

Diagnostic value comparative analysis of the commercial kits for the detection of SARS-CoV-2 in clinical samples: a systematic review and meta-analysis

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ABSTRACT

Background and Objectives: Rapid and accurate identification of suspicious SARS-CoV-2 patients is essential in controlling the infection. Numerous commercial kits are developed which target diverse regions of the SARS-CoV-2 virus genome. This systematic review addresses the lack of comprehensive analyses comparing the diagnostic value of commercial kits for SARS-CoV-2 detection. We aimed to compare diagnostic value of commercial SARS-CoV-2 kits in clinical samples using a systematic review and meta-analysis method.

Materials and Methods: A comprehensive search was conducted on main databases of Medline (PubMed), Embase, Web of Science and Scopus from 2019 to October 2021 using the appropriate keywords. Systematic Reviews and Meta-Analysis guideline PRISMA checklist was used to select eligible studies.

Results: The most frequent introduced kits were from USA (33 cases) and China (27). Among all studies, 11, 9 and 7 papers had assessed FDA –CDC, Sansure and Allplex kits, respectively. The majority of the kits were based on RT-PCR (52 cases) and the most frequent genes target was N protein (63 cases). The overall sensitivity of the kits was 80.5%. The lowest sensitivity was reported for Daan Kit, while the highest sensitivity was seen for many kits. The specificity of the kits ranged from 87.9% to 99.8% and the overall specificity was 97.9%. Both PPV and NPV of the kits ranged from 87.9% to 99.8% for PPV and 82.9% to 99.8% for NPV.

Conclusion: Based on DOR obtained from three different formulas, GeneFinder, InBios, NxTAG, Simplexa and FDA-CDC kit have better detection performance. The GeneFinder Kit appears to be among the more suitable options regarding cost-effectiveness for each reaction.

Keywords: SARS-CoV-2; Diagnostic tests; Sensitivity; Specificity; Meta-analysis

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INTRODUCTION

The COVID-19 pandemic still threatens many countries' system, and many measures have been implemented to repel the pandemic. Prevention of the disease transmission and the quick and accurate identification of the affected patients are the most important factors for the treatment of infection. Misdiagnosis and the existence of asymptomatic patients are main contributors to the transmission (1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-stranded RNA virus with a genome size ranging from 29.8 to 29.9 kb. The genome consists of *orf1ab* encoding polyproteins at the 5' end and structural genes at 3' end, which encode different proteins (2). Key genes such as *RdRP* gene (RNA-dependent RNA polymerase gene), *E* gene, and the *N* gene exhibit conserved sequences, making them suitable targets for detection via reverse-transcription polymerase chain reaction (RT-PCR) (3). While the World Health Organization (WHO) does not endorse virus culture for routine diagnostic procedures, nucleic acid-based amplification tests (NAATs) are recommended by the WHO and the Centers for Disease Control and Prevention (CDC) (4).

While several FDA-approved commercial kits are based on RT-qPCR, their diagnostic performance does not seem to be consistent. Most previous studies have only considered individual kits and they largely lacked a systematic comparison involving different viral targets and sensitivities (5, 6). This discrepancy has consequences in the reliability of diagnostic results, and such kits need to be thoroughly evaluated before clinical use (7).

This systematic review addresses the lack of comprehensive analyses comparing the diagnostic value of commercial kits for SARS-CoV-2 detection. The aim of the study was a comparison of the diagnostic performance of the kits for the detection of SARS-CoV-2 RNA in clinical specimens.

MATERIALS AND METHODS

Search strategy. A comprehensive search was conducted through the main electronic databases PubMed, Embase, Web of Science and Scopus from 2019 to October 2021 using the following keywords: "COVID", "COVID-19", "SARS-CoV-2", "Corona-

virus 2019", "New Coronavirus" "CoV-19", "Coronavirus disease 2019", "COVID-19 Coronavirus", "2019 Novel Coronavirus", "Detection", "Diagnosis", "Detection performance", "Molecular detection", "qPCR", "real-time PCR", "real-time polymerase chain reaction", "PCR", "Multiplex-PCR", "quantitative PCR", "RT-PCR", "Gold nanoparticle", "Silver nanoparticle", "Type of nanoparticle", "LAMP", "Nano-LAMP", "RT-LAMP", "Loop-Mediated Isothermal Amplification", "Rapid colorimetric detection", "Direct RT-qPCR", and "Next-generation sequencing" ("AND" and/or "OR"). Search was limited to English language. Systematic Reviews and Meta-Analysis guideline PRISMA checklist was used for selecting eligible studies (5). It is noted that selection of English language articles may result in language bias, potentially excluding noteworthy findings from research conducted in other languages.

Inclusion/exclusion criteria and studies selection. Studies were screened and selected based on an evaluation of their titles, abstracts, and full texts. Two researchers independently reviewed the full texts of eligible articles. Studies were included if they provided data on commercial SARS-CoV-2 detection kits. The following publication types were excluded: conference abstracts; narrative or systematic reviews; letters to editors; notes; book chapters; cohort studies; case reports; commentaries; protocols; and non-English articles. Extracted data included: kit abbreviation and name, manufacturer and country, assay type, target gene, sample type, number of samples and positive samples, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), limit of detection (LOD), positive Ct value, other tested pathogens, cross-reactivity, and price per PCR reaction. Data extraction was performed independently by two teams, and any disagreements were resolved by a third reviewer.

