European Review for Medical and Pharmacological Sciences 2021; 25: 503-517

Point-of-care testing for the detection of SARS-CoV-2: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: To evaluate the diagnostic accuracy of the Food and Drug Administration Emergency Use Authorization (FDA-EUA) authorized point-of-care tests (POCTs) for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

MATERIALS AND METHODS: A systematic literature search was conducted using the PubMed, Embase, and Web of Science databases for articles published till August 10, 2020. We included studies providing information regarding diagnostic test accuracy of FDA-EUA POCTs for SARS-CoV-2 detection. The methodologic quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. The review protocol is registered in the International Prospective Register of Systematic Reviews (protocol number CRD42020202248).

RESULTS: We included 26 studies describing a total of 3242 samples. The summary sensitivity and specificity were 0.94 [95% confidence interval (CI): 0.88-0.97] and 1.00 (95% CI: 0.99-1.00), respectively. The area under the summary receiver operating characteristic curve was 1.00 (95% CI: 0.99-1.00). A pooled analysis based on the index test revealed a summary sensitivity and specificity of Cepheid Xpert Xpress SARS-CoV-2 [0.99 (95% CI: 0.97-1.00) and 0.99 (95% CI: 0.94-1.00, respectively)] and ID NOW COVID-19 [0.78 (95% CI: 0.74-0.82) and 1.00 (95% CI: 0.98-1.00), respectively].

CONCLUSIONS: FDA-EUA POCTs, especially molecular assays, have high sensitivity, specificity, and overall diagnostic accuracy for detecting SARS-CoV-2. If approved, FDA-EUA POCTs can provide a rapid and practical way to identify infected individuals early on and help to limit the strain on the healthcare system. However, more high-quality clinical data are required to support our results.

Key Words:
COVID-19, SARS-CoV-2, Diagnosis, Point-of-care test, Rapid test.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was declared a public health emergency of international concern on January 30, 2020[1], and declared a pandemic on March 11, 2020, by the World Health Organization (WHO)[2]. Currently, the gold standard for identification of SARS-CoV-2 is the Reverse Transcription-Polymerase Chain Reaction (RT-PCR) assay[3]; however, RT-PCR requires trained laboratory staff and expensive equipment and has a long turnaround time[4].

Given the high global burden of COVID-19, the need to develop point-of-care tests (POCTs) has been increasing. POCTs are rapid diagnostic tests that can be performed at the site of sample collection, such as the bedside, urgent care centers, and emergency departments, without a time-consuming laboratory process[5-8]. The rapidity and convenience of POCTs not only can help fast epidemiological tracing with quarantine of individuals infected with SARS-CoV-2 but also reduce the financial cost and strain on the healthcare system during the pandemic[9-11]. The U.S. Food and Drug Administration (FDA) issued Emergency Use Authorizations (EUAs) to several manufacturers of POCTs for SARS-CoV-2 diagnosis[12]. Currently, six Clinical Laboratory Improvement Amendment of 1988 (CLIA)-waived POCTs are EUA approved for SARS-CoV-2 testing. The species and characteristics of FDA-EUA POCTs are shown in Table I. In the present study, we aimed to evaluate the overall diagnostic accuracy of currently available FDA-EUA POCTs for the detection of SARS-CoV-2.

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Materials and Methods

The methods and results of this review are presented according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[13]. The review protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) (protocol number CRD42020202248).

Search Strategy

We searched PubMed, EMBASE, and Web of Science databases using the following terms: ("COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "coronavirus disease-19") AND ("emergency use authorization" OR "FDA-EUA") AND ("diagnosis" OR "detection" OR "point-of-care testing" OR "rapid test"). We limited the articles to those that were published in English, without any date restrictions. The most recent search was performed on August 10, 2020.

Eligibility Criteria

Studies were considered eligible if they assessed the accuracy of FDA-POCTs for the diagnosis of SARS-CoV-2 in human respiratory specimens. Studies using RT-PCR or real-time RT-PCR as reference standards were eligible for inclusion in the current study. Reviews, editorials, expert opinions, and animal experiments were excluded. Reports that presented duplicate data and studies with insufficient data to construct 2 × 2 contingency tables were also excluded.

Study Selection and Data Extraction

Three authors (SHY, SY, and HC) independently assessed the studies retrieved by the search, for eligibility. If there was disagreement between the reviewers' assessments, consensus was reached through discussion. Author names, publication year, country of origin, study period, age of study participants (children were defined as ≤ 18 years of age), type of specimen, type of index test, brand name of the index test, reference standard, number of samples tested, and the values of true positive, false positive, true negative, and false negative were extracted. If studies consisted of multiple groups, each group was considered as an individual study. If articles provided insufficient data to construct the 2 × 2 table, we attempted to contact the corresponding authors via email to obtain more information.

Table I. The six commercial SARS–CoV-2 diagnostic assays given an EUA from the FDA for use outside the clinical laboratory environment as of August 10, 2020.

Date EUA Issued	Test Name	Manufacturer	Test Type	Specific Test assay	Time to result	Target
03/20/2020	Xpert Xpress SARS-CoV-2	Cepheid	Molecular (NAAT)	Real-time RT-PCR	~45 min	Envelope (E) gene and nucleocapsid (N) gene (N2 region)
03/23/2020	Accula SARS-Cov-2	Mesa Biotech Inc.	Molecular (NAAT)	RT-PCR + lateral flow assay	~30 min	Nucleocapsid protein (N) gene
03/27/2020	ID NOW COVID-19	Abbott Diagnostics Scarborough, Inc.	Molecular (NAAT)	Isothermal nucleic acid amplification assay	~13 min	RdRP gene
05/08/2020	Sofia SARS Antigen FIA	Quidel Corporation	Antigen	Immunofluorescence-based lateral flow assay	~15 min	Nucleocapsid protein antigen
06/10/2020	Cue COVID-19	Cue Health Inc.	Molecular (NAAT)	Isothermal nucleic acid amplification assay	~25 min	Nucleocapsid protein (N) gene
07/02/2020	BD Veritor System for Rapid Detection of SARS-CoV-2	Becton, Dickinson and Company	Antigen	Chromatographic digital immunoassay	~15 min	Nucleocapsid protein antigen

EUA = emergency use authorization; FDA = the U.S. Food and Drug Administration; NAAT = nucleic acid amplification test; RT-PCR = reverse transcription polymerase chain reaction; SARS–CoV-2 = severe acute respiratory syndrome coronavirus 2.

