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Diagnostic accuracy of rapid antigen test for SARS-CoV-2: A systematic review and meta-analysis of 166,943 suspected COVID-19 patients

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ABSTRACT

To assess the diagnostic accuracy of the rapid antigen test (RAT) compared with RT-PCR (reference standard) for SARS-CoV-2, we searched MEDLINE/PubMed and Web of Science for relevant records. The QUADAS-2 tool was used to assess study quality, and quantitative synthesis was conducted using a bivariate random-effects model. The meta-analysis included 135 studies (166,943 samples). The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.76 (95%CI: 0.73–0.79), 1.00 (95%CI: 1.00–1.00), 276.1 (95%CI: 184.1–414.1), 0.24 (95%CI: 0.21–0.27), and 1171 (95%CI: 782–1755), respectively. Compared to other sample types, nasal samples had the best RAT sensitivity [0.79 (95%CI: 0.71–0.87)]. The sensitivities of the different RAT kits ranged from 0.41 (95%CI: 0.23–0.61) to 0.90 (95%CI: 0.70–0.97). Sensitivity was markedly better in samples with lower Ct, and RAT achieved excellent pooled sensitivity at 1.00 (95%CI: 0.70–1.00) among samples with Ct < 20. Testing within 10 days of symptom onset resulted in a high sensitivity. For ≤ 3, ≤ 7, and ≤ 10 days, the sensitivities were 0.91 (95%CI: 0.83–0.96), 0.89 (95%CI: 0.84–0.93), and 0.88 (95%CI: 0.83–0.92), respectively. RAT kits show high sensitivity and specificity in early infection, especially when the viral load is high. Moreover, using nasal samples for antigen testing, which are moderately sensitive and patient-friendly, is a reliable alternative to nasopharyngeal sampling. RAT might be effective for fighting the COVID-19 pandemic; however, it must be complemented by the careful handling of negative test results.

1. Introduction

Coronavirus disease COVID-19 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), became a global pandemic within a short period (Lai et al., 2020; "WHO Director-General’s opening remarks at the media briefing on COVID-19 - 11 March 2020," 2021). The rapid and precise diagnosis of COVID-19 is essential to enable prompt and accurate public health surveillance, prevention, and control (Jin et al., 2020).

Two major types of diagnostic tests for COVID-19 are currently available: a direct method to examine clinical specimens for the presence of viral particles, viral antigens, or viral nucleic acids, and a serological test to detect anti-SARS-CoV-2 antibodies (Borges et al., 2021). Reverse transcription polymerase chain reaction (RT-PCR) is currently the gold standard for detecting SARS-CoV-2 because of its ability to directly measure the genomic portion of the virus (Yüce et al., 2021). However, RT-PCR may be unsuitable in emergency settings because it may take several hours to obtain results. It also requires expensive technology and competent operators, and these may be unavailable in remote health clinics, especially in underdeveloped countries (Khandker et al., 2021). To improve this situation, the rapid antigen test (RAT) for COVID-19, which does not require specific and costly machinery, emerged as an essential alternative tool to aid the clinical diagnosis of COVID-19 (Yamayoshi et al., 2020, p. 1). It is low-cost and straightforward, with a shorter turnaround time. Thus, it can be used as a point-of-care test, allowing for the immediate isolation of infected individuals and permitting the early implementation of appropriate infection control measures, which is critical in a pandemic (Torres et al., 2021).

As numerous COVID-19 antigen tests are rapidly evolving, a growing number of independent validations have been conducted. Studies on the diagnostic accuracy of RAT vary widely in terms of quality, methodology, and results, generally showing excellent specificity but variable sensitivity. The different results may be due to differences in study...
design, manufacturers of RAT kits, patient selection, type of specimen, and stage of disease at the time of sample collection (Khandker et al., 2021). Therefore, the efficacy of RAT still needs to be thoroughly investigated. This systematic review and meta-analysis aimed to assess the diagnostic accuracy of RAT compared to RT-PCR methods as a reference standard.

2. Materials and methods

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the protocol of this study was registered in the PROSPERO database (CRD42022339683).

2.1. Literature search

The MEDLINE/PubMed and Web of Science databases were searched for relevant studies published up to 10 May 2022. We used a combination of free text and MeSH terms to identify relevant studies. The main search terms were: “SARS-CoV-2”, “COVID-19”, “antigen test”, “Specificity”, and “Sensitivity”. The detailed search strategies are presented in Table S1. Two researchers independently conducted a literature search to minimize potential biases.

2.2. Inclusion and exclusion criteria

Any study that satisfied the following requirements was considered eligible for inclusion in our meta-analysis: (i) use of RAT as an index test, (ii) measurement of the performance of RAT against RT-PCR as a reference standard, and (iii) availability of the sensitivity and specificity of RAT. The following were the exclusion standards: (i) duplicate original investigation, reviews, editorials, letters, comments, and meta-analysis articles, and (ii) unavailability of data (by article review or calculation) necessary for a meta-analysis.

2.3. Data extraction and quality assessment

We extracted the following data from the full texts and supplemental materials of all qualified articles: the first author’s last name, the publication year, the country of residence of the study participants, and true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values. The diagnostic parameters were calculated using the sensitivity and specificity values if they were unavailable. The risk of bias of each included publication was assessed using The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (Whiting et al., 2011). Two researchers carried out the assessment process independently. A third researcher was invited to reach a settlement in case of disagreement.