Data analysis. The diagnostic performance of the kits, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were assessed using Comprehensive Meta-Analysis (CMA) software (v2.2.064). Each parameter was treated as an event rate with the corresponding sample size, and the results were reported with 95% confidence intervals. Due to significant heterogeneity among the studies, as assessed by the Q-test and the I^2 statistic, a random-effects meta-analysis was performed. Ad-

ditionally, sensitivity and specificity were calculated from true positive, false negative, false positive, and true negative values using a bivariate model in STATA v17.0, yielding paired performance estimates, a coupled forest plot, and a summary receiver operating characteristic (SROC) curve. Publication bias was not evaluated because there is no reliable method for assessing bias in diagnostic test accuracy reviews (6). The p-value <0.05 was considered significant in all analyses. For further interpretation, additional diagnostic metrics, including the positive likelihood ratio (PLR), negative likelihood ratio (NLR), accuracy, Youden's index, and diagnostic odds ratio (DOR), were calculated based on published data (7).

RESULTS

The results of database searching. Of the 89,739 items screened, 58,220 duplicates were removed. After applying the inclusion/exclusion criteria and conducting detailed reviews, 48 studies were ultimately included in the qualitative and meta-analyses (Fig. 1). The features of the included studies are presented in Table 1.

The included studies and their used kits were as follows (the abbreviations were taken by us for easy representation of kits in the text, figures and Tables of the article): Guo et al. [Multiple Real-Time PCR Kit (Beijing), Novel Coronavirus Real Time Multiplex RT PCR Kit (ZJ Bio-Tech)] (8), Freire-Paspuel et al. [Viasure RT-qPCR kit (Viasure), FDA EUA 2019-nCoV CDC kit (FDA-CDC)] (9), Wang et al. [Liferiver novel coronavirus nucleic acid detection kit (Liferiver), Daan novel coronavirus nucleic acid detection kit (Daan), Genekey novel coronavirus nucleic acid detection kit (Genekey), Yaneng novel coronavirus nucleic acid detection kit (Yaneng)] (10), Goldenberger et al. [Cepheid® Xpress SARS-CoV-2 assay (Cepheid), cobas® SARS-CoV-2 assay (Cobas)] (11), Nagura-Ikeda et al. [SARS-CoV-2 direct detection RT-qPCR kit (TaKaRa), Ampdirect 2019 novel coronavirus detection kit (Shimadzu), SARS-CoV-2 detection kit (Toyobo)] (12), Chen et al. [LightMix SarbecoV E-gene kit (LightMix), NxTAG® CoV Extended Panel (NxTAG)] (13), Matsumura et al. [FDA-CDC, Roche E/N/RdRP kit (Roche), TaqPath COVID-19 CE-IVD RT-PCR Kit (TaqPath, BGI's Real-Time Fluorescent RT-PCR Kit (BGI))] (14), Zhen et al. [The New York SARS-CoV-2 RT-PCR Diagnostic EUA

Panel (Wadsworth), Simplexa® COVID-19 Direct Kit (Simplexa), GenMark ePlex SARS-CoV-2 assay EUA (GenMark), Panther Fusion® SARS-CoV-2 Assay (Panther)] (15), Kasteren et al. [RealStar® SARS-CoV-2 RT-PCR Kit (RealStar), BGI, Viasure, RADI COVID-19 Detection Kit (RADI), COVID-19 genesig® Real-Time PCR assay (Genesig), RIDA® GENE SARS-CoV-2 test (RIDA), Allplex™ 2019-nCoV Assay kit (Allplex)] (16), Lu et al. [Novel Coronavirus Nucleic Acid Diagnostic Kit (Sansure), BioGerm novel coronavirus nucleic acid detection kit (BioGerm)] (17), Pasomsub et al. [Sansure] (18), Haq et al. [BGI] (19), Freire-Paspuel et al. [AccuPower SARS-CoV-2 Multiplex RT-PCR kit (AccuPower), FDA-CDC] (20), Freire-Paspuel et al. [Isopollo COVID-19 detection kit (Isopollo), FDA-CDC] (21), Sarigul et al. [Bio-Speddy R COVID-19 RT-qPCR Detection Kit v2.0 (Bio-Speddy), Diagnovital R SARS-CoV-2 Real-Time PCR Kit v2.0 (Diagnovital)] (22), Alcoba-Florez et al. [Real Accurate Quadruplex corona-plus PCR Kit (PathoFinder), TaqPath] (23), Zou et al. [Daan] (24), Visseaux et al. [RealStar] (25), Kitagawa et al. [Loopamp® 2019-SARS-CoV-2 Detection Reagent Kit (Loopamp)] (26), Freire-Paspuel et al. [FDA-CDC] (27), Wen et al. [BioGerm, Sansure, Cepheid] (28), Sasaki et al. [Shimadzu] (29), Tedim et al. [Bio-Rad SARS-CoV-2 detection kit (Bio-Rad), GeneFinder™ COVID-19 Plus RealAmp Kit (GeneFinder)] (30), Mollaei et al. [TIB MOLBIOL Real Time PCR kit (TIB), Sansure] (31), Lee et al. [Allplex, PCR 20 K COVID-19 Detection kit (Optolane)] (32), Hernandez et al. [QuantuMDx SARS CoV 2 RT PCR Detection Assay (QuantuMDx), GeneFinder™ COVID-19 Plus RealAmp Kit (GeneFinder), Allplex, Genesig, Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic Kit (Sansure), Smart Detect™ SARS-CoV-2 rRT-PCR Kit (InBios), ProTect™ COVID 19 PCR Kit (ProTect), PCL COVID19 Speedy RT-PCR (PCL), MiRXES Fortitude Kit 2.1 (MiRXES)] (33), Chung et al. [PowerCheck™ 2019-nCoV (PowerCheck), Allplex, DiaPlexQ™ Novel Coronavirus Detection Kit (DiaPlex), STANDARD M nCoV Real-Time Detection Kit (Biosensor), Real-Q 2019-nCoV Detection kit (Bioseum)] (34), Roy et al. [Sansure] (35), Fukumoto et al. [Shimadzu] (36), Freire-Paspuel et al. [AccuPower, Allplex, FDA-CDC] (37), Reijns et al. [TaqPath, Abbott RealTime SARS-CoV-2 assay (Abbott)] (38), Freire-Paspuel et al. [COVID-19 Nucleic Acid Test Kit (eDiagnosis), Sansure, FDA-CDC] (21), Freire-Paspuel et al. [Daan, GenomeCoV19 kit