Assessment of Methodologic Quality

The methodological quality of the selected studies was independently assessed using Quality Assessment of Diagnostic Accuracy studies-2 (QUADAS-2)[14] by two reviewers (SHY and SE). Any discrepancies were arbitrated by discussion.

Statistical Analysis

The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and corresponding 95% confidence intervals (CIs) of the corresponding index test were calculated using the accuracy data (true positive, false positive, false negative, and true negative) extracted from each eligible study. We used summary receiver operating characteristic (SROC) curves to calculate the area under the curve.

Statistical heterogeneity was evaluated from the forest plots of the studies' estimates, using the Cochran's Q test ($p<0.05$, significant) and I^2 statistic ($I^2>50\%$, significant) with 95% CIs. In the presence of significant heterogeneity, we conducted subgroup analysis and univariate meta-regression analysis to assess heterogeneity using the following as covariates with 95% CIs: index test (Xpert *vs*. ID NOW), sample size (<100 *vs*. ≥100), age of participants (adults *vs*. adults and children), type of specimen (nasal or nasopharyngeal specimen; nasopharyngeal swab [NPS]/nasal swab/nasal or nasopharyngeal samples *vs*. other specimens; oropharyngeal swab [OPS] or tracheal aspirate [TA]), country (USA *vs*. other country), and type of transport medium (viral transport medium [VTM] *vs*. others [universal transport medium (UTM), saline, either UTM or VTM]).

Publication bias was assessed using the Deeks' funnel plot, and $p<0.1$ indicated the presence of publication bias. All statistical analyses were performed using STATA software, Version 16.1 (StataCorp, College Station, TX, USA) with the MIDAS module and MedCalc Statistical Software version 19.5.3 (MedCalc Software, Ostend, Belgium). p-values<0.05 were considered statistically significant.

Results

Study Selection and Article Characteristics

The search led to 100 results; after removing the duplicates, the remaining 68 abstracts were screened; 46 articles were excluded, resulting in 22 articles included for the full-text review. Of these, six studies were excluded due to insufficient data, to construct a 2 × 2 contingency table. One study was excluded because it used stool specimens. Therefore, 26 articles comprising 3242 samples were finally included in the systematic review and meta-analysis[11,15-27] (Figure 1).

The main characteristics of the included articles are summarized in Table II. The number of patients in the studies ranged from 10 to 524. The studies were conducted between February and May 2020, and most studies were conducted in the USA[11,16,17,19-27]. All the FDA-EUA POCTs included in this review are molecular assays, and the test samples used were respiratory tract specimens. Thirteen studies (50%) used Xpert Xpress SARS-CoV-2 (Xpert; Cepheid, Sunnyvale, CA, USA)[15,18-20,23-25,27], 12 studies (46.2%) used ID NOW COVID-19 (ID NOW; Abbott Diagnostics, Inc., Scarborough, ME, USA)[11,16,21,22,24,26,27], and 1 study (3.8%) used the Accula SARS-CoV-2 POCT (Accula; Mesa Biotech Inc, 2020)[17] as the index assay. All studies used real-time RT-PCR as the reference standard. Most of the studies (n=18)[11,15,17,19,20,22,24-27] used NPS specimens. The age of the participants was not specified in about half of the studies (11/26, 42.3%)[11,16,19,21,23,25,26]; five studies (19.2%)[15,20] included adults only, and ten studies (38.5%)[17,18,20,22,24,27] included both adults and children.

Quality Assessment

Quality was assessed using QUADAS-2 (Figure 2). For the risk of bias, regarding the patient selection domain, 46.2% of the studies were scored as having "high" risk of bias because they did not report the methods used for the enrollment (whether consecutive or random), or the exclusion criteria. Regarding the index test domain, half of the studies (50.0%) were scored as "unclear" risk of bias because the authors did not clarify whether the index test results were identified without the knowledge of the results of the reference standard. However, if the index test was an RT-PCR, the studies were judged to be at low risk of bias (50.0%), because RT-PCR was regarded as an objective method. Regarding the reference standard domain, all the studies were considered to be at "low" risk of bias because they all used the real-time RT-PCR as the reference standard. Regarding the flow and timing domain, 15 studies (57.7%) had an unclear risk of bias because the interval between the index test and the reference

Table II. Characteristics of studies included in the meta-analysis.

