Diagnostic Accuracy of Rapid Antigen Tests for SARS-CoV-2 Approved for Use in China

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Abstract. Rapid antigen tests (RATs), a simple, inexpensive test that can be performed at home by residents, have been widely used in COVID-19 diagnosis around the world. Until 29th April 2022, the Chinese National Medical Products Administration (CNMPA) has approved a total of 31 items of RAT products. Review the existing research evaluating the diagnostic accuracy of CNMPA-approved RATs, then collect the raw data of included texts, calculate the sensitivity and specificity in each study, and compare them with these two aspects to provide optimal choice for RAT used in real-life practice. Using the Cochrane and WHO COVID-19 databases, studies with full texts published between 2020-2022 were included if they aimed detection for SARS-CoV-2 infection, had CNMPA-approved RAT for index testing and compared with RT-PCR results. Studies were excluded if they failed to provide primary data for accuracy testing or the data provided did not allow the calculation of sensitivity or specificity. No language restrictions were applied in this review, and all study designs that provided diagnostic accuracy data were accepted. Results: 22 studies were included in this review. All CNMPA-approved RATs included in the review performed well in diagnostic specificity except for four individual studies. However, the sensitivity of CNMPA-approved RATs varied widely among different RATs and different studies. The two worst sensitivity-performing RATs were Savant and LEPU, while the best was Wondfo.

Keywords: SARS-CoV-2, Rapid Antigen Tests, Diagnostic Accuracy, Sensitivity and specificity.

1. Introduction

Since December 2019, the COVID-19 pandemic has greatly impacted our daily lives. COVID-19 is a disease caused by the SARS-CoV-2 infection, which will transmit from human to human[1]. People with COVI-19 could develop pneumonia, sometimes leading to life-threatening cases for patients with severe illnesses[2, 3]. According to the latest epidemiology data from the WHO issued on 30th September 2022, there were already 614,385,693 confirmed COVID-19 cases and 6,522,600 deaths globally[4]. Furthermore, there are still 6,522,600 cases newly reported in China during the week up to 30th September, which shows that controlling the COVID-19 epidemic in China still requires more effort[5]. Identifying and surveillance of COVID-19 infection cases is vital in pandemic control. Especially for a country like China with a relatively high population density, loosening the diagnosis and monitoring for COVID-19 cases will bring unpredictable casualties domestically and globally[6].

The Reverse transcription-quantitative polymerase chain reaction (RT-PCR) is recognized as the COVID-19 infection diagnosis' gold standard[7]. However, RT-PCR relies on laboratory instruments and medical personnel, which limits its use during daily practice[8, 9]. The rapid antigen test (RAT) plays an important role in COVID-19 diagnosis worldwide as a simple, inexpensive test that residents can perform at home[10]. It has been widely used in China's community-based isolation and control events during the COVID-19 epidemic. However, evidence showed that RATs from different manufacturers perform differently in diagnostic performance, and even the same RAT product could perform differently on diagnostic accuracy in patients with different viral loads (usually estimated by Ct value)[11]. Especially in high-risk areas, the sensitivity and specificity of used RATs products are crucial for local COVID-19 control.

As of 29th April 2022, the Chinese National Medical Products Administration (CNMPA) has approved a total of 31 items of RAT products[12]. These approved RATs products are used as supplements for PCR to serve the needs of domestic COVID-19 prevention and control, and they can

be purchased through pharmacies, medical and health institutions, local retail outlets, and online shops[13]. Although the public can get the name list of RATs approved for sale in China through government announcements, the diagnostic accuracy data for those items is not provided in the official notification. Although there are studies on the diagnostic performance of RATs, there is still a lack of retrospective evaluation of the RATs approved by CNMPA in the Chinese domestic market, especially in real-world settings. Thus, this paper will review the studies on the diagnostic accuracy of CNMPA-approved RATs, collect the raw data and calculate the sensitivity and specificity of each item, and then compare the different CNMPA-approved RATs based on the results. The outcome of this review will provide selection references for residents, medical institutions, and departments related to COVID-19 control when purchasing CNMPA-approved RATs.