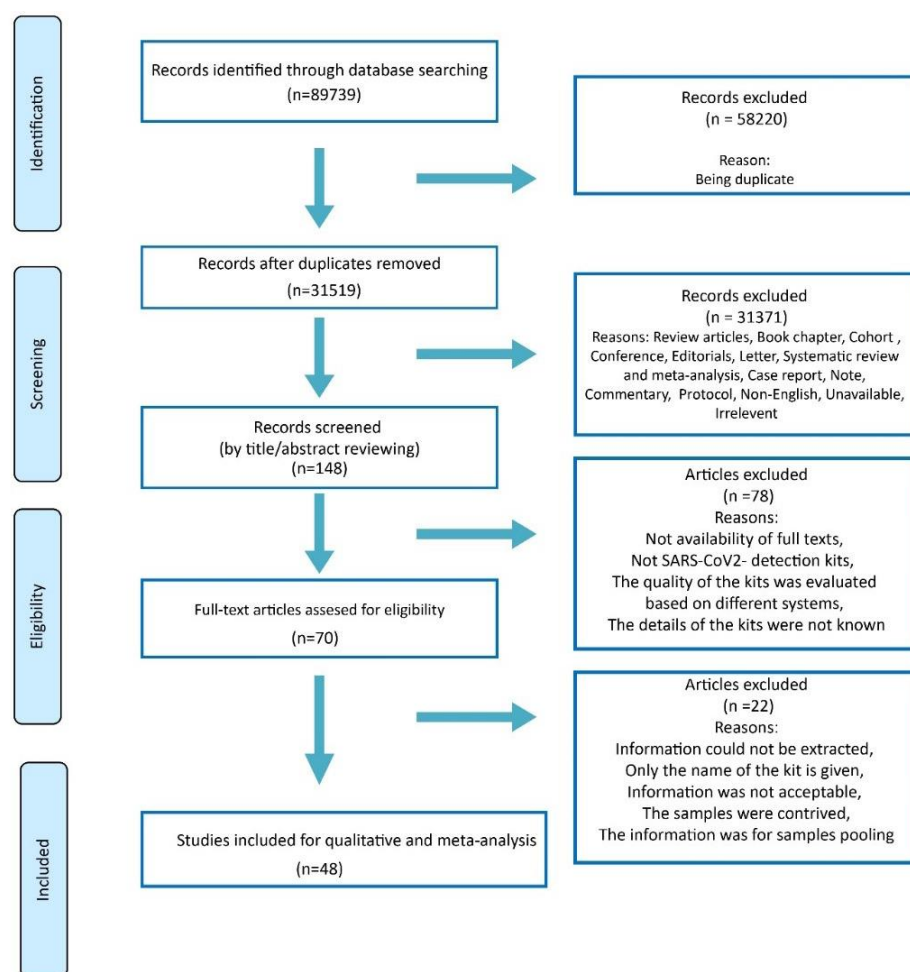


Fig. 1. PRISMA flow diagram of study selection

(ABM), FDA-CDC] (39), Lu et al.-2 [Liferiver] (40), Alaifan et al. [SARS-CoV-2 kit (Un-Named)] (7), Hur et al. [Allplex, PowerChek 2019-nCoV Real-time PCR (PowerChek), Real-Q 2019-nCoV Detection (Real-Q), Biosenser] (41), Tsang et al. [Cepheid] (42), Moore et al. [FDA-CDC, Abbott, ID NOW™ COVID-19 assay (IDNOW)] (43), Gupta et al. [Light-Mix] (44), He et al. [Daan] (45), Szymczak et al. [Cepheid] (46), Goldfarb et al. [Cepheid] (47), Fan et al. [BGI] (48), Nawattanapaiboon et al. [Sansure] (49), Lim et al. [RealStar, Sansure] (50), Roumani et al. [Allplex] (51), Schermer et al. [RealStar] (45), Huang et al. [ZJ Bio-Tech] (52).

General data. The kits were made in the USA (32 cases), China (27 cases), South Korea (23 cases), Germany (8 cases), Japan (6 cases), UK (3 cases), Spain (2 cases), Canada (2 cases), Singapore (2 cases), Turkey (2 cases), and the Netherlands (1 case) (Table 1).