Year, Author	Country	Study periods	Age	Specimen	Media	Index test assay	Reference standard	TP	FP	FN	TN
2020 Cradic et al[11]	USA	NA	NA	NPS	UVT	ID NOW COVID-19	Real-time RT-PCR	12	0	1	169
2020 Cradic et al[11]	USA	NA	NA	OPS	Dry OPS	ID NOW COVID-19	Real-time RT-PCR	12	0	1	169
2020 Cradic et al[11]	USA	NA	NA	NS	Dry NS	ID NOW COVID-19	Real-time RT-PCR	12	0	1	169
2020 Goldenberger et al[15]	Switzerland	Mar 2020*	adults	NPS	UTM and ESwab™	Xpert Xpress SARS-CoV-2	Real-time RT-PCR	10	0	0	9
2020 Harrington et al[16]	USA	NA	NA	NS	VTM	ID NOW COVID-19	Real-time RT-PCR	139	2	47	336
2020 Hogan et al[17]	USA	Apr 7–Apr 13, 2020	adults and children	NPS	VTM or saline	Accula SARS-CoV-2 POCT	Real-time RT-PCR	34	0	16	50
2020 Hou et al[18]	China	Feb–Apr, 2020	adults and children¶	OPS	NA	Xpert Xpress SARS-CoV-2	Real-time RT-PCR	147	5	6	127
2020 Lieberman et al[19]	USA	NA	NA**	NPS	VTM	Xpert Xpress SARS-CoV-2	Real-time RT-PCR	13	0	0	13
2020 Loeffelholz et al[20]	USA	Mar 1–Apr 2, 2020	adults	NPS	VTM	Xpert Xpress SARS-CoV-2††	Real-time RT-PCR	12	0	1	75
2020 Loeffelholz et al[20]	FR and USA	Mar 1–Apr 2, 2020	adults	NPS	VTM	Xpert Xpress SARS-CoV-2††	Real-time RT-PCR	60	0	0	69
2020 Loeffelholz et al[20]	USA	Mar 1–Apr 2, 2020	adults and children	NPS, NPS/OPS, OPS, TA	VTM or Saline†	Xpert Xpress SARS-CoV-2††	Real-time RT-PCR	74	2	0	23
2020 Loeffelholz et al[20]	UK	Mar 1–Apr 2, 2020	adults	NPS, NPS/OPS	VTM	Xpert Xpress SARS-CoV-2††	Real-time RT-PCR	30	9	0	26
2020 Loeffelholz et al[20]	IT	Mar 1–Apr 2, 2020	adults and children	NPS	VTM	Xpert Xpress SARS-CoV-2††	Real-time RT-PCR	35	0	0	44
2020 Loeffelholz et al[20]	USA	Mar 1–Apr 2, 2020	adults	NPS	VTM	Xpert Xpress SARS-CoV-2††	Real-time RT-PCR	8	0	0	10
2020 Mitchell et al[21]	USA	NA	NA	Nasopha-ryngeal specimen	VTM	ID NOW COVID-19	Real-time RT-PCR	33	0	13	15
2020 Moore et al[22]	USA	Mar 27–Apr 9, 2020	adults and children	NPS	VTM	ID NOW COVID-19	Real-time RT-PCR	94‡	0	23	79
2020 Moore et al[22]	USA	Mar 27–Apr 9, 2020	adults and children	NPS	VTM	ID NOW COVID-19	Real-time RT-PCR	94‡	0	31	73

Table continued

Table II. ***(Continued)*****.** Characteristics of studies included in the meta-analysis.

Year, Author	Country	Study periods	Age	Specimen	Media	Index test assay	Reference standard	TP	FP	FN	TN
2020 Moran et al[23]	USA	NA	NA	Nasal and nasopharyngeal specimen	NA	Xpert Xpress SARS-CoV-2	Real-time RT-PCR	42	1	0	60
2020 Smithgall et al[24]	USA	Apr 8–Apr 13, 2020	adults and children	NPS	VTM or UTM	ID NOW COVID-19	Real-time RT-PCR	65	0	23	25
2020 Smithgall et al[24]	USA	Apr 8–Apr 13, 2020	adults and children	NPS	VTM or UTM	Xpert Xpress SARS-CoV-2	Real-time RT-PCR	87	2	1	23
2020 Stevens et al[25]	USA	Mar 31–Apr 7, 2020	NA[§]	NPS	VTM	Xpert Xpress SARS-CoV-2	Real-time RT-PCR	53	0	1	50
2020 Thwe et al[26]	USA	Apr–May, 2020	NA	NPS	Dry NPS	ID NOW COVID-19	Real-time RT-PCR	6	0	4	119
2020 Thwe et al[26]	USA	Apr–May, 2020	NA	NPS	Dry NPS	ID NOW COVID-19	Real-time RT-PCR	1	0	1	8
2020 Thwe et al[26]	USA	Apr–May, 2020	NA	NPS	Dry NPS	ID NOW COVID-19	Real-time RT-PCR	1	0	1	20
2020 Zhen et al[27]	USA	Mar–Apr, 2020	adults and children	NPS	UTM	Xpert Xpress SARS-CoV-2	Real-time RT-PCR	57	0	1	50
2020 Zhen et al[27]	USA	Mar–Apr, 2020	adults and children	NPS	UTM	ID NOW COVID-19	Real-time RT-PCR	50	0	7	50

USA = the United States of America; NA = not available; UVT = universal viral transport medium; RT-PCR = reverse transcription polymerase chain reaction; NPS = nasopharyngeal swab; OPS = oropharyngeal swab; NPS/OPS = combined NPS-OPS in the same transport vial; NS = nasal swab; VTM = viral transport medium; UTM = universal transport media; UK = the United Kingdom; FR = France; IT = Italy; TA = tracheal aspirates; *Collected within a week during the first wave of the 2020 pandemic in Basel, Switzerland ¶ 77.2% of the patients were ≤ 65 years old, and 22.8% of patients were> 65 years old. [**]Overwhelmingly adult. [††]Research use only (RUO)-labeled Xpert kits were used. The RUO version of Xpert allows users to see amplification curves and PCR cycle threshold values for all three targets; the envelope (E), nucleocapsid (N2), and RNA-dependent RNA polymerase (RdRp) genes. [†]Tracheal aspirates were diluted with saline. [‡]Invalid and inconclusive results were excluded. [§]Performed at the Stanford Healthcare Virology Laboratory that serves both adult and pediatric tertiary care hospitals.