2. Methods

The Cochrane COVID-19 Study Register (CCSR) is an annotated reference database of studies on COVID-19. It is continually updated from PubMed, Embase, CENTRAL, ClinicalTrials.gov, ICTRP, and medRxiv[14]. The WHO COVID-19 Global literature on coronavirus disease is also a continually-updated global literature collection of research related to COVID-19, which includes a comprehensive study collection on COVID-19[15]. Having these two comprehensive databases up-to-date in the field of COVID-19 was less likely to generate possible omissions in the study inclusion. Thus, our literature search was conducted on these two databases mentioned above. The searching terms used in the CCSR and the WHO Database were: COVID-19 testing; SARS-CoV-2 testing; diagnostic accuracy; the name of each RAT item approved by CNMPA; diagnostic performance; self-testing; sensitivity and specificity, and Rapid antigen test.

Studies were eligible for inclusion if they included the characteristic of: 1) at least a CNMPA-approved RAT for the index test; 2) reference standard is RT-PCR; 3) aiming for COVID-19 detection; 4) full text is available; 5) published between 2020-2022. Studies were excluded if: 1) the data provided do not allow the calculation of sensitivity or specificity; 2) studies do not provide the primary data. No language restrictions were applied in this review, and all study designs that provided diagnostic accuracy data were accepted.

3. Results and Discussion

Overall, 2064 records were retrieved from the two databases. After deduplicating 564 studies and excluding 1462 irrelevant studies, 39 studies were included for full-text screening. Eighteen studies that failed to meet the inclusion criteria were further excluded, resulting in 22 studies included in this review. The flow chart in Figure 1 presents the selection process in this review. The reasons for studies being excluded in the stage for full-text screening are also shown in the figure.

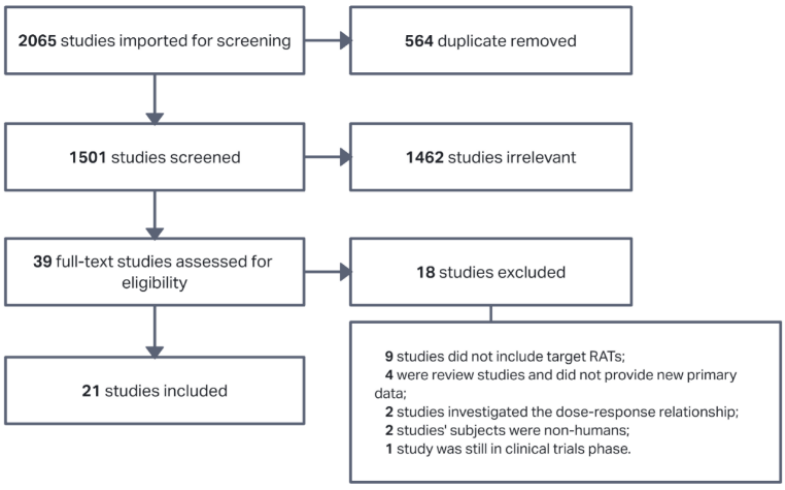

Figure 1. Selection Process of Primary Studies Included in This Review

Among them, Wonderfo (Guangzhou Wondfo Biotech Co., Ltd.), ALLTEST (Hangzhou ALLTEST Biotech Co., Ltd.), and Bioeasy (Shenzhen Bioeasy Biotechnology Co., Ltd.), these three RATs were found to have the most significant number of literature. During the screening process, it was found that there are still many CNMPA-approved RATs that do not hold a sufficient number of studies that successfully met our inclusion criteria to support the conclusion of their diagnostic accuracy evaluation, which included a total of 21 items in the Chinese market. These RATs either had been just approved in China or were rarely used in foreign markets outside China, resulting in a lack of research on their real-life diagnostic accuracy performances. They need more studies to test their actual performance of diagnostic accuracy in real-world settings. Thus, these RATs will not be further discussed in our study. Table 1 below presents the name, mechanism, and outcomes of included RATs evaluation studies that were eligible for the sensitivity and specificity calculation.