The FDA –CDC, Sansure, and Allplex kits were assessed in 10, 9 and 7 reports, respectively.

The majority of the kits were based on RT-PCR (51 cases), while a few of other methods also existed (2 cases of RT-LAMP and one case of ddPCR, LOAA dPCR, and NGS). Also, the gene targets of the kits were N (62 cases), E (50 cases), RdRp (41 cases), ORF1ab (30 cases), S (12 cases), and ORF3a (1 case) (Table 1). The Ct values considered positive were different based on the kits used, but most of them applied ≤ 40 as positive Ct value (Table 1).

Sensitivity, specificity, PPV, and NPV of the kits.

Fifty-nine reports of kit sensitivity were included for a random-effects model meta-analysis. The sensitivities of the kits were presented as event rates and CIs. The overall sensitivity of the kits was 90.4% (CI 95%: 87.8-92.4) (Fig. 2). The lowest sensitivity was reported for Daan Kit (mean 38.2%), while the

highest sensitivity (about 100%) was seen for many kits. A significant heterogeneity between-studies were observed (Q-value of 116.03 and I-squared of 91.74) (Fig. 2).

Forty-six reports were included for the assessment of the specificity indexes. The specificity of the kits ranged from 87.9% to 99.8% and the pooled specificity was 98.3% (CI 95%: 97.7-98.8) (Fig. 3). There was significant heterogeneity between the studies regarding specificity (Q-value: 49.09, I-squared: 53.97) (Fig. 3).

Only 19 appropriate reports existed for PPV and NPV of the kits. Both PPV and NPV of the kits ranged from 87.9% to 99.8% for PPV and 82.9% to 99.8% for NPV. Also, significant heterogeneity was observed between studies reporting PPV and NPV with Q-value of 47.8 (for PPV) and 77.25 (for NPV) and I-squared of 65.19 (for PPV) and 78.29 (for NPV) (Figs. 4 and 5).

Bivariate model analysis. A random-effects bivariate model analysis was applied for data analysis. The overall sensitivity and specificity were 0.99 (CI 95%: 0.95-1.00) and 0.99 (CI 95%: 0.98-1.0), respectively (Fig. 6A). The heterogeneity between the sensitivities and the specificities were 14.23%, 4.16%, respectively with the I-squared of 7.4%. The results of overall summary point, the confidence/prediction regions, and the area under the curve (AUC) are also shown in the SROC plot. The AUC was 1.00 (CI 95%: 0.99-1.0) (Fig. 6B).

Bivariate model analysis of the commercial kits for the detection of SARS-CoV-2. A) A double forest plot of sensitivity and specificity of the kits. B) SROC curve of sensitivity and specificity of the kits (Fig. 6).

Cross reactivity. Only in 13 studies the kits were evaluated for detecting other pathogens rather than SARS-CoV-2.

There was no reported cross reactivity with other members of SARS-CoV-2 family and non- SARS-CoV-2 viruses in any paper (Table 1).

Concordance of kits. Concordance between samples or methods was only reported for few kits so meta-analysis was not applicable and only the average concordance is reported. The overall kit concordance between samples and methods was 95% and 92%, respectively (Table 1). The lowest concordance between samples was 89.2% and the lowest concordance was 72% (Table 1).

Table 1. The concordance of each kit

Kit Abbreviation	Beijing	BioGerm	Cepheid	Cobas	Daan	Genekey	GenMark	Lifetiver	Panther	Sansure	Shinadzu	Simplexa	Wadsworth	Yaneng	ZJ Bio-Tech	Average
																(Total)
Concordance between samples-Average (%)	89.2	97	100	100	100	100	96	90	96	93.25	92.13	100	98	90	90.8	95
Concordance between methods-Average (%)	87.2	96.44	97	100	93.6	91.5	95.7	92.9	97.4	85.1	90.2	81.9	95.7	97.6	92	92
																(Total)