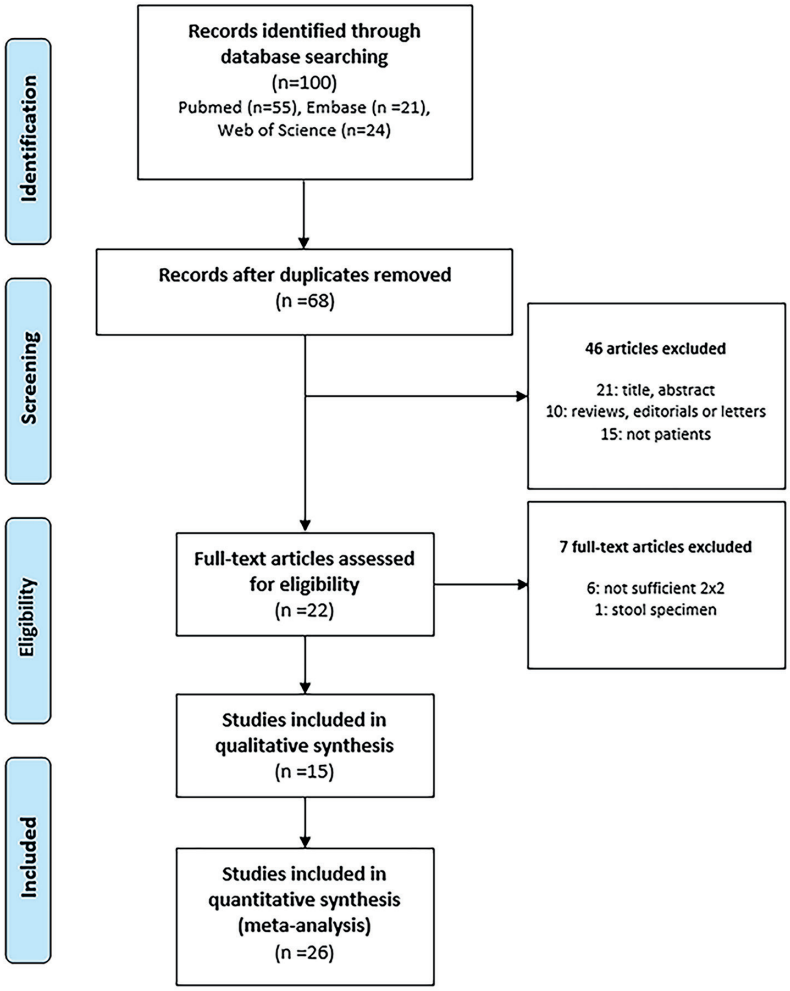

Figure 1. Flow diagram of the study selection.

test was not provided. Regarding applicability, we scored as low concern for all the studies in all the three domains.

Diagnostic Performance of Emergency Use Authorization Point-Of-Care Tests

The sensitivities and specificities of the individual studies ranged from 50% to 100% and 74% to 100%, respectively. As shown in Figure 3, the summary sensitivity and specificity were 0.94 (95% CI: 0.88-0.97) and 1.00 (95% CI: 0.99-1.00), respectively. The summary PLR and NLR were 483.6 (95% CI: 68.2-3429.7) and 0.06 (95% CI: 0.03-0.12), respectively. The DOR was 8490 (95% CI: 1243-57971). The area under the SROC curve was 1.00 (95% CI: 0.99-1.00) (Figure 4). The Higgins I^2 statistics demonstrated substantial heterogeneity in terms of both the sensitivity (I^2 = 94%) and specificity (I^2 = 95%). Publication bias was not detected according to Deeks' funnel plot (p=0.92) (Figure 5).

Heterogeneity Exploration

Potential sources of heterogeneity were investigated using meta-regression (Table III). Among the several covariates, index type, age, type of specimen, and transport medium were significant factors affecting heterogeneity in the joint model. When comparing the sensitivity and specificity estimates with the covariates, the pooled sensitivity was significantly higher in studies conducted on adults only than studies conducted on adults and children. The pooled specificity was significantly higher in studies conducted on nasal or nasopharyngeal specimen (p<0.01).

Subgroup Analysis

We performed subgroup analysis separately for each index test because the principle of each

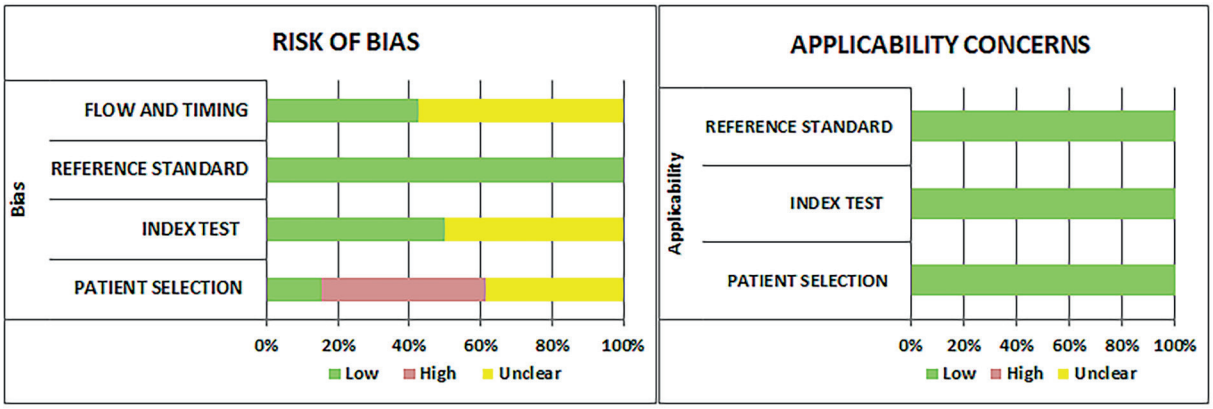

Figure 2. Quality assessment using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) of the included studies.

Table III. Stratified meta-regression analyses.