2.4. Statistical analysis

The extracted data were recorded for further analysis using STATA software (Stata Corporation, College Station, TX, USA). We used a bivariate random-effects model to perform the quantitative synthesis. We calculated each parameter of individual studies by the following formulas to derive the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio:

- Sensitivity: TP/(TP + FN).
- Specificity: TN/(TN + FP).
- Positive likelihood ratio = Sensitivity/(1 – Specificity).
- Negative likelihood ratio = (1 – Sensitivity)/Specificity.
- Diagnostic odds ratio = Positive likelihood ratio/Negative likelihood ratio.

The forest plots were employed to show the overall effects. The area under the curve (AUC) was calculated using an optimal cutoff value by a summary receiver operating characteristic (SROC) curve. To access interstudy heterogeneity, bivariate boxplots, qualitative Q tests, and quantitative I² tests were utilized. Publication bias was evaluated by Deeks’ funnel plot. The Fagan nomogram and the likelihood ratio scattergram were used to access the diagnostic value and clinical application value, respectively. All tests were two-sided. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Features of eligible studies

According to our search criteria, 1453 publications were initially selected. A total of 1119 articles were excluded during the initial screening process, including reviews (n = 128), editorials (n = 9), letters (n = 22), commentaries (n = 8), and duplicates (n = 952). A total of 354 articles were selected for full-text review to determine if they qualified for the meta-analysis. Of these, 199 articles including articles irrelevant to the objective of the meta-analysis (n = 143), repetitive studies (n = 12), and articles with insufficient data (n = 44) were excluded. The remaining 135 studies met the eligibility criteria and were included in the meta-analysis. The inclusion and exclusion processes are shown in Fig. 1.

The 135 studies selected for this meta-analysis included 166,943 samples. All included studies were published between 2020 and 2022 and involved 37 countries; the top three countries in terms of the number of studies were Italy (n = 18), the USA (n = 15), and Spain (n = 15). All articles were not pre-prints. Except for three manufacturer-dependent studies, the remaining were all manufacturer-independent studies. Forty different RAT kits were investigated. Different types of specimens (nasal, nasopharyngeal, oropharyngeal, throat, and saliva swabs) were collected from suspected symptomatic or asymptomatic participants (Table 1). Ninety-three studies evaluated the diagnostic efficacy with nasopharyngeal swabs, and 26 studies assessed the performance with nasal swabs. Cycle threshold (Ct) values for positive RT-PCR were provided in 27 studies. Thirteen studies reported the time of symptom onset in RT-PCR-positive patients.

3.2. Quality assessment

Fig. S1 and Table S2 show the quality of the studies in our meta-analysis, based on the QUADAS-2 tool. In the majority (78.5%, 106/135) of the included studies, all patients were consecutively or randomly included, and inappropriate exclusions and case-control designs were avoided. All the studies were judged to have a low risk of bias in the index test and reference standard domains. Regarding the flow and time domains, 73.3% (99/135) of the studies were considered to have a low risk of bias, as they received the same reference standard, and all selected patients were enrolled in the analysis. The patient selection, index tests, and reference standards were considered to meet the objectives of this meta-analysis.

3.3. Publication bias

Deeks’ funnel plot (Fig. S2) did not display significant asymmetry on visual inspection; the P-value of 0.78 for the slope coefficient also suggested symmetry in the data and no striking publication bias in this study.

3.4. Analysis of heterogeneity

We found that P values of the Q test for sensitivity and specificity were both < 0.001 based on heterogeneity statistics, suggesting significant interstudy heterogeneity. In addition, as the bivariate boxplot shows in Fig. S3, most studies clustered within the median distribution with 28 outliers, further indicating the presence of interstudy heterogeneity. Thus, a bivariate random-effects model was appropriate for
3.5. Diagnostic performance

The meta-analysis demonstrated a pooled sensitivity of 0.76 (95% CI: 0.73–0.79) (Fig. 2A) and a pooled specificity of 1.00 (95% CI: 1.00–1.00) (Fig. 2B). The pooled positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 276.1 (95% CI, 184.1–414.1), 0.24 (95% CI, 0.21–0.27), and 1171 (95% CI, 782–1755), respectively. Additionally, the summary AUC was 0.97 (95% CI, 0.96–0.98) (Fig. 3), which reveals that RAT is of high diagnostic value for COVID-19. As shown in Fig. 3, there was no shoulder-arm-shaped distribution in the SROC curve, and the proportion of heterogeneity due to the threshold effect was 0.12, indicating that the heterogeneity of this meta-analysis was independent of the threshold effect.

The results of the statistical analysis were used to set the pretest probability to 12%. The Fagan plot presented in Fig. 4A shows that the posttest probability increased to 97% if the antigen test was positive and was as low as 3% if the antigen test was negative. When we assumed a higher pretest probability of infection of 24% (doubling the prevalence rate), both the positive and negative posttest probabilities improved to 99% and 7%, respectively. When the prevalence rate was halved to 6%, the probability of a positive posttest dropped to 95%, and the probability of a negative posttest dropped to 1%.

The likelihood ratio scattergram (Fig. 4B) showed that more than three-quarters of the studies (77.8%, 105/135) along with the summary point of likelihood ratios obtained as functions of mean sensitivity and specificity were in the right upper quadrant. These findings suggest that RAT helps confirm the presence of SARS-CoV-2 when the test result is positive and not for its exclusion when negative.