Sensitivity of kits

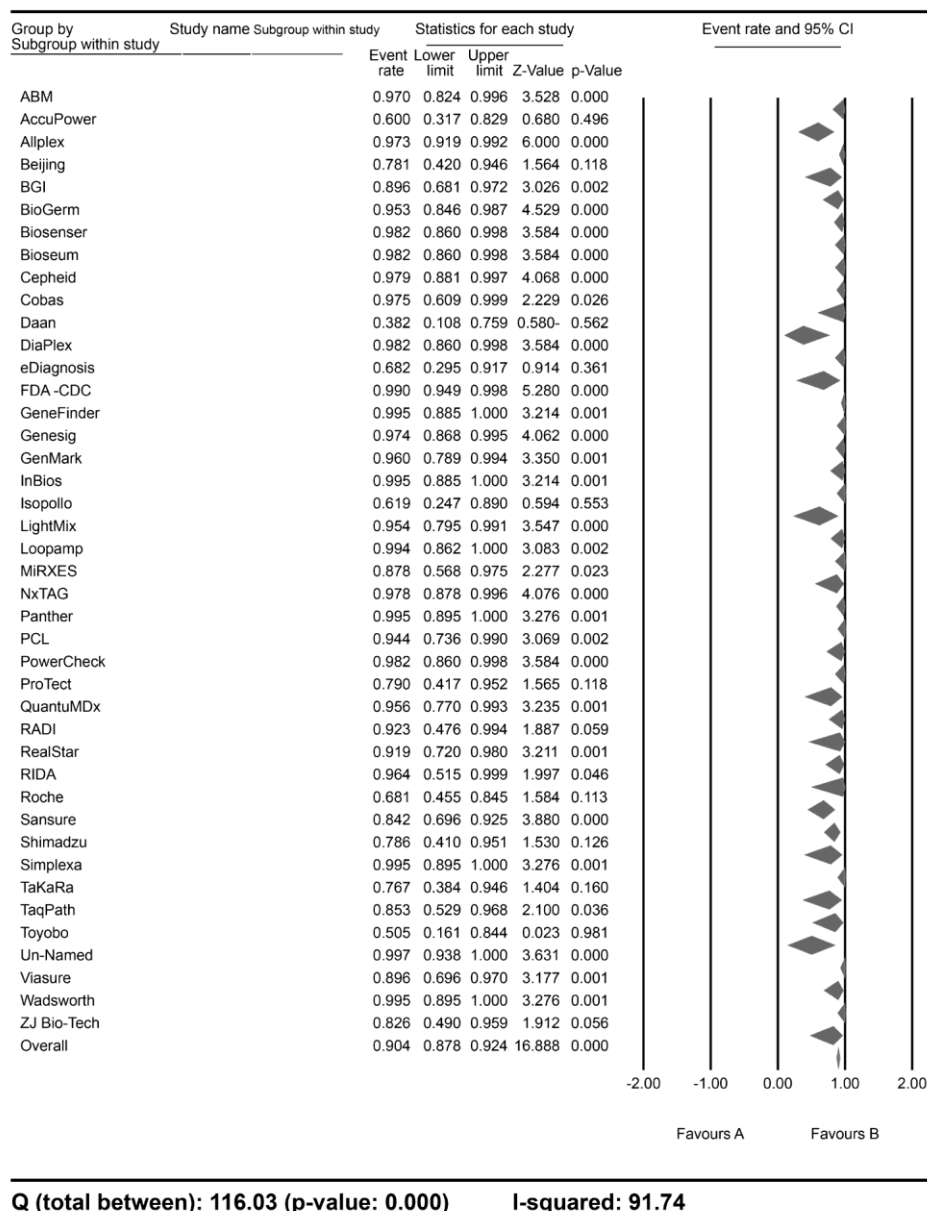


Fig. 2. Sensitivity of the kits

DISCUSSION

Development of simple and rapid SARS-CoV-2 diagnostic method will indirectly reduce the global incidence of COVID19 (43). The high rate of virus transmission necessitates the development of several protocols to control the infection. Many attempts have been made to detect SARS-CoV-2 early by amplifying and identifying viral gene sequences (53). After the supply of the first batch of SARS-CoV-2

diagnostic kits in January 2020, new diagnostic kits have been produced and introduced in the market (54). However, sensitivity, specificity, PPV, NPV and other diagnostic indices have not been reviewed systematically or meta-analyzed. The kits were produced mostly by the USA (33 cases), China (27 cases), and South Korea (23 cases).

The sensitivity and specificity information of 42 out of 55 studied kits was available. Out of 42 kits, 28 diagnostic kits had sensitivity higher than 90%.

