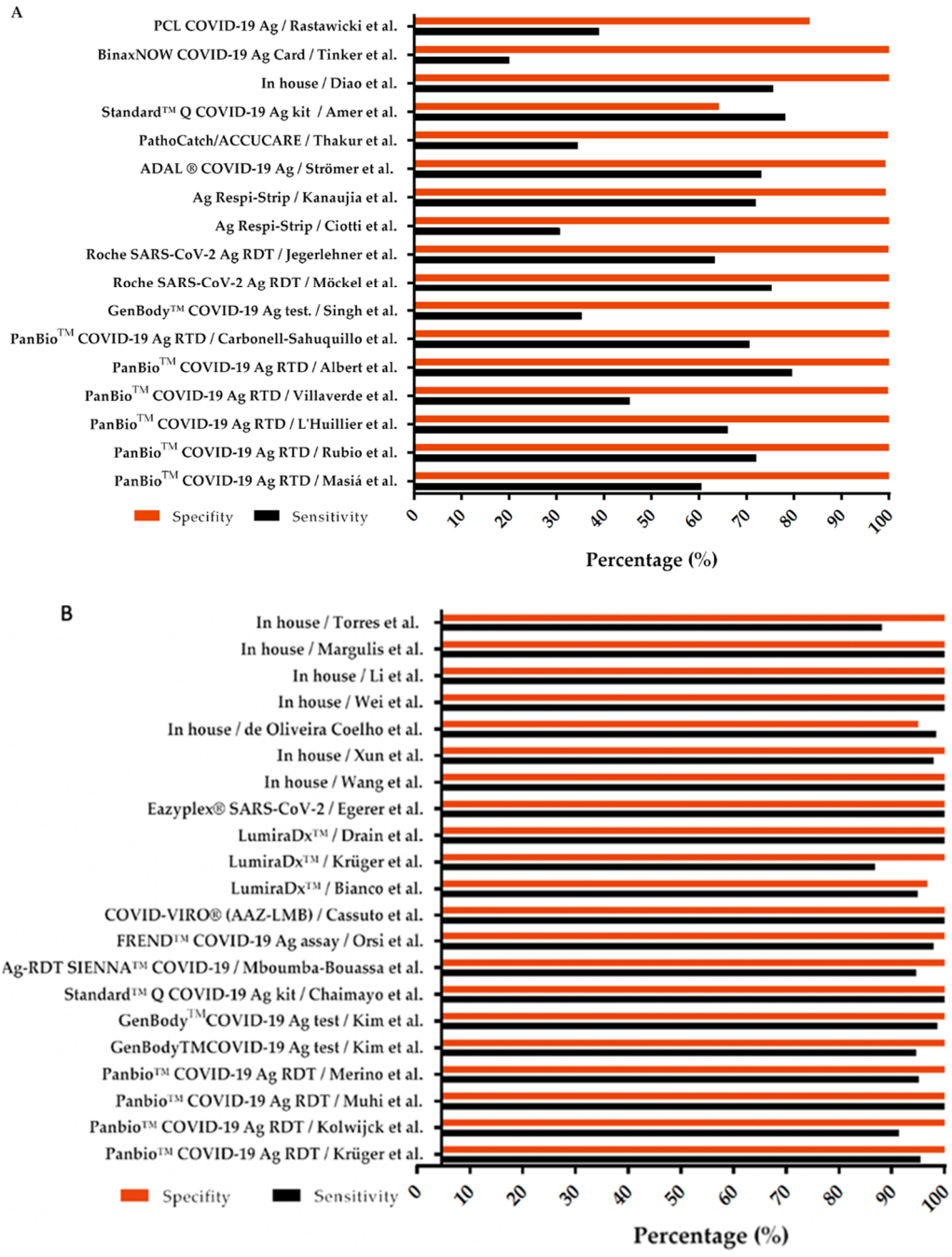

Figure 2. Sensitivity and specificity of the tests. (**A**) Direct diagnostic tests with <80% sensitivity; (**B**) direct diagnostic tests with ≥80% sensitivity. Tests that did not have sensitivity and specificity values were not added [17–45,47–51,53–55].