3.6. Subgroup analyses

In Table 2, all the samples achieved a specificity of 1.00. When assessing studies evaluating nasopharyngeal swab as the sample type for Ag-RDT, the pooled sensitivity from 93 studies with 76,945 samples was
| DOI                  | Author                  | Year | Country     | Rapid Antigen Test Kit                          | Specimen Types            | TP  | TN  | FP  | FN  | SS |
|---------------------|-------------------------|------|-------------|-------------------------------------------------|---------------------------|-----|-----|-----|-----|----|
| 10.3390/v14030468   | Lau                     | 2022 | Singapore   | LIASON® SARS-CoV-2 Antigen assay                 | nasopharyngeal swabs      | 26  | 288 | 1   | 35  | 350|
| 10.1186/s12898-020-01452-5 | Chaimayo           | 2020 | Thailand    | STANDARD Q COVID-19 Ag Test                      | nasopharyngeal and throat swabs | 59  | 389 | 5   | 1   | 454|
| 10.1002/jmv.26830    | Ciotti                  | 2021 | Italy       | Coris bioconcept COVID-19 ag resip-strip test   | nasal swabs               | 36  | 107 | 0   | 5   | 148|
| 10.1002/jca.23745    | Bianco                  | 2021 | Italy       | LumiraDx SARS-CoV-2 Ag Test Antigen Rapid Test kit | nasal swabs               | 269 | 561 | 48  | 29  | 907|
| 10.1002/jjbb.2021.07.003 | Kanaujia              | 2021 | India       | Coris bioconcept COVID-19 ag respi-strip test   | nasal swabs               | 79  | 265 | 0   | 25  | 369|
| 10.1101/0.2021.104713 | Toptan                | 2021 | Germany     | R-Biopharm                                       | nasal swabs               | 45  | 9   | 0   | 13  | 67 |
| 10.3390/v14030468   | Salcedo                 | 2022 | USA         | Rapid antigen tests (EZ5Bio, Inc., Cambridge, MA, USA) | nasal swabs               | 51  | 113 | 1   | 8   | 173|
| 10.1101/0.2021.104713 | Fourati               | 2022 | France      | COVID-VIBO® analysis                             | nasal swabs               | 215 | 1614| 0   | 77  | 1906|
| 10.1101/0.2021.104713 | Mockel                 | 2021 | Germany     | Roche SARS-CoV-2 antigen assay                   | nasal swabs               | 85  | 358 | 1   | 29  | 473|
| 10.1101/0.2021.104713 | Takeuchi               | 2021 | Japan       | QuickNavi™-COVID19 Ag                            | nasal swabs               | 91  | 1081| 0   | 14  | 1186|
| 10.1101/0.2021.104713 | Hausler                | 2021 | Germany     | LIASON® SARS-CoV-2 Ag assay (DiaSorin, Saluggia, Italy), BIOSYNEX Ag-RDT | nasal swabs               | 68  | 1632| 0   | 101 | 1801|
| 10.3390/v14030468   | Klimon                  | 2022 | Poland      | Humasis COVID-19 Ag Test kit                     | nasal swabs               | 29  | 271 | 4   | 4   | 308|
| 10.1093/ajcp/aqab173 | Drain                   | 2022 | USA         | LumiraDx SARS-CoV-2 Ag Test                      | nasal swabs               | 23  | 194 | 0   | 5   | 222|
| 10.1002/jmv.26830    | Mitchell                | 2021 | USA         | Sofia SARS rapid antigen                         | nasal swabs               | 36  | 107 | 0   | 5   | 148|
| 10.1101/0.2021.104713 | Thirion-Romo         | 2021 | Mexico      | Roche SARS-CoV-2 antigen assay                   | nasal swabs               | 256 | 579 | 9   | 216 | 1060|
| 10.1002/jmv.26830    | Hartard                 | 2021 | France      | LIASON® SARS-CoV-2 Ag assay (DiaSorin, Saluggia, Italy) | nasal swabs               | 39  | 330 | 2   | 7   | 378|
| 10.1101/0.2021.104713 | Almendares             | 2022 | USA         | BinaXNOW COVID-19 Ag Card test kit               | nasal swabs               | 157 | 3116| 4   | 142 | 3419|
| 10.1101/0.2021.104713 | Rahman                 | 2021 | Bangladesh  | Lumipulse® G SARS-CoV-2 Ag assay                 | nasal swabs               | 155 | 397 | 3   | 39  | 594|
| 10.1101/0.2021.104713 | Escrivá                | 2021 | Spain       | STANDARD Q COVID-19 Ag Test                     | nasal swabs               | 261 | 593 | 0   | 46  | 900|