Specificity of kits

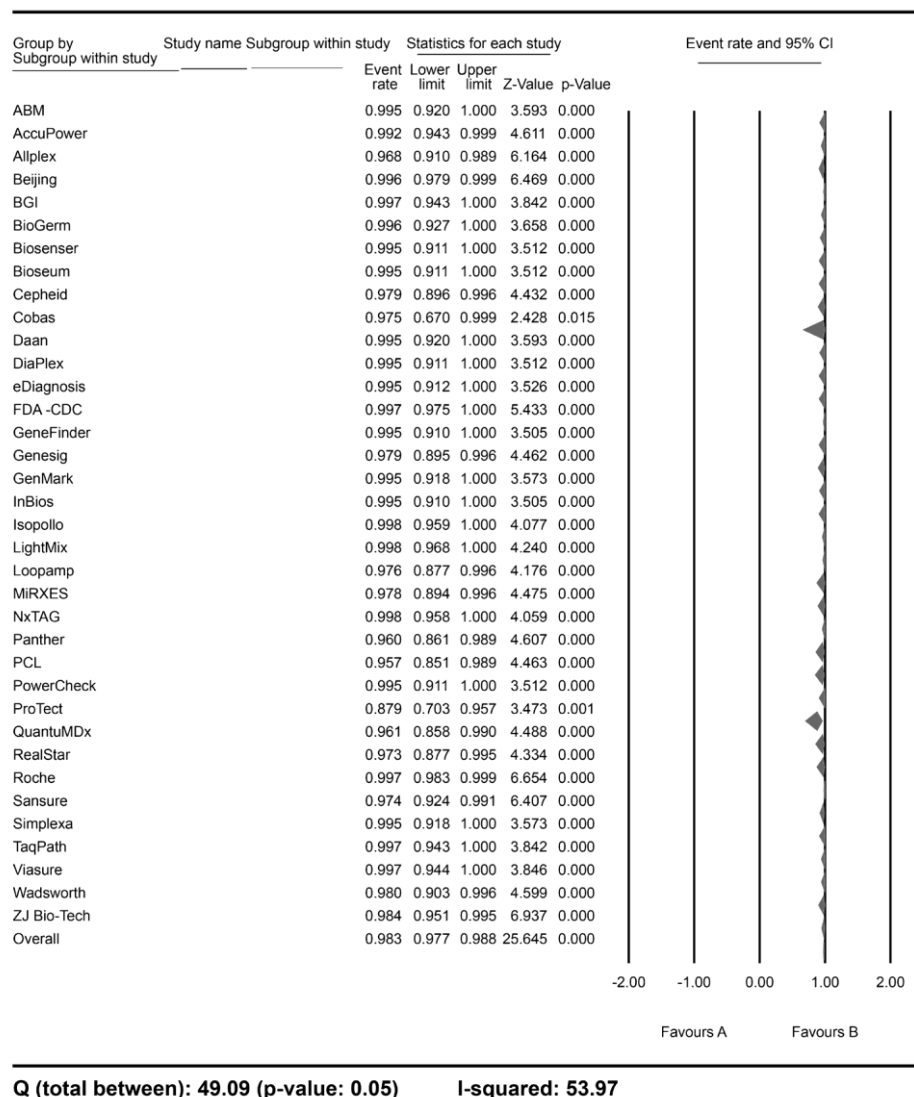


Fig. 3. Specificity of the kits

AccuPower SARS-CoV-2, Toyobo, and Isopollo kits had low sensitivity and poor performance compared to the CDC EUA 2019-nCoV kit. The Isopollo kit was unlicensed and should not be used in clinical setting. The FDA-CDC kit had higher sensitivity and other diagnostic indices comparing to DiaPlex, Biosensor, PowerCheck, BioSewoom, Cepheid, and NxTAG kits, but lower sensitivity than the GeneFinder, InBios, and Simplexa kits. The diagnostic indices of the FDA-CDC kit were gathered from ten different studies but many of them lacked data on the diagnostic indicators such as PPV and NPV and LOD. Among commercial SARS-CoV-2 diagnostic kits, GeneFinder, InBios, NxTAG, Simplexa and Wadsworth

kits had higher sensitivity, specificity and diagnostic performances.

Among the analyzed kits only Pro-Tect kit showed specificity lower than 90%. Some of the diagnostic kits were able to target multiple genes, but they had low diagnostic performance.

Among the aforementioned commercial kits, the GeneFinder, InBios and Simplexa diagnostic kits had higher DOR (39601) and FDA-CDC (29879) and NxTAG (22182) kits had an acceptable DOR. GeneFinder, InBios and Simplexa diagnostic kits had higher PLR, NLR, accuracy, Youden's index and PPV, but it should be noted that the results of the GeneFinder kit related to two studies and InBios and Simplexa