3.2. Immunoglobulin Detection Tests

Regarding immunoglobulin detection tests, we identified nine studies that assessed IgM and IgG levels [56–64], three evaluating only IgG [65–67], and one evaluating IgA, IgG, and IgM [68]. A total of 10 antibody tests were performed by lateral-flow assays (considering gold and fluorescence assays) [57–65,68], 1 by electrochemical enzyme immunoassay

(ELISA) [56], 1 by magnetofluidic immuno-PCR platform [66], and 1 by the Split Luciferase (spLUC) antibody sensor [67].

Among the 13 selected studies, 10 presented high values of sensitivity and specificity (>80%) [56–58,60,61,64–68], and 1 reported 100% of sensitivity and specificity [56]. Lower sensitivity values were observed in the first days after infection [57,61,62,64] than the days postinfection. Accuracy was reported in three studies [56,63,65], and values lower than 80% were found only in the study by Fauziah et al. [62]. The accuracy of 100% was verified in the study by Kumar et al. [56].

Cross-reactions were analyzed in six studies for *Mycoplasma pneumoniae* [60,68], *Toxoplasma gondii* [60], *Measles virus* [60], *Cytomegalovirus* [60], HIV [60], *Hepatitis B virus* [60], *Dengue virus* [61,63], Typhoid fever [63], Influenza [67], patients exhibiting multiple autoantibodies [60], patients with respiratory tract infections [68], and patients with pulmonary tuberculosis and latent tuberculosis [61]. Other coronaviruses were tested only in the study by Elledge et al. [67]. Cross-reactions were found in samples with *Mycoplasma pneumoniae* [60,68], *Toxoplasma gondii* [60], *Dengue virus* [61], and in samples from patients with respiratory tract infections [68].

The sensitivity and specificity of these tests are shown in Figure 3.

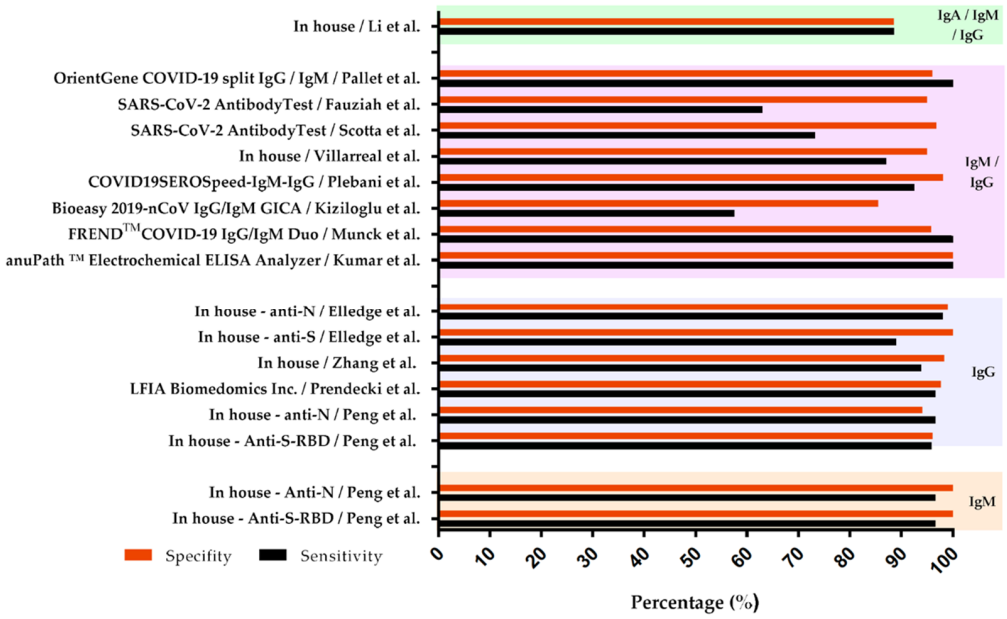

Figure 3. Sensitivity and specificity of POC and RDT serological tests for detecting antibodies against SARS-CoV-2 [58–68].