(continued on next page)
| DOI | Author | Year | Country | Rapid Antigen Test Kit | Specimen Types | TP | TN | FP | FN | SS |
|----|--------|------|---------|-----------------------|----------------|----|----|----|----|----|
| 10.1016/j.jvec.2021.104961 | Merino-Amador | 2021 | Spain | ClinicTest Rapid COVID-19 Antigen Test (ClinitekRT) (Siemens, Healthineers, Erlangen, Germany) | nasopharyngeal swabs | 179 | 256 | 2 | 13 | 450 |
| 10.1016/j.diagmicrobio.2021.115591 | Onsongo | 2022 | Kenya | NowCheck SARS-CoV-2 Ag test kit | oro-nasopharyngeal swabs | 129 | 845 | 0 | 23 | 997 |
| 10.1016/j.jvec.2020.104659 | Linares | 2020 | Spain | Panbio COVID-19 Ag Rapid Test Device | nasopharyngeal swabs | 44 | 195 | 0 | 16 | 255 |
| 10.1016/j.jiid.2020.10.073 | Nalumansi | 2021 | Uganda | STANDARD Q COVID-19 Ag Test | nasopharyngeal swabs | 63 | 159 | 13 | 27 | 262 |
| 10.3390/ijerph.19073826 | Cattelan | 2022 | Italy | LumiraDx SARS-CoV-2 Ag Test Device | nasal swabs | 174 | 51 | 3 | 54 | 282 |
| 10.1016/j.cmi.2020.11.004 | Albert | 2021 | Spain | Panbio COVID-19 Ag Rapid Test Device | nasopharyngeal swabs | 43 | 358 | 0 | 11 | 412 |
| 10.1016/jinf.000000000000003101 | González-Donapetry | 2021 | Spain | Roche SARS-CoV-2 antigen assay | nasopharyngeal swabs | 14 | 422 | 0 | 4 | 440 |
| 10.5201/eid2705.204688 | Igloi | 2021 | Netherlands | COVID-VIRO® analysis | nasopharyngeal swabs | 158 | 780 | 4 | 28 | 970 |
| 10.1002/jmv.26896 | Courtellemont | 2021 | France | COVID-VIRO® analysis | nasopharyngeal swabs | 117 | 127 | 0 | 4 | 248 |
| 10.1371/journal.pone.02547018 | Krüger | 2021 | Germany | Panbio COVID-19 Ag Rapid Test Device | nasopharyngeal swabs | 92 | 1001 | 1 | 14 | 1108 |
| 10.1016/j.jiacc.2021.03.021 | Asai | 2021 | Japan | Lumipulse® G SARS-CoV-2 Ag assay | saliva | 49 | 238 | 4 | 13 | 305 |
| 10.3390/v13050818 | Cento | 2021 | Italy | LumiraDx SARS-CoV-2 Ag Test Device | nasopharyngeal swabs | 297 | 596 | 17 | 50 | 960 |
| 10.3389/fpubh.2021.728969 | Alqahtani | 2021 | Bahrain | Panbio COVID-19 Ag Rapid Test Device | nasal swabs | 602 | 3420 | 30 | 131 | 4183 |
| 10.3346/jkms.2021.36.e101 | Oh | 2021 | Korea | STANDARD Q COVID-19 Ag Test | nasopharyngeal swabs | 7 | 78 | 0 | 33 | 118 |
| 10.1371/journal.pone.0259527 | Thell | 2021 | Austria | Roche SARS-CoV-2 antigen assay | nasopharyngeal swabs | 171 | 325 | 3 | 42 | 541 |
| 10.1017/ice.2021.281 | Smith | 2021 | Maryland | Sofia SARS rapid antigen | nasopharyngeal swabs | 180 | 2645 | 7 | 55 | 2887 |
| 10.4269/ajtmh.21-0809 | Mungomklang | 2021 | Thailand | STANDARD Q COVID-19 Ag Test | nasopharyngeal swabs | 35 | 1024 | 3 | 38 | 1100 |
| 10.1017/ice.2020 | James | 2021 | USA | BinaxNOW COVID-19 Ag Card test kit | nasal swabs | 86 | 2184 | 3 | 66 | 2339 |
| 10.1016/j.cmi.2020.09.057 | Diao | 2021 | China | FIC assay | nasopharyngeal swabs | 152 | 50 | 0 | 49 | 251 |
| 10.1016/j.jiacc.2021.07.005 | Kiyasu | 2021 | Japan | QuickNavi™COVID-19 Ag test kit | nasopharyngeal swabs | 151 | 1746 | 0 | 37 | 1934 |
| 10.1016/j.cmi.2021.02.001 | Merino | 2021 | Spain | Panbio COVID-19 Ag Rapid Test Device | nasopharyngeal swabs | 325 | 592 | 7 | 34 | 958 |
| 10.1371/journal.pone.0258394 | Jo | 2022 | Korea | STANDARD Q COVID-19 Ag Test | nasopharyngeal swabs | 121 | 198 | 2 | 9 | 330 |
| 10.5201/eid2711.211449 | Surasi | 2021 | USA | BinaxNOW COVID-19 Ag Card test kit | nasal swabs | 34 | 110 | 0 | 26 | 170 |
| 10.3390/diagnostics11112110 | Altawalah | 2021 | Kuwait | LIAISON® SARS-CoV-2 Ag assay (DiaSorin, Saluggia, Italy), STANDARD COVID-19 Ag Test | nasopharyngeal swabs | 113 | 150 | 0 | 37 | 300 |
| 10.1111/apm.13189 | Jakobsen | 2021 | Denmark | LIAISON® SARS-CoV-2 Ag assay (DiaSorin, Saluggia, Italy), STANDARD COVID-19 Ag Test | nasal swabs | 32 | 7008 | 0 | 34 | 7074 |
| 10.3390/diagnostics12024477 | Yin | 2022 | Belgium | Lumipulse® G SARS-CoV-2 Ag assay (Biosynex Ag-RDT) | nasopharyngeal swabs | 95 | 396 | 4 | 7 | 502 |
| 10.3346/s15010-021-01723-5 | Fitounsi | 2021 | France | Lumipulse® G SARS-CoV-2 Ag assay (Biosynex Ag-RDT) | nasopharyngeal swabs | 121 | 816 | 3 | 27 | 967 |
| 10.1371/journal.pone.0260862 | Polleireis | 2021 | USA | BinaxNOW COVID-19 Ag Card test kit | nasal swabs | 25 | 177 | 0 | 12 | 214 |
| 10.1016/j.jiijd.2021.04.048 | Caputo | 2021 | Italy | Lumipulse® G SARS-CoV-2 Ag assay | nasopharyngeal swabs | 436 | 3661 | 102 | 67 | 4266 |
| 10.3201/eid2710.210080 | Tinker | 2021 | USA | BinaxNOW COVID-19 Ag Card test kit | nasal swabs | 8 | 1500 | 0 | 32 | 1540 |
| 10.1016/j.jvec.2021.105023 | Okoye | 2022 | USA | BinaxNOW COVID-19 Ag Card test kit | nasal swabs | 45 | 3759 | 2 | 4 | 3810 |
| 10.1016/j.jiviromet.2021.114299 | Paul | 2021 | India | COVID-VIRO® analysis | nasal swabs | 72 | 50 | 0 | 26 | 148 |
| 10.1016/j.jiacc.2021.10.024 | Suzuki | 2022 | Japan | RapidTesta SARS-CoV-2 | nasopharyngeal swabs | 53 | 1045 | 8 | 21 | 1127 |
| 10.1080/23744235.2021.1914857 | Homza | 2021 | Czech Republic | ECOTEST Covid-19 Antigen Rapid Test | nasopharyngeal swabs | 125 | 321 | 0 | 39 | 494 |
| 10.1002/jmv.27220 | Carbonell-Sahuquillo | 2021 | Spain | Panbio COVID-19 Ag Rapid Test Device | nasopharyngeal swabs | 24 | 323 | 0 | 10 | 357 |
| 10.1016/j.jiijd.2021.03.051 | Bouassa | 2021 | France | SIENNA™ COVID-19 Antigen Rapid Test | nasal swabs | 90 | 50 | 0 | 10 | 150 |
| 10.1016/j.diagmicrobio.2021.115591 | Sazed | 2021 | Bangladesh | COVID-VIRO® analysis | nasal swabs | 121 | 245 | 2 | 12 | 380 | (continued on next page)
| DOI | Author | Year | Country | Rapid Antigen Test Kit | Specimen Types | TP | TN | FP | FN | SS |
|-----|--------|------|---------|------------------------|----------------|----|----|----|----|----|