In general, the specificity of each included RATs was relatively high. Except 1 LEPU study (89.2%), 1 Orient Gene study (74.4%), and 2 Bioeasy studies (85.6%, 93.1%), the specificity of other RATs was all higher than 97%. Several studies have even investigated 100% specificities. Savant has the lowest sensitivity of 16.7% compared to the primary data, while ALLTEST holds the highest sensitivity of 97.3% in one of its studies[16, 17]. By comparing RATs with two or more included performance data for the same RAT, the sensitivity results obtained by different studies are still quite different. The largest difference showed in LEPU, with a 71% difference in sensitivity from the lowest 21.0% to the highest 92.0%[18, 19]. No significant differences in the sensitivity and specificity of RATs were found under different mechanisms. Since no positive cases were found in the RT-PCR test or the research subjects were all RT-PCR positive patients in some included studies, one of the sensitivity or specificity data could not be obtained, which will be discussed separately.

Table 1. Diagnostic performances of included CNMPA-approved RATs

Antigen detection test	Mechanism	Sensitivity (%), (95%CI)	Specificity (%), (95%CI)
Guanzhou Wondfo	CGT	96.2 (96.4-98.5)	99.7 (98.5-100.0)
		85.7 (74.3-92.6)	100.0 (98.6-100.0)
		75.6 (68.3-81.8)	100.0 (97.2-100.0)
		73.0 (65.0-79.7)	98.6 (95.2-99.6)
Beijing Savant	IFA	16.7 (10.0-26.5)	100.0 (89.0-100.0)
Nanjing Vazyme	CGT	72.0 (57.0-84.0)	100.0 (95.0-100.0)
Beijing Hotgen	CGT	96.6	99.8
		-	99.8 (98.8-100.0)
LEPU medical	CGT	92.0	99.3
		45.5 (35.6-55.8)	89.2 (83.8-93.3)
		21.0 (14.2-30.0)	-
Wantai BioPharm	CGT	93.44	100.0
Zhejiang Orient Gene//Healgen Scientific	CGT	82.1 (73.2–88.5)	-
		79.5 (72.3-85.6)	74.4 (67.3-80.1)
		57.6 (40.8-72.8)	100.0 (93.44-100.0)
ACON Biotech	LAT	79.0 (74.7-82.8)	97.2 (93.9-98.9)
		50.0 (37.7-62.3)	-
Hangzhou ALLTEST	LAT	27.5 (21.3-34.3)	99.8 (99.3-100.0)
		97.3 (94.2-99.0)	99.5 (97.3-100.0)
		94.4 (89.2-97.5)	100.0 (98.8-100.0)
		85.0 (73.4-92.9)	100.0 (98.7-100.0)
Shenzhen Bioeasy	IFA	46.7 (39.3-54.2)	99.0 (98.5-99.4)
		93.9 (86.5-97.4)	100.0 (92.1-100.0)
		85.0 (75.6-91.2)	100.0 (89.0-100.0)
		73.1 (53.9-86.3)	85.6 (79.0-90.4)
		66.7 (41.7-84.8)	93.1 (90.1-94.8)

CGT, Colloidal gold test; IFA, Immunofluorescence assay; LAT, Latex agglutination test.

For Wonderfo antigen test, the highest sensitivity evaluation study was from its manufacturer (96.2%), which also had the largest testing sample size (n=859). Considering that this result was likely to be affected by its company's interests, the sensitivity performance was likely to be overestimated. Regardless of the data analysis provided by the manufacturer, the overall diagnostic sensitivity and specificity for Wonderfo rapid test were relatively good. With a sensitivity range of 73.05-85.7% and a specificity of 98.6% and above

Only one literature meeting the inclusion criteria was retrieved for the Savant antigen test (Beijing Savant Biotechnology Co., Ltd.). In this trial, a total of 109 samples were tested for Savant, and Savant successfully classified all 31 RT-PCR negative samples as RAT negative. However, regarding individual study evaluations, Savant had the worst sensitivity performance, with only 13 of 65 RT-PCR positive samples identified, resulting in its accuracy of only 40.4% (Kappa coefficient: 0.1)[17]. During the experiment, the researchers conducted operator training, single-blind, repeated experiments with inconsistent results for the quality control process. The possibility that the low sensitivity is due to measurement error is relatively small, although considering that Savant has only one article for consideration in this review.