4. Discussion

The COVID-19 pandemic has been a global public health challenge for over a year. The need for rapid screening of SARS-CoV-2 infection has led to a constant search for the development of diagnostic tests [7,8]. Therefore, we conducted a systematic review of studies of POC and RDT tests for COVID-19 one year after our first analysis to verify whether there was progress in the tests' research considering the discoveries about SARS-CoV-2.

In this paper, we selected 52 studies that reported using POC and RDT tests to diagnose COVID-19. The data were divided into POC and RDT tests for direct detection of SARS-CoV-2 (Table 1) and POC and RDT serological tests to detect antibodies against SARS-CoV-2 (Table 2).

Most of the selected POC and RDT studies showed good sensitivity and specificity. Our results indicate good performance for saliva samples, NPS/OP swabs, and throat samples, suggesting that these samples can be used as an alternative to NPS or nasal swabs commonly used for the diagnostic testing of SARS-CoV-2. [17].

Regarding the pediatric samples, we found lower sensitivity values when compared with samples from adult patients [22,24,25,28]. Furthermore, age was associated with antigen-test performance irrespective of Ct values and symptom duration [17]. Although children are more likely to be asymptomatic or have mild symptoms, they can transmit SARS-CoV-2, making screening essential to help contain the spread of the virus [69].

Lower sensitivity was also observed in samples that showed high Ct values in RT-PCR [17–19,24,26–28,30–34,36,38,39,42,43,47,53], indicating a lower viral load. In SARS-CoV-2 infection, the viral load peaks in the first week after the onset of symptoms in the upper respiratory tract. Ag-RDTS and nucleic-acid amplification tests must function better during this period [70,71]. Although the diagnostic tests are usually performed when symptoms appear (high viral load), there are reports in the literature of vaccinated infected individuals with reduced viral load [72–74]. Thus, infected individuals may lead to occult transmission of the virus.

Regarding serological tests POC and RDT for detecting antibodies, most showed high sensitivity and specificity values, indicating good clinical performance. However, we observed lower sensitivity values in tests that performed the analysis in the first days after SARS-CoV-2 infection [57,61,62,64] than in postinfection studies.

The lower sensitivity verified may be related to the time required to develop antibodies. Although IgM and IgG seroconversion can occur simultaneously or sequentially and antibody titers can plateau after six days [75], most patients do not produce an antibody response until the second week after the initiation of symptoms [76].

Thus, for a more accurate diagnosis of COVID-19, tests based on direct detection are preferable in the first days of symptoms, about 3 to 7 days of infection, and antibody tests should be used after this period due to their greater sensitivity [8,59]. Moreover, combining techniques can increase the sensitivity in diagnosing SARS-CoV-2 infection [6,59,77].

On the other hand, it is of concern that only a few studies have reported cross-reaction assays. Although many manufacturers have tested cross-reacting for different pathogens and presented data of low homology between the proteins of SARS-CoV-2 and other human coronaviruses (used for manufacturing), cross-reaction is not commonly addressed [78–84]. Cross-reactivity has been reported in COVID-19 and Dengue cases [85–88], both in serology for COVID-19 in patients with Dengue and serology for Dengue among patients with COVID-19 [89].

In addition, coinfection between SARS-CoV-2 and other pathogens such as influenza and the *Dengue virus* has been reported [90–97]. The similar clinical symptoms of SARS-CoV-2 and other febrile illnesses favor misdiagnosis. Incorrect or later diagnosis can affect clinical management, exacerbate complications, and increase mortality. Therefore, it is essential to identify coinfections rapidly. Testing for SARS-CoV-2 in areas with overlapping outbreaks is not enough to rule out the possibility of coinfection, and PCR tests are required to confirm the infection.

Concerning the findings of our first review [16], 117 more studies were published, and 30 more trials were tested in one year. Likewise, cross-reaction was evaluated in 13.05% of studies in the first year analyzed and 28.85% in the second year. Although the percentage of articles that reported accuracy remained similar (26.09% in 2020 and 26.93% in 2021), the accuracy values obtained increased. Likewise, sensitivity and specificity parameters were improved. However, there was no statistical difference observed (Figure 4).