| 10.3390/diagnostics1122300 | Jegerlehner | 2021 | Switzerland | OnSite® COVID-19 Ag Rapid Test | nasopharyngeal swabs | 92 | 1319 | 2 | 49 | 1462 |
| 10.1016/j.ijid.2021.07.010 | Bullete | 2021 | Spain | Panbio COVID-19 Ag Rapid Test Device | nasopharyngeal swabs | 100 | 1220 | 2 | 40 | 1362 |
| 10.4103/ijmr.IJMR_3305_20 | Gupta | 2021 | India | STANDARD Q COVID-19 Ag Test | nasopharyngeal swabs | 63 | 252 | 1 | 14 | 330 |
| 10.1007/s41999-021-00584-3 | Paap | 2021 | Netherlands | Roche SARS-CoV-2 antigen assay | nasopharyngeal swabs | 27 | 363 | 45 | 26 | 461 |
| 10.1371/journal.pone.0250866 | Moreen | 2021 | Netherlands | BD Veritor System for Rapid Detection of SARS-CoV-2 | nasopharyngeal and throat swabs | 16 | 334 | 0 | 1 | 351 |
| 10.1136/bmj.n1657 | Fiana | 2021 | UK | SARS-CoV-2 antigen rapid lateral flow test (LFT) | nasopharyngeal and throat swabs | 28 | 5431 | 3 | 42 | 5504 |
| 10.1128/Spectrum00342-21 | Chiu | 2021 | USA | LFA-based INDIACOID COVID-19 rapid antigen test (INDICAID rapid test) | nasal swabs | 158 | 23462 | 42 | 30 | 23692 |
| 10.1016/j.ajem.2021.10.022 | Turcato | 2022 | Italy | STANDARD Q COVID-19 Ag Test | nasopharyngeal swabs | 329 | 3470 | 32 | 68 | 3899 |
| 10.3390/diagnostics1122217 | Tonen-Wolyec | 2021 | France | BIOSYNEX Ag-RDT | nasopharyngeal swabs | 20 | 84 | 0 | 2 | 106 |
| 10.1007/s11845-021-02863-1 | Kolesova | 2021 | Italy | Elecsys® SARS-CoV-2 Antigen assay | nasopharyngeal swabs | 64 | 34 | 0 | 12 | 110 |
| 10.1007/s11845-021-02776-z | Denina | 2021 | Italy | LumiraDx SARS-CoV-2 Ag Test | nasal swabs | 16 | 160 | 14 | 1 | 191 |
| 10.1038/s41598-021-90026-8 | Takeuchi | 2021 | Japan | QuickNavi™ COVID-19 Ag | nasal swabs | 37 | 811 | 0 | 14 | 862 |
| 10.1002/jca.24203 | Begum | 2022 | Bangladesh | InTec Rapid SARS-CoV-2 Antigen Test | nasal swabs | 101 | 102 | 0 | 11 | 214 |
| 10.1016/j.jciv.2021.104878 | Ferré | 2021 | France | Panbio COVID-19 Ag Rapid Test Device | nasal swabs | 33 | 636 | 0 | 19 | 688 |
| 10.1128/JCM.03077-20 | Pollock | 2021 | USA | MSD S-PLEX SARS-CoV-2 N assay | nasal swabs | 112 | 89 | 1 | 24 | 226 |
| 10.3390/jiperf18179151 | Kyritsi | 2021 | Greece | Rapid Test Ag 2019-nCoV (PROGNOSIS, BIOTECH, Larissa, Greece) | nasal swabs | 141 | 458 | 1 | 24 | 624 |
| 10.1155/2021/s3983733 | Loconsole | 2021 | Italy | Lumipulse® G SARS-CoV-2 Ag assay | nasopharyngeal swabs | 205 | 677 | 18 | 11 | 911 |
| 10.1016/j.jjgid.2021.09.008 | Leiner | 2021 | Germany | Standard F COVID-19 Ag FIA | oro-nasopharyngeal swabs | 491 | 3208 | 80 | 297 | 4076 |
| 10.1371/journal.pone.0253321 | Nsoga | 2021 | Switzerland | Panbio COVID-19 Ag Rapid Test Device | oropharyngeal swabs | 136 | 232 | 2 | 32 | 402 |
| 10.3390/diagnostics12040847 | Ahmed | 2022 | Malaysia | Panbio COVID-19 Ag Rapid Test Device | nasopharyngeal swabs | 101 | 51 | 2 | 3 | 157 |
| 10.23749/mdx.v1125.s12097 | Visci | 2021 | Italy | LIAISON® SARS-CoV-2 Ag assay (DiaSorin, Saluggia, Italy), Roche SARS-CoV-2 antigen assay | nasopharyngeal swabs | 78 | 113 | 8 | 10 | 209 |
| 10.1371/journal.pone.0263327 | Mori | 2022 | Japan | Roche SARS-CoV-2 antigen assay | nasopharyngeal swabs | 42 | 1014 | 0 | 14 | 1070 |
| 10.1371/journal.pone.0249710 | Sood | 2021 | USA | BinaxNOW COVID-19 Ag Card test kit | nasal swabs | 127 | 539 | 9 | 99 | 774 |
| 10.1002/ecll.obab059 | Massia | 2021 | Spain | Panbio COVID-19 Ag Rapid Test Device | nasal swabs | 118 | 709 | 0 | 77 | 904 |
| 10.1002/jmv.27249 | Cassuto | 2021 | France | COVID-VIRO® analysis | nasal swabs | 31 | 202 | 0 | 1 | 234 |
| 10.1007/s15100-020-01542-0 | Lanzler | 2020 | Austria | Panbio COVID-19 Ag Rapid Test Device | nasal swabs | 31 | 2 | 0 | 20 | 53 |
| 10.1128/JCM.00083-21 | Pollock | 2021 | USA | BinaxNOW COVID-19 Ag Card test kit | nasal swabs | 227 | 2003 | 12 | 66 | 2308 |
| 10.3390/diagnostics12030710 | Lee | 2022 | Korea | STANDARD Q COVID-19 Ag Test | nasopharyngeal swabs | 58 | 104 | 0 | 13 | 175 |
| 10.1016/j.diagmicrobio.2021.115531 | Braumlich | 2022 | Germany | Roche SARS-CoV-2 antigen assay | nasopharyngeal swabs | 45 | 2867 | 21 | 45 | 2978 |
| 10.1128/Spectrum01008-21 | Siddiqui | 2021 | USA | BinaxNOW COVID-19 Ag Card test kit | nasal swabs | 179 | 5826 | 13 | 43 | 6061 |
| 10.1016/j.jjgid.2021.05.063 | Leixner | 2021 | Austria | AMP Rapid Test SARS-CoV-2 Ag swabs | nasopharyngeal swabs | 65 | 297 | 1 | 29 | 392 |
| 10.1128/JCM.00991-21 | L’Huillier | 2021 | Switzerland | Panbio COVID-19 Ag Rapid Test Device | nasopharyngeal swabs | 79 | 703 | 0 | 40 | 822 |
| 10.3390/jcm10071471 | Amer | 2021 | Egypt | STANDARD Q COVID-19 Ag Test | oro-nasopharyngeal swabs | 54 | 9 | 5 | 15 | 83 |
| 10.3390/jcm10071471 | Amendola | 2021 | Italy | Lumipulse® G SARS-CoV-2 Ag assay | saliva | 22 | 80 | 5 | 20 | 127 |
| 10.1016/j.jjgid.2021.04.087 | Perea | 2021 | Chile | STANDARD Q COVID-19 Ag Test | nasopharyngeal swabs | 51 | 766 | 3 | 22 | 842 |
| 10.1016/j.jiac.2021.07.006 | Kurihara | 2021 | Japan | QuickChaser® Auto SARS-CoV-2 | nasopharyngeal swabs | 62 | 1316 | 2 | 21 | 1401 |
| 10.1016/j.jciv.2020.104455 | Scohy | 2020 | Brussels | | nasal swabs | 32 | 42 | 0 | 74 | 148 |
The pooled sensitivity decreased as Ct values increased. Samples after symptom onset exceeded 10 days, the sensitivity notably decreased and specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.76 (95%CI: 0.73–0.79), 1.00 (95%CI: 1.00–1.00), 276.1 (95% CI, 184.1–414.1), 0.24 (95% CI, 0.21–0.27), and 1171 (95% CI, 782–1755), respectively. A positive likelihood ratio > 10 confirms the diagnosis of the disease, while a negative likelihood ratio < 0.1 excludes the possibility of the disease. When the diagnostic odds ratio > 1, the larger the value, the better the ability to distinguish between healthy people and patients. Our results indicated that RAT had a high diagnostic value.