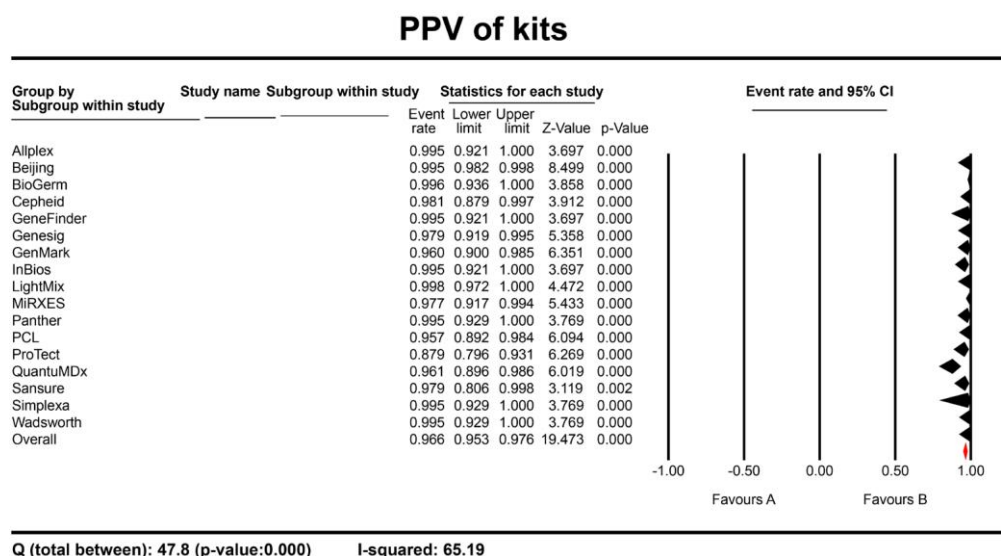


Fig. 4. PPV of the kits

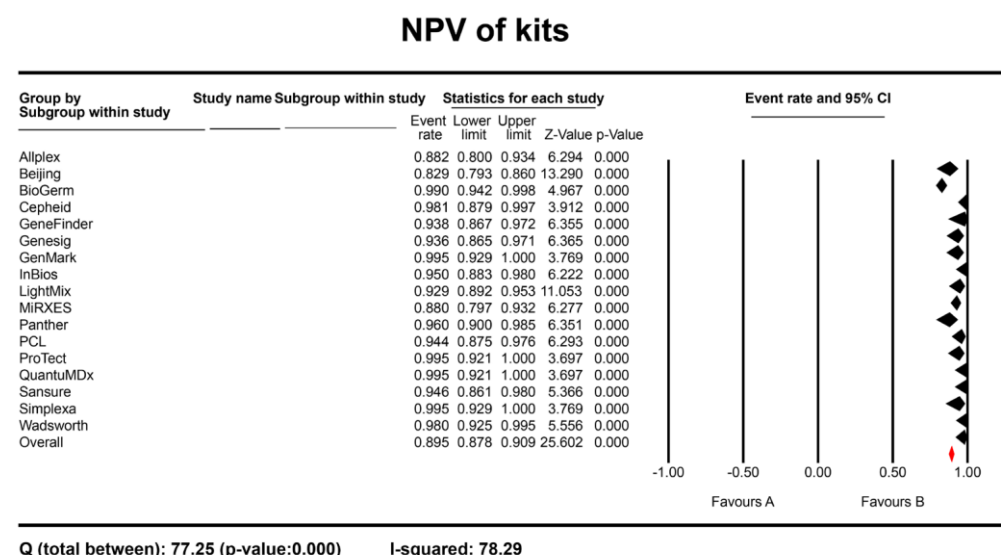


Fig. 5. NPV of the kits

data were extracted from one study. The Wadsworth, Panther, and Loopamp kits had almost the same sensitivity, but the results indicated that the Wadsworth kit performed better in terms of specificity and other diagnostic indicators than the others. DiaPlex, Biosensor, PowerCheck and BioSewoom kits had exactly the same diagnostic criteria. While the Biosensor and PowerCheck kits were the results of the evaluation of two studies and the DiaPlex and BioSewoom were the results of the evaluation of one study.

The N and ORF3a gene were the most and the least

gene targets, respectively. Because of SARS-CoV-2 genes diversity, a kit targeting more genes is more accurate, especially in detection of new variants. According to the WHO recommendation, accurate diagnosis is possible by targeting at least two viral genes (N and RdRp or E and RdRp). Therefore, the use of single-target kits such as Toyobo and Isopollo are not recommended. It is found that 11 kits had 3 gene targets, 25 kits had 2 gene targets, and 10 kits had 1 gene target. Of the 11 kits mentioned, 6 kits had sensitivity higher than 90% and only GeneFinder

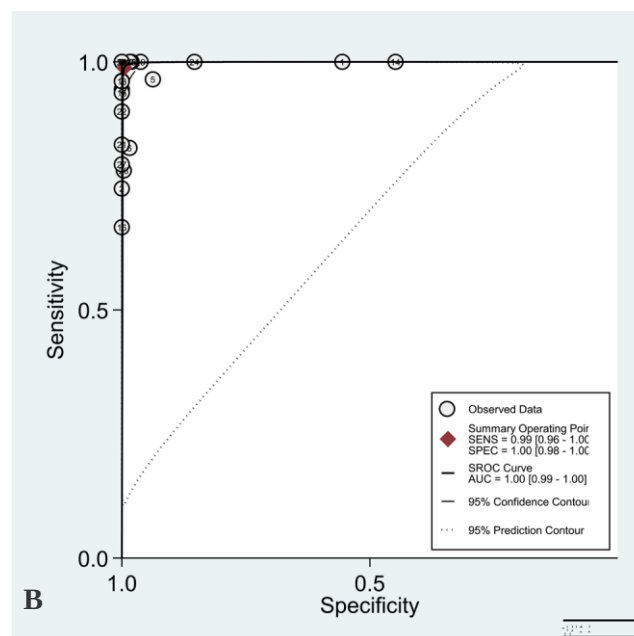
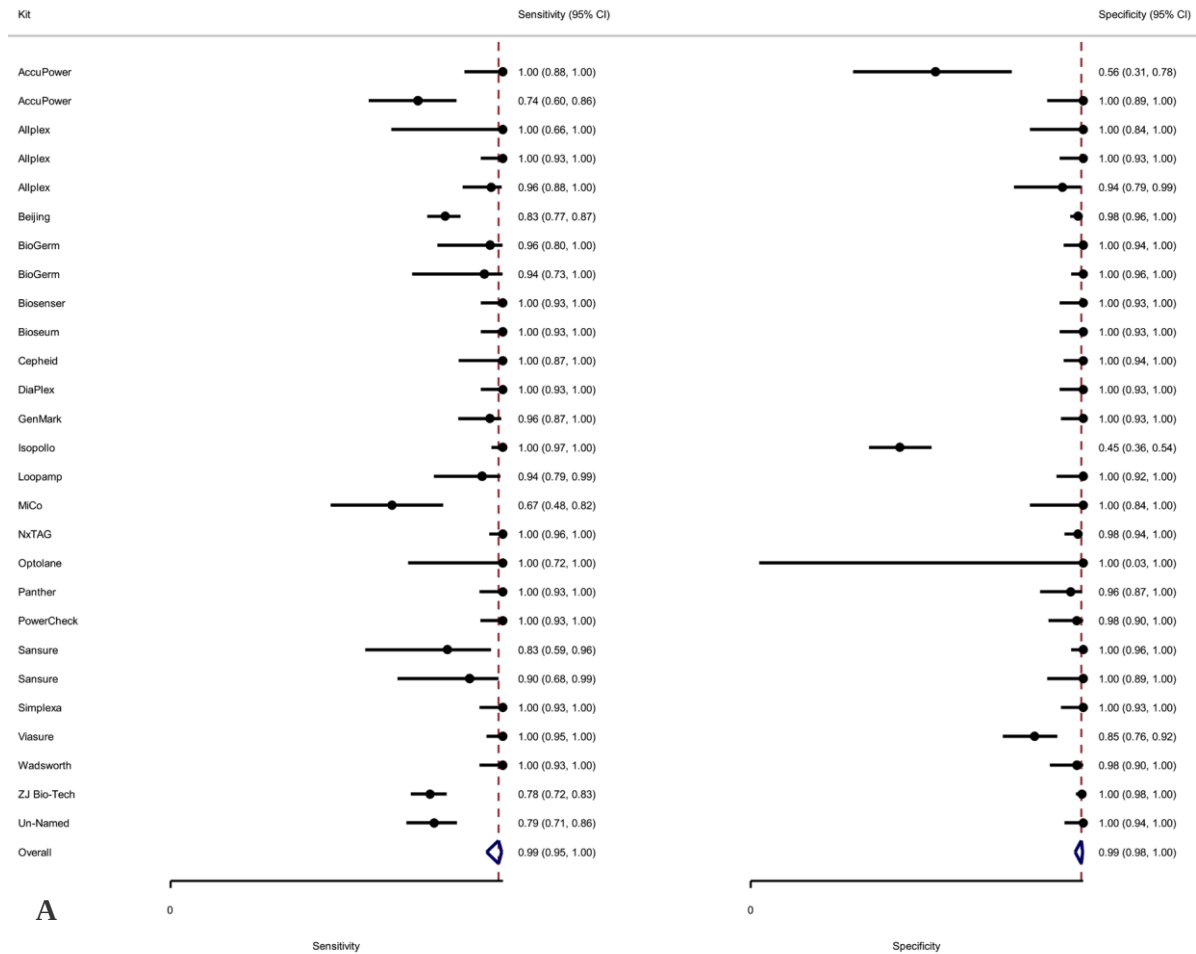