Parameter	Category	No. of Studies	Sensitivity		Specificity		LRT Chi-Square	*p* (Joint Model)
			pooled value [95% CI]	*p*	pooled value [95% CI]	*p*		
Index test	Xpert	13	0.98 [0.98 - 0.99]	0.61	0.99 [0.97 - 1.00]	0.88	49.64	<0.01
	ID NOW	12	0.78 [0.74 - 0.82]		1.00 [1.00 - 1.00]			
Age	Adults	5	1.00 [0.99 - 1.00]	<0.01	1.00 [0.98 - 1.00]	<0.01	71.97	<0.01
	Adults and children	10	0.93 [0.86 - 1.00]		1.00 [0.99 - 1.00]			
Specimen	Nasal or nasopharyngeal specimen	22	0.93 [0.87 - 0.98]	0.14	1.00 [1.00 - 1.00]	<0.01	7.59	<0.05
	Others¶	4	0.99 [0.96 - 1.00]		0.96 [0.89 - 1.00]			
Media	VTM	11	0.96 [0.91 - 1.00]	0.85	1.00 [0.99 - 1.00]	<0.01	43.78	<0.01
	Others	8	0.96 [0.90 - 1.00]		1.00 [0.99 - 1.00]			
Size (n)	≥100	16	0.92 [0.86 - 0.99]	0.12	1.00 [1.00 - 1.00]	<0.01	1.69	0.43
	<100	10	0.97 [0.93 - 1.00]		1.00 [0.99 - 1.00]			
Country	USA	22	0.92 [0.87 - 0.98]	0.13	1.00 [1.00 - 1.00]	<0.01	3.57	0.17
	Other countries	4	0.99 [0.97 - 1.00]		1.00 [0.98 - 1.00]			

CI = confidence interval; ID NOW = ID Now COVID-19; LRT = likelihood-ratio test; VTM = viral transport medium; Xpert = Xpert Xpress SARS-CoV-2; USA = the United States of America. ¶Oropharyngeal swab, tracheal aspirate, or mixed (e.g., nasopharyngeal and oropharyngeal) samples.

assay is different: Xpert uses RT-PCR, and ID NOW uses an isothermal nucleic acid amplification method.

Diagnostic Performance of Xpert Xpress SARS-CoV-2

The sensitivities and specificities of the individual studies ranged from 92% to 100% and 74% to 100%, respectively (Figure 6). The summary sensitivity was 0.99 (95% CI: 0.97-1.00) and the summary specificity was 0.99 (95% CI: 0.94-1.00) (Figure 6). The summary PLR and NLR were 100.1 (95% CI: 17.4-575.4) and 0.01 (95% CI: 0.00-0.03), respectively. The DOR was 8538 (95% CI: 1087- 67079). The area under the SROC curve was 1.00 (95% CI: 0.99-1.00) (Figure 7). Publi-