We assessed sensitivity at three different cutoff points on the days after the onset of symptoms. For ≤ 3, ≤ 7, and ≤ 10 days, the sensitivity and specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.76 (95% CI: 0.73–0.79), 1.00 (95% CI: 1.00–1.00), 276.1 (95% CI, 184.1–414.1), 0.24 (95% CI, 0.21–0.27), and 1171 (95% CI, 782–1755), respectively. A positive likelihood ratio > 10 confirms the diagnosis of the disease, while a negative likelihood ratio < 0.1 excludes the possibility of the disease. When the diagnostic odds ratio > 1, the larger the value, the better the ability to distinguish between healthy people and patients. Our results indicated that RAT had a high diagnostic value.

Possibly due to differences in sensitivity, specificity, and patient...
population between the studies, we detected a high degree of heterogeneity; however, the bivariate random-effects model we used provided a relatively robust statistical result. Performance between manufacturer-dependent studies and manufacturer-independent studies may differ hugely, but when we removed the 3 manufacturer-dependent studies, the overall effect remained unchanged, (Sensitivity: 0.76 versus 0.76; Specificity: 1.00 versus 1.00; AUC: 0.97 versus 0.97), indicating that our results were not driven by the 3 manufacturer-dependent articles. Furthermore, SROC did not detect marked heterogeneity in the pooled sensitivity and specificity. Tests for publication bias also indicated no noticeable bias. Thus, the statistical analysis of this meta-analysis was reliable to some extent.