Fig. 6. Bivariate model analysis of the commercial kits

and InBios kits had high sensitivity, specificity, DOR and other diagnostic indicators. However, the Simplexa kit is one of the kits with two gene targets.

The pooled sensitivity of kits was higher than the sensitivity reported in the non-kit molecular technique study (76%) (55). The sensitivity of the kit was comparable to other methods mentioned in another meta-analysis article. In this study, pooled sensitivity of multiple techniques were reported including: RT-PCR technique (94.5%), RT-LAMP (91.9%), CRISPR (94.4%), IgG-detecting ELISA (88.3%), IgM-detecting ELISA (73.1%), IgA-detecting ELISA (83.7%), Antiviral Neutralization Bioassay (95.6%), Biosensors (96.4%), Chemiluminescence Immunoassay for IgG (79.8%), 0. Chemiluminescence Immunoassay for IgM (61.7%), Chemiluminescence Immunoassay for IgM-IgG (90.1%), Lateral Flow Immunoassay for IgG (87.3%), Lateral Flow Immunoassay for IgM (62.4%), Lateral Flow Immunoassay for IgM-IgG (83.7%), Lateral Flow Immunoassay for N Protein (74.7%), Chemiluminescent Microparticle Immunoassay (90.3), and Fluorescence Immunoassay (64.4%). Specificity of these test was close to 100% (56). Cost analysis was carried out on the existing data of 18 diagnostic kits. Among them, the TaqPath (\$5020 per 1000T/Kit) and the Cepheid kit (\$149 per 10T/Kit) were the cheapest and expensive kits, respectively. Despite the low price of the TaqPath kit, it has a low sensitivity and DOR. On the other hand, although the 5 kits have a lower price than the GeneFinder kit, due to better accuracy of the GeneFinder, it is still the recommended one.

Despite the significant heterogeneity between studies, the specificity of the kits was mostly high, ranging from 87.9% to 99.8%. The differences in sensitivity and specificity may be attributed to differences in the extraction kit and the target gene(s) used. Also, the PPV and NPV of the kits were high and none of the kits had any cross-reaction with other respiratory pathogens. Most of analyzed kits have been used through RT-PCR as standard diagnostic methods to confirm SARS-CoV-2 infection, and only in two cases RT-LAMP was performed.

In summary, the results of the bivariate analysis show that the overall sensitivity and specificity are very high (close to 100%) and there is very little heterogeneity between the studies. In the present study, it was found that AUC was equal to 1, which indicates the high accuracy (result of high sensitivity and specificity) of the kits.

Limitations: An important limitation was the unavailability of sensitivity and specificity of some of the diagnostic kits. In addition, the unavailability of price and LOD of all kits was the other limitation for further analyses. A key limitation to our work was our focus on English-language publications, which could introduce a language bias and hinder the applicability of our findings. It will be important for future studies to consider literature published in other languages to allow for an even more complete picture of the area.

CONCLUSION

The results reveal superior performance of commercial SARS-CoV-2 detection kits, including GeneFinder, InBios, NxTAG, Simplexa, and Wadsworth. Although the GeneFinder kit appears to be a promising diagnostic test with respect to cost-effectiveness per reaction, it is worth to point out that this conclusion is derived from a few studies only. These results need to be verified and compared across different population with detailed data on further studies. The data show that among the commercial SARS-CoV-2 diagnostic kits, GeneFinder, InBios, NxTAG, Simplexa and Wadsworth, have better performance than others. But GeneFinder Kit is more suitable than all kits in terms of all diagnostic performance and cost effective in each reaction.

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