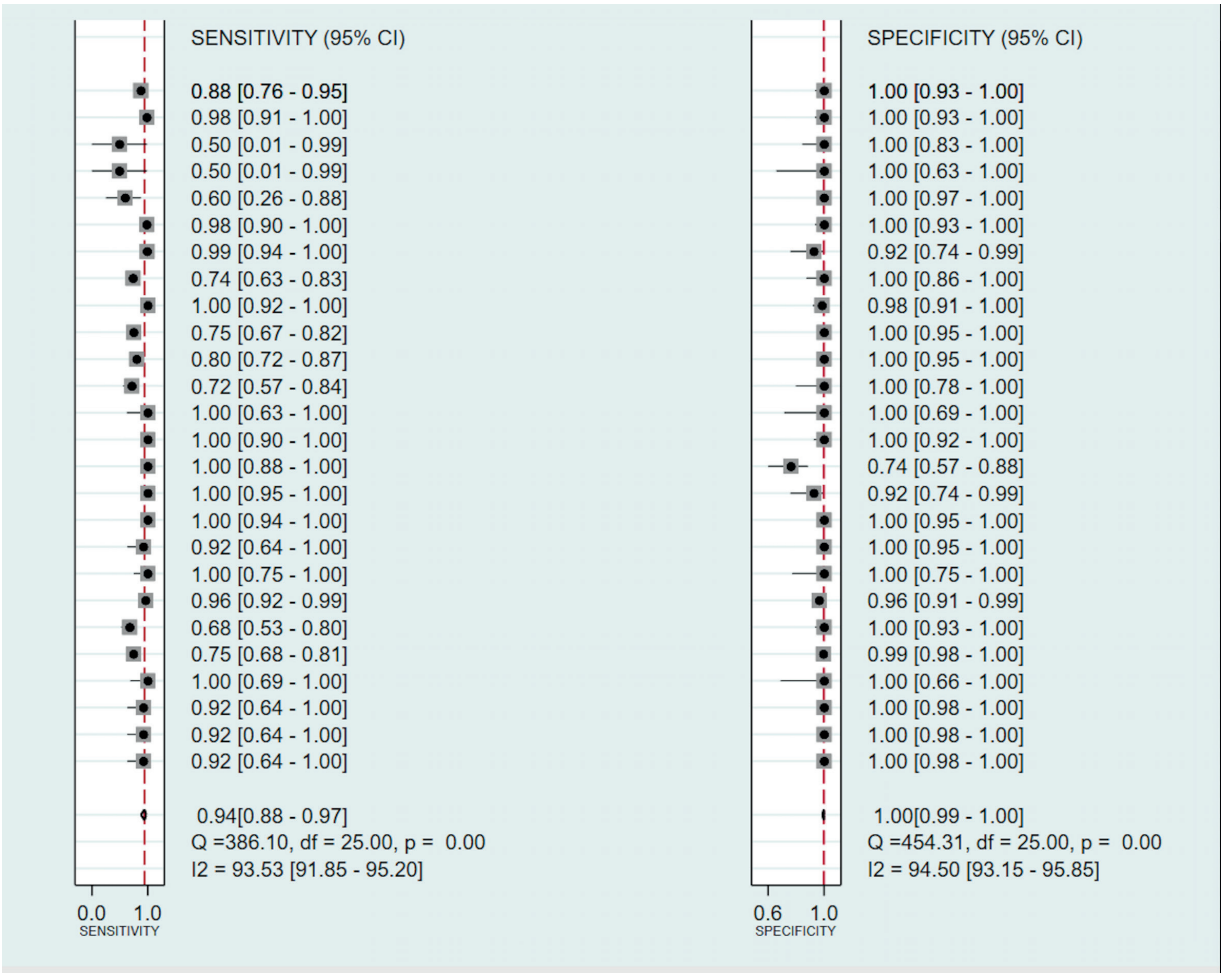

Figure 3. Coupled forest plots of summary sensitivity and specificity. Numbers are pooled estimates with 95% confidence intervals (CIs) in parentheses. Corresponding heterogeneity statistics are provided at the bottom-right corners. Horizontal lines indicate 95% CIs.

cation bias was not detected using Deeks' funnel plot (p=0.70) (Figure 8). Sensitivity and specificity showed I^2>50%, indicating considerable heterogeneity. The age of the study participants (p<0.05), type of specimen (p<0.05), and transport medium (p<0.01) were significant covariates affecting heterogeneity in the meta-regression analysis. When comparing sensitivity and specificity estimates with covariates, the pooled specificity was higher in studies with nasal or nasopharyngeal specimen (p<0.05), adults only (p<0.01), and using VTM (p<0.01) (Table IV).

Diagnostic Performance of ID NOW COVID-19

The sensitivities and specificities of the individual studies ranged from 50% to 92% and 99% to 100%, respectively (Figure 9). The summary sensitivity was 0.78 (95% CI: 0.74-0.82) and sum-

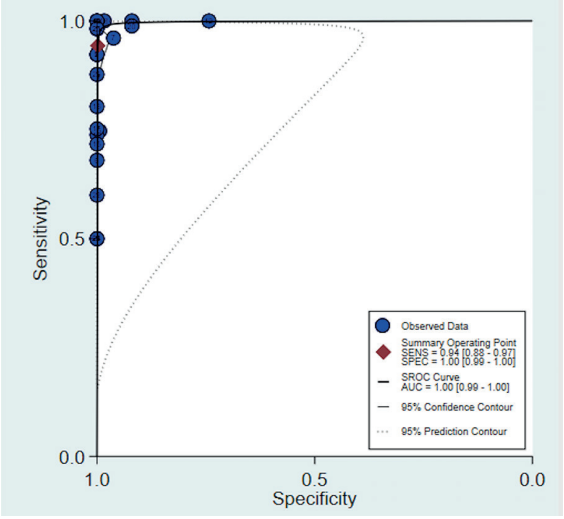

Figure 4. Summary receiver operating characteristic curve of diagnostic performance of point-of-care tests for the SARS-CoV-2 detection.

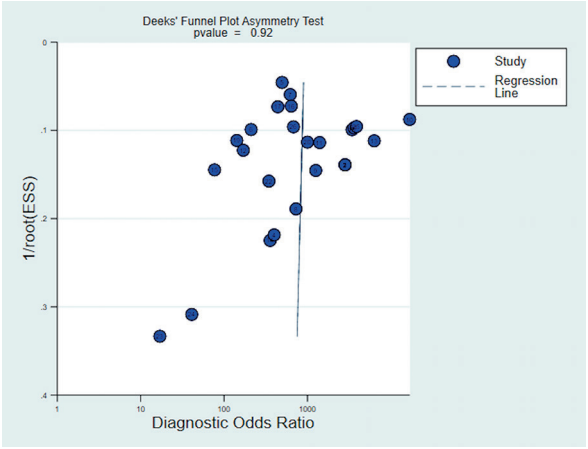

Figure 5. Deeks' funnel plot asymmetry test. Likelihood of publication bias was low with *p* value of 0.92 for slope coefficient. ESS = effective sample size.

mary specificity was 1.00 (95% CI: 0.98-1.00) (Figure 9). The summary PLR and NLR were 1005.4 (95% CI: 37.6-26906.6) and 0.22 (95% CI: 0.18-0.26), respectively. The DOR was 4551 (95% CI: 162-127532). The area under the SROC curve was 0.89 (95% CI: 0.86-0.91) (Figure 10). The Higgins I^2 statistics demonstrated that there was low heterogeneity in terms of either the sensitivity (I^2=27%) or specificity (I^2=0%); thus, we did not perform meta-regression analysis. Deeks' funnel plot demonstrated no significant publication bias (p=0.64) (Figure 11).

Diagnostic Performance of Accula SARS-CoV-2 Test

There was only one study that used the Accula SARS-CoV-2 test as the index test[17]; therefore, subgroup analysis could not be performed. The study showed that the sensitivity and specificity of Accula SARS-CoV-2 were 0.68 (95% CI: 0.53-0.81) and 1.00 (95% CI: 0.93-1.00), respectively. The NLR and the accuracy were 0.32 (95% CI: 0.21-0.48) and 0.84 (95% CI: 0.75-0.91), respectively.

Table IV. Stratified meta-regression analyses of studies using Xpert Xpress SARS-CoV-2 as an index test.