By analyzing the data, we hypothesized that the pretest probability was 12%, resulting in a positive posttest probability of 97% and a negative posttest probability of 3%; this suggested a very high probability that a patient with SARS-CoV-2 infection would test positive in the antigen test. According to our findings, pretest probability is positively correlated with posttest probability. This suggests that RAT is more applicable to high-risk populations. Considering that the RAT provided 1.00 specificity in our study along with its rapid turnaround time, it could be used as a screening tool in particular situations, such as highly suspicious contacts, or for triage in an emergency department. A positive antigen test will confirm the infection and prevent the virus from spreading, as well as accelerate and optimize the management of infected individuals. By quickly identifying infected patients, the decision-making process of the entire emergency department is
Nasopharyngeal swabs generally have the highest detection rate for the diagnostic testing of respiratory viruses including SARS-CoV-2 (Lee et al., 2021). However, they must be collected by trained healthcare professionals using protective equipment, and their collection often causes considerable discomfort to patients (Lindner et al., 2021). In comparison, nasal sample collection is notably painless, and self-collection is possible (Lee et al., 2022). Moreover, nasal sampling is associated with less coughing or sneezing during collection, leading to less droplet exposure, thus reducing the transmission risk among healthcare workers (Takeuchi et al., 2021). Recent studies have reported that the diagnostic sensitivity of RT-PCR for nasal specimens is comparable to that for nasopharyngeal specimens (Pere et al., 2020; Tu et al., 2020). Interestingly, our analysis revealed that the sensitivity for nasal swabs (0.79) was higher than that for nasopharyngeal swabs (0.76) for RAT in cases where both swabs reached a specificity of 1.00. Therefore, the results indicate that using a more superficially collected nasal swab specimen is a good alternative for detecting SARS-CoV-2.

The overall sensitivity of the different RAT kits varies widely, ranging from 0.90 (95% CI: 0.70–0.97) to 0.41 (95% CI: 0.23–0.61). Three RAT kits (LumiraDx SARS-CoV-2 Ag Test, Panbio COVID-19 Ag Rapid Test Device, and STANDARD Q COVID-19 Ag Test) in our research have been authorized by the World Health Organization (WHO) for emergency use (Coronavirus Disease (COVID-19) Pandemic — Emergency Use Listing Procedure (EUL) Open for IVDs, 2020). For suspected patients, WHO recommends that a RAT kit reach a minimum performance criterion of 0.80 sensitivity and 0.97 specificity (Antigen-Detection in the Diagnosis of SARS-CoV-2 Infection, 2021). Only the LumiraDx SARS-CoV-2 Ag Test met this criterion, with a sensitivity of 0.83 (95% CI: 0.76–0.88) and specificity of 0.97 (95% CI: 0.94–0.99). The other two kits did not reach a sensitivity of 0.80 (sensitivity of 0.73 for Panbio and 0.70 for Standard Q), although both had a specificity of 1.00. Therefore, these results suggest an urgent need to further validate the performance of RAT kits on the emergency use list.

Previous studies have shown that lower Ct values represent higher viral loads, resulting in significantly higher RAT sensitivity, antigen concentration, and Ct values that are highly correlated (Pollock et al., 2021), and these were confirmed by our study. An outstanding sensitivity of 1.00 was achieved for Ct values < 20, after which the sensitivity of the RAT gradually declined as Ct values increased. Several studies have reported that the infectivity of SARS-CoV-2 persists for only approximately 8–10 days after the onset of symptoms (Bullard et al., 2020; Hirotsu et al., 2021; Million et al., 2020; Perera et al., 2020; van Kampen et al., 2021; Wolfel et al., 2020). Based on the results of the meta-analysis, the sensitivity within 10 days after the appearance of symptoms (0.88) was relatively favorable, which was not much lower than that within 3 days (0.91). Our findings support the use of RAT as an early stage screening tool for symptomatic patients, particularly those with high viral loads.

When Ct values were > 24, Bullard et al. observed that infectious viruses could not be isolated from the diagnostic samples (Bullard et al., 2020). In our research, although the pooled sensitivity was relatively improved.
assumed that the missed cases of RAT will not cause a large-scale
symptoms can be considered a stage of low contagiousness (CDC, 2020).
for Disease Control and Prevention, 10 days after the appearance of
transmission. Our findings suggest that RAT sensitivity was as low as
0.36 ten days after symptom onset. However, according to the Centers
- study that RAT had high sensitivity and specificity and performed better in samples with high viral
load, but in contrast to the earlier studies, we have a new finding that
nasal swabs have a higher sensitivity than nasopharyngeal swabs for
RAT. In addition, the strength of the present study lies in the number of
studies (and samples) analyzed compared with previous studies (Arshadi
et al., 2022; Chen et al., 2021; Hayer et al., 2021). Although our study
did not assess the impact of the SARS-CoV-2 variant, RAT may not be
influenced by the variant because RAT targets the nucleocapsid antigen
whereas the mutant has a variable mutation at the spike antigen (Gupta
et al., 2021).