In Vazyme's study (Nanjing Vazyme Biotech Co., Ltd.), a total of 47 samples were tested. The person who performed the operations were health workers in these medical facilities with sampling and testing in strict accordance with the operating specifications, and the results were obtained with a sensitivity of 72.0% and specificity of 100.0%[20]. However, since the study sample was from COVID testing trucks and two hospitals that admitted patients with COVID-19 infection, the mean Ct value (25.6) of these samples should also be considered.

In the two assessments included for Hotgen antigen test (Beijing Hotgen Biotech Co., Ltd.), the highest sensitivity results (96.6%) came from its own supplier and had a high probability of being overestimated by its own interest. However, since all the subjects tested in Thomas's study were patients with COVID-19, sensitivity calculations were not feasible. For both studies, Hotgen's specificity was consistent at 98%. Similarly, Wantai (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd.) included only one study on accuracy assessment from its supplier, and the only data showed relatively high sensitivity and specificity. However, considering the limitation of the number included and the possibility of overestimation from its supplier, the reference value of this data for real-life applications is limited.

LEPU antigen test (LEPU Medical Technology (Beijing) Co., Ltd.) held the largest sensitivity range of all the other RATs, with three studies included. Of these, the highest sensitivity result (92.0%) was provided by its manufacturer. Except from this, the other two studies both tested relatively low sensitivity results, including 45.5% (n=101) in Baro's study and 21.0% (n=100) in Saeed's study[19, 21]. In Baro's study, although the use of double-blind was mentioned, the training and operation regulations of sampling personnel were not described in detail, which may affect the accuracy of the evaluation. Since all the subjects who conducted RAT tests in Saeed's study were RT-PCR positive, specificity calculation was not feasible. In terms of overall performance, excluding the data provided by interested suppliers, the sensitivity and specificity results of LEPU antigen detection are relatively low compared to other RATs. LEPU antigen test needs to be carefully chosen when used in real-life COVID-19 testing.

The three studies included for Orient Gene/Healgen antigen test (Zhejiang Orient Gene Biotech Co., Ltd.) differ in sensitivity and specificity results. Of these, Norgren's study had the largest sample size (n=332) but the lowest specificity (74.4%) within all RATs[22]. In the study by Norgren et al., operation records in the sampling process were mentioned. However, the training of operators and blinding were not explained, which might affect the quality of evidence. Moreover, in the study of Victor et al., Healgen was found to react with other non-coronaviruses, which may also explain its low specificity[11]. The results of Magyar et al. yielded the lowest sensitivity of Healgen (n=87). However, the average Ct value of its research sample was only 23.4, and the sensitivity was likely to be affected. In the study of Peto, the sensitivity of Orientate Gene was better in the subgroup with an

average Ct less than 28, but it turned out to be very unsatisfactory in the group with a Ct value greater than 28.

The sensitivity span among the studies included in ACON (ACON Biotech (Hangzhou) Co., Ltd.) was 51.5%. In the study of Schuit et al. (n=620), ACON is more sensitive in the infection dominated by Delta than in the Omicron period. However, this difference was not reflected in the smaller sample size (n=60) in the study by Sanjat et al. ACON achieved its lowest sensitivity in the study by Roderick et al. (27.5%)[23]. Although their trial has a considerable sample size (n=1229), most of the samples were conducted by ordinary subjects who had not been trained for the correct RAT using methods. Furthermore, the overall sensitivity of the RATs tested with ACON in Roderick's study was relatively low, ranging from 20.9% to 27.5%. Therefore, the extremely low sensitivity was likely mainly due to the incorrect manipulation of the study subjects, rather than ACON itself having such low sensitivity.