Parameter	Category	No. of Studies	Sensitivity		Specificity		LRT Chi-Square	*p (Joint Model)*
			pooled value [95% CI]	*p*	pooled value [95% CI]	*p*		
Age	Adults	5	0.99 [0.98-1.00]	0.08	0.99 [0.97-1.00]	<0.01	9.86	<0.05
	Adults and children	5	0.99 [0.97-1.00]		0.98 [0.94-1.00]			
Specimen	Nasal or nasopharyngeal specimen	10	0.99 [0.98 - 1.00]	0.70	0.99 [0.99 - 1.00]	<0.05	10.18	<0.05
	Others¶	3	0.99 [0.96 - 1.00]		0.90 [0.80 - 1.00]			
Media	VTM	7	0.99 [0.98 - 1.00]	0.51	1.00 [1.00 - 1.00]	<0.01	22.50	<0.01
	Others	4	0.99 [0.98 - 1.00]		0.99 [0.96 - 1.00]			
Size (n)	≥100	6	0.98 [0.96-1.00]	0.57	0.99 [0.98-1.00]	<0.05	1.49	0.47
	<100	7	1.00 [0.98-1.00]		0.99 [0.96-1.00]			
Country	USA	9	0.99 [0.98 - 1.00]	0.66	0.99 [0.96 - 1.00]	0.19	1.58	0.45
	Other countries	4	0.98 [0.96 - 1.00]		1.00 [0.99 - 1.00]			

CI = confidence interval; LRT = likelihood-ratio test; VTM = viral transport medium; USA = the United States of America. ¶ Oropharyngeal swab, tracheal aspirate, or mixed (e.g., nasopharyngeal and oropharyngeal) samples.

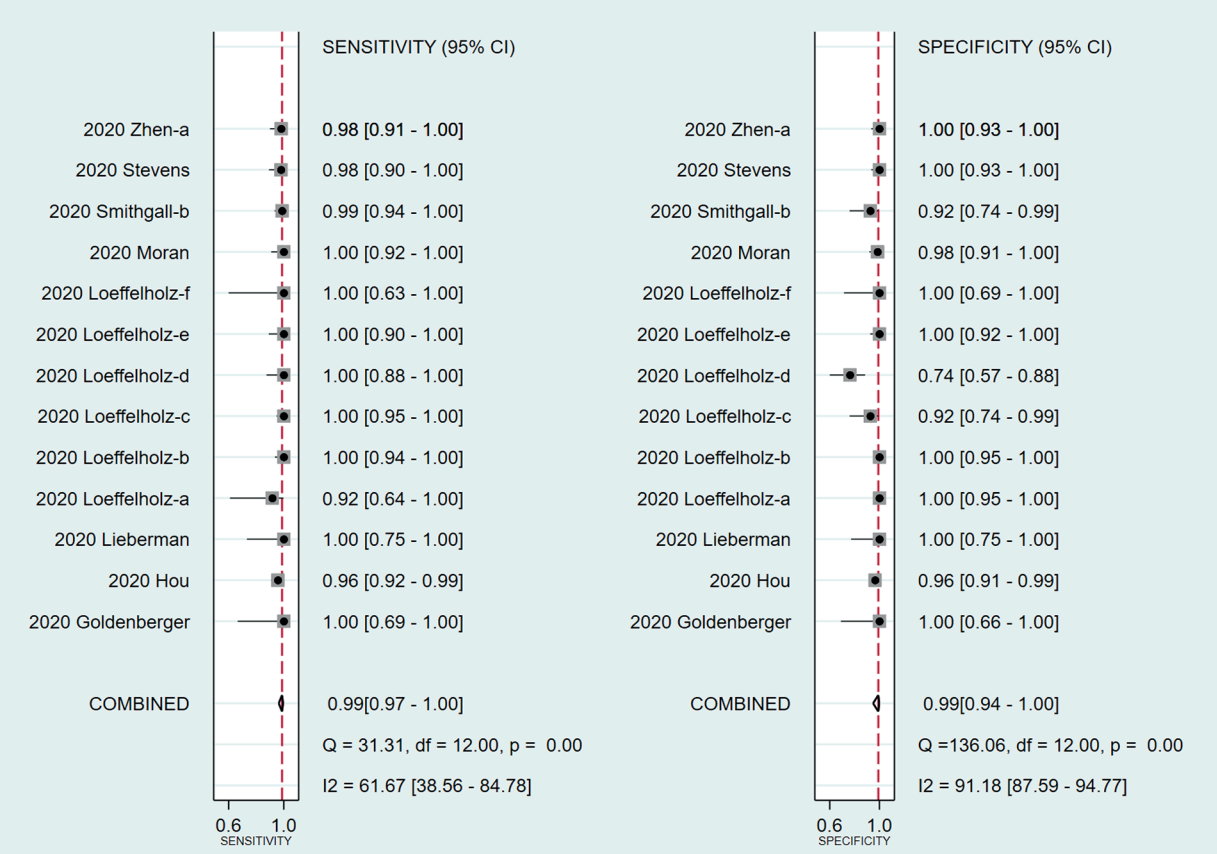

Figure 6. Coupled forest plots of the summary sensitivity and specificity of Xpert Xpress SARS-CoV-2. Numbers are pooled estimates with 95% confidence intervals (CIs) in parentheses. Corresponding heterogeneity statistics are provided at the bottom-right corners. Horizontal lines indicate 95% CIs.

Discussion

The timely and accurate confirmation of SARS-CoV-2 infection is critical to contain the spread of infection and reduce mortality[27]. Approximately, 80-85% of those affected are asymptomatic or have mild symptoms, but some people develop severe disease, requiring mechanical ventilation and intensive care, and sometimes the disease can be fatal. Those at risk of severe illness include older adults; people with pre-existing medical conditions such as cardiovascular disease, cancer, and immune deficiencies; and people living in a nursing home[6,28-31]. For this reason, having a fast, convenient, and highly accessible method of laboratory diagnosis is important for infection control and appropriate management of those at risk of severe illness[11,27].