Our study has some limitations, due to the lack of detailed infor-
mation in the articles, the data of ≤ 10 days included data of both ≤ 7
days and 8–10 days, resulting in some overlap between the data of ≤ 10
days and ≤ 7 days, which may account for the similar sensitivity of the
two (Sensitivity: 0.89 versus 0.88), whether the sensitivity of ≤ 7 days
was similar with that of 8–10 days after symptom onset need to further
study. We did not evaluate all RAT kits, but only part of them because of
the limited data.

5. Conclusions

RAT kits show high sensitivity and specificity in the early stages of
infection, especially when the viral load is high. In addition, using nasal
samples for antigen testing, which is moderately sensitive and patient-
friendly, is a reliable alternative to nasopharyngeal sampling. RAT
might be an effective tool for the clinical management of patients in
hospital settings, especially during the initial triage, as it aids the rapid
identification of positive patients to prevent transmission, thus helping
disrupt the COVID-19 pandemic. RAT also seems applicable to other
areas, such as regular mass screening or airport screening, because it
should allow for a more convenient and time-saving experience for
people who travel. However, this important epidemiological benefit
must be complemented with the thoughtful and responsible handling of
negative test results.

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Ethical approval statement

No ethics approval was required for this work.

CRediT authorship contribution statement

Jia-Wen Xie: Methodology, Writing – original draft. Yun He: Software, Investigation. Ya-Wen Zheng: Formal analysis, Investigation.
Mao Wang: Validation, Data curation. Yong Lin: Visualization, Supervision. Li-Rong Lin: Conceptualization, Writing – review & editing.

Conflict of interest

The authors declared that they have no conflicts of interest to this work.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the

Table 2
Pooled sensitivity and specificity among subgroups of studies.

| Subgroups               | No. of study | Total Sample Size | Pooled Sensitivity (95% CI) | Pooled Specificity (95% CI) |
|-------------------------|--------------|-------------------|----------------------------|----------------------------|
| **Sample Types**        |              |                   |                            |                            |
| nasopharyngeal          | 93           | 76,945            | 0.76 (0.72-0.79)           | 1.00 (1.00-1.00)            |
| nasal                   | 26           | 64,125            | 0.79 (0.71-0.85)           | 1.00 (0.99-1.00)            |
| other                   | 16           | 22,372            | 0.76 (0.66-0.84)           | 1.00 (0.99-1.00)            |
| **RAT Kit**             |              |                   |                            |                            |
| COVID-19 Ag analysis    | 4            | 2536              | 0.90 (0.70-0.97)           | 1.00 (1.00-1.00)            |
| Lumipulse® G            | 10           | 8895              | 0.86 (0.79-0.91)           | 0.98 (0.96-0.99)            |
| SARS-CoV-2 Ag assay     |              |                   |                            |                            |
| BIOSYNEX Ag-RDT         | 3            | 1382              | 0.85 (0.77-0.90)           | 0.99 (0.98-1.00)            |
| LuminA® SARS-CoV-2 Ag Test | 7           | 4115              | 0.83 (0.76-0.88)           | 0.97 (0.94-0.99)            |
| QuickNavi®              | 3            | 3982              | 0.81 (0.76-0.85)           | 1.00 (1.00-1.00)            |
| Panbio COVID-19 Ag Rapid Test Device | 25 | 30,332 | 0.73 (0.67-0.79) | 1.00 (1.00-1.00) |
| LIASON® SARS-CoV-2 Ag assay | 7 | 3532 | 0.72 (0.60-0.82) | 1.00 (0.97-1.00) |
| Roche SARS-CoV-2 antigen assay | 9 | 6,048 | 0.71 (0.62-0.78) | 0.99 (0.96-1.00) |
| STANDARD Q COVID-19 Ag Test | 17 | 20,765 | 0.70 (0.59-0.79) | 1.00 (0.99-1.00) |
| Biohit COVID-19 Ag Card test kit | 10 | 23,344 | 0.65 (0.50-0.77) | 1.00 (1.00-1.00) |
| Elecsys® SARS-CoV-2 Antigen assay | 6 | 4,750 | 0.65 (0.44-0.81) | 1.00 (0.98-1.00) |
| Coris bioclot COVID-19 Ag rapid-stripe test | 4 | 747 | 0.41 (0.23-0.61) | 1.00 (0.53-1.00) |

Days after symptom onset

| ≤ 3 days | 10 | 870 | 0.91 (0.83-0.96) | / |
| ≤ 7 days | 13 | 1,862 | 0.89 (0.84-0.93) | / |
| ≤ 10 days | 13 | 1918 | 0.88 (0.83-0.92) | / |
| > 10 days | 4 | 72 | 0.36 (0.21-0.55) | / |

Ct Values

| ≤ 20 | 15 | 368 | 1.00 (0.70-1.00) | / |
| 20-25 | 11 | 342 | 0.94 (0.87-0.97) | / |
| 25-30 | 23 | 579 | 0.70 (0.53-0.84) | / |
| > 30 | 24 | 715 | 0.24 (0.16-0.33) | / |