The highest sensitivity result of ALLTEST (97.3%) was detected in the survey with a sample size of 420, and it was also the highest sensitivity result included in this review. In this article, the authors highly appraised its performance in COVID-19 detection. However, when analyzing its sample composition, it was found that the Ct values ≤ 20 of COVID-19 infection confirmed samples included in the study accounted for more than 80% of the total RT-PCR-positive samples. This sample composition also makes the number of positive cases detected by RAT in the sample higher than that of other studies with a more even distribution of Ct values, thus affecting the sensitivity evaluation of RAT, which means that the sensitivity of this study was likely to be overestimated. In the trial of Skvarc et al., ALLTEST also obtained a good diagnostic effect with sensitivity of 94.4% and specificity of 100%[24]. In Skvarc's study, health workers in the laboratory were used to sample the experimental subjects, and it was mentioned that sampling and testing were carried out under the instructions and standards of the user test. Although the use of blinding was not mentioned in the methods, all sampling sites were local healthcare institutions, making it less likely that the study had a predictable direction of measurement bias. However, because it was conducted in local settings with high COVID-19 prevalence, its specificity performance may be overestimated, especially when all test samples' Ct values have not been fully obtained. In the study of Ifko et al. (n=333), ALLTEST also showed a satisfactory sensitivity result of 85.0%[25]. The study did not elaborate on the procedures of the sampling operation, but it mentioned that the positive or presumed false negative samples were subsampled by the same health worker, which probably means that the experimental design was not implemented in a blinded method. The subsampling procedure may have been biased, possibly leading to an overestimation of the sensitivity and specificity of ALLTEST, given the researchers' awareness that the sample may be from a suspected COVID-19 patient. Not only that, but the fact also showed that the hospital sites where the assessment was conducted may have selected the best patients to be tested in the study, suggesting a high possibility of selection bias.

For patients with obvious clinical symptoms and signs, the viral load of samples included was likely to be higher than that of unincluded patients with no obvious clinical symptoms or asymptomatic infection. Though it was not obtained in their study, it still confirmed that the study might probably overestimate the accuracy of ALLTEST. The poorest sensitivity performance (46.7%) was estimated in the study with a sample size of 2803. In this study, although the experimental subjects were single-blind as the experimental subjects did not know their RT-PCR results, the RAT sampling and other operations were all performed by the study subjects at home. Thus, the quality of the RAT samples in this study was doubted. Incorrect sampling and other operations would possibly result in a lower RAT sensitivity.

Meanwhile, the acquisition of RAT results was collected in the form of online questionnaires, and different patients were likely to have deviations in the reading standards of the results, so this study was likely to have recall bias and huge measurement bias. Although most of the ALLTEST accuracy results appeared satisfactory, the included studies were subject to some degree of bias. There were still doubts about the accuracy and generalizability of this evidence, and more studies are required to provide high-quality evidence on its testing accuracy for further analysis.

The overall sensitivity of Bioeasy was good, all above 66% in four included studies. Among them, two studies were higher than the sensitivity of 80% recommended by WHO. Both studies have good operational quality control during sampling, testing, and reading. In the study of Thomas et al., it is mentioned that the measurement results of Bioeasy were read by the immunofluorescence mechine from its manufacture, which reduced measurement bias.

It is worth mentioning that, in all assessments with Ct subgroup analysis, results were of high consistency showing higher sensitivity with lower Ct values samples tested. This finding was in line with current findings in the dose-response studies on the relationship between Ct value and RAT positive results.

4. Conclusion

More high-quality studies still need to complement the accuracy assessment of COVID-19 RATs in real-life settings, especially for CNMPA-approved RATs lacking inclusion study in this review. All CNMPA-approved RATs included in the review performed well in diagnostic specificity except for four individual studies. However, the sensitivity of CNMPA-approved RATs varied widely among different RATs and different studies. For all RATs, the accuracy assessment data provided by their suppliers is relatively high, and there is a high probability that stakeholders overestimated the sensitivity. The two worst sensitivity-performing RATs were Savant and LEPU, while the best was Wondfo (sensitivity results above 73% for all included studies). The sensitivities of different brands of RATs assessed in the same study tended to be similar, even though the results were quite different compared to other studies for the same RAT brand. Moreover, these studies also reflect the problem of lacking uniform research design, operation, and evaluation criteria for the RAT accuracy evaluation process in real-life practice. Differences in trial design, sampler training, specification and implementation of sampling standards, and details of subgroup analyses limit the comparability of diagnostic accuracy assessments across different RATs to a large extent.

No significant differences in the sensitivity and specificity of RATs were found under different mechanisms. High consistency results were found in the included studies about higher sensitivity with lower Ct values samples tested.

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