Several factors might be related to the heterogeneous performance of the tests, such as the quality of the individual smear, whether the sample is fresh or not, the storage conditions of the sample, anatomical collection site, viral load of the sample, day of onset of symptoms, among others [25,28,98]. These issues make it difficult to compare the tests directly.

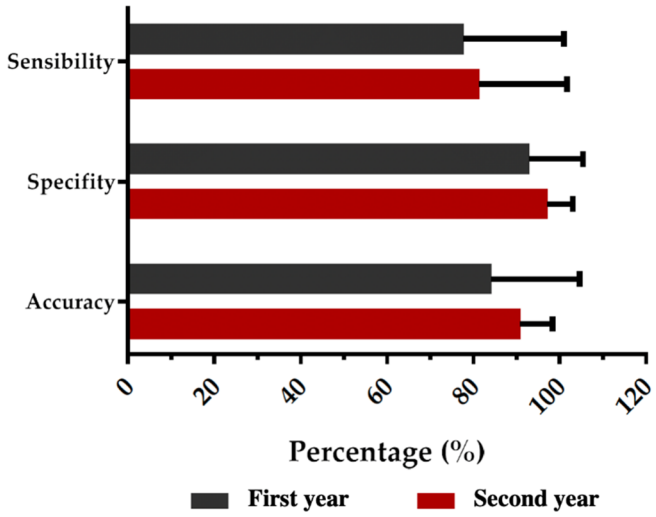

Figure 4. Comparison of sensitivity, specificity, and accuracy of POC and RDT serological tests between the first and second year of the COVID-19 pandemic. Shapiro–Wilk's tests was used to evaluate the normality presented by the groups. Kruskal–Wallis tests were performed to compare the medians of multiple groups, considering significant the value of $p < 0.05$. No statistical difference was observed.

It also explains why we observe so many performance divergences reported by studies or test manufacturers. We still found few trials that revealed the accuracy of the tests, raising uncertainties about the accuracy of the COVID-19 POC and RDT tests.

Considering the importance of an accurate diagnosis, we expected to find more studies evaluating cross-reactions with other pathogens, especially with endemic coronaviruses, in this second year of the pandemic.

We believe next-generation tests should incorporate phylogenetic and structural analyses to select antigens used in their manufacturing process. For example, in the first semester of the pandemic, 45 epitopes with mutations in the main antigen of SARS-CoV-2 [99] were reported, denoting the need for the preemptive use of antigens with variants for the development of serological tests.

With the infection of hundreds of millions of people, mutations have become much more frequent, reaching more than 50 occurrences only in the spike protein of the Omicron variant, which is responsible for a robust escape from neutralization steps [100]. Therefore, the incorporation of mutations of importance in epitopes should be the main focus in developing tests that use antibodies/antigens.

Although the POC and RDT tests were critical to fighting COVID-19, our findings corroborate that the POC and RDT tests still need further validation regarding test accuracy and cross-reactivity with other pathogens [101].

Overall, we have identified some limitations in the analyzed studies: discrepant sample numbers for validations, differences in the samples used, and a low number of studies assessing accuracy and cross-reactivity. In addition, this systematic review also has limitations: we could not perform a meta-analysis due to the variability of the methods and results found in the studies.

5. Conclusions

Although more than a year of the COVID-19 pandemic has passed, POCs and RDTs tests are still needed since they contribute to the management of COVID-19. This study provides an overview of studies reporting the use of POC and RDT tests to diagnose COVID-19 published from November 2020 to November 2021. We identified heterogeneous performance across assays that may be related to various factors such as quality of the sample, viral load, and anatomical collection site.

Combining viral antigen or genome-detection methodologies with antibody-detection tests is recommended to increase diagnostic accuracy. However, information about test accuracy has been limited, and some cross-reactions with different pathogens have been found. Given these findings, further validations on cross-reactivity with other pathogens and the accuracy of the tests are needed.

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