In this meta-analysis, FDA-EUA POCTs for the detection of SARS-CoV-2, specifically molecular assays, showed high overall sensitivity (0.94), specificity (1.0), and accuracy (1.0) for diagnosing SAS-CoV-2 infection. The overall sensitivity

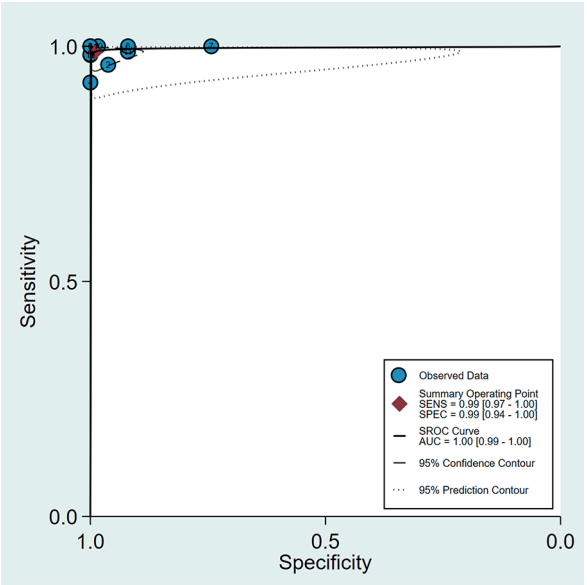

Figure 7. Summary receiver operating characteristic curve of the diagnostic performance of Xpert Xpress SARS-CoV-2 for SARS-CoV-2 detection.

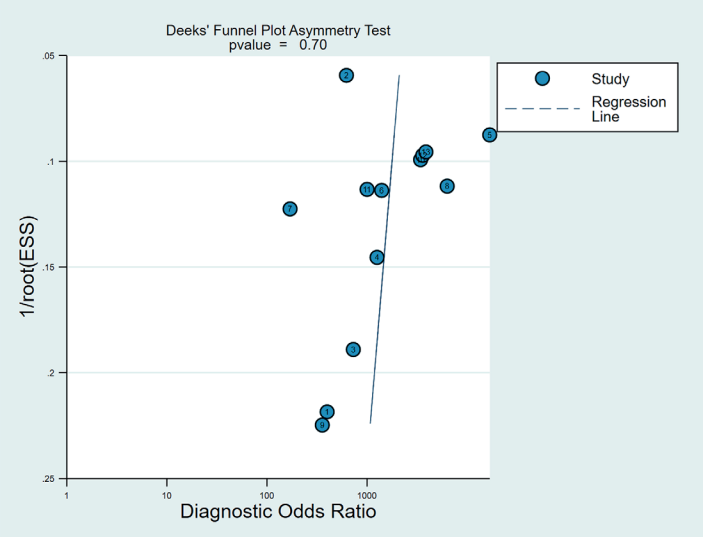

Figure 8. Deeks' funnel plot asymmetry test for studies of Xpert Xpress SARS-CoV-2. Likelihood of publication bias was low with a *p* value of 0.70 for the slope coefficient. ESS = effective sample size.

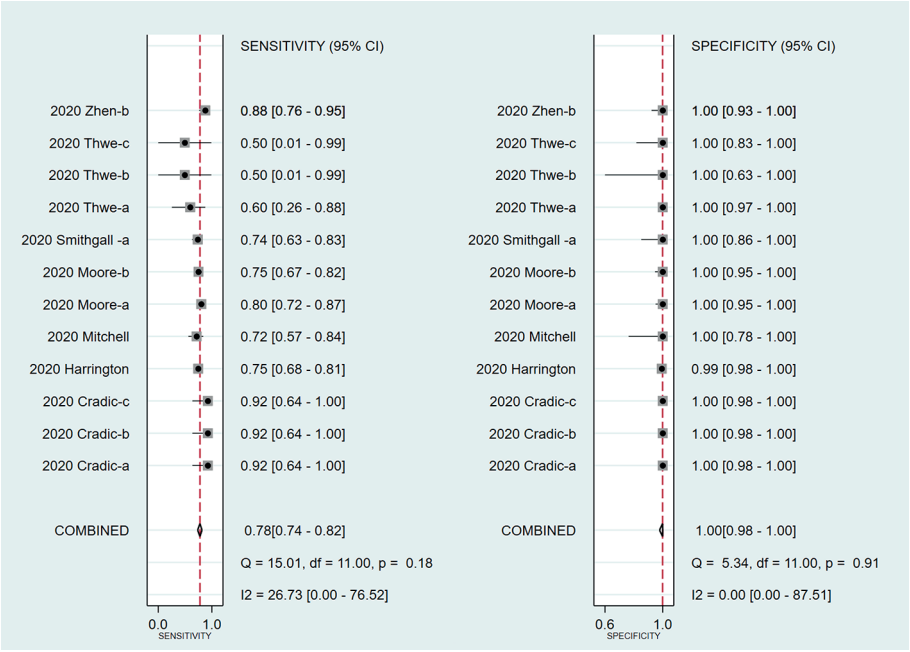

Figure 9. Coupled forest plots of the summary sensitivity and specificity of ID NOW COVID-19. Numbers are pooled estimates with 95% confidence intervals (CIs) in parentheses. Corresponding heterogeneity statistics are provided at the bottom-right corners. Horizontal lines indicate 95% CIs.

varied according to the index test: Xpert showed high sensitivity (0.99) and specificity (0.99) with a very high diagnostic accuracy (1.0). Xpert test uses RT-PCR and detects the pan-sarbecovirus E gene and the N2 region of the N gene of SARS-CoV-2 using an NPS, nasal wash, or nasal aspirate specimen; it takes less than 45 minutes to obtain a result[32]. ID NOW test uses isothermal nucleic acid amplification of the RNA-dependent RNA polymerase (RdRP) gene of SARS-CoV-2 using a nasal swab, NPS, or throat swab specimen; results are available in less than 13 minutes[33]. However, ID NOW has a lower sensitivity and diagnostic accuracy than the Xpert test (0.78 *vs.* 0.99 and 0.89 *vs.* 1.0, respectively). In addition, Xpert can be run on random-access platforms with a higher throughput, but the ID NOW platform can run only a single specimen at once[24]. However, both tests displayed a similar high specificity for the detection of SARS-CoV-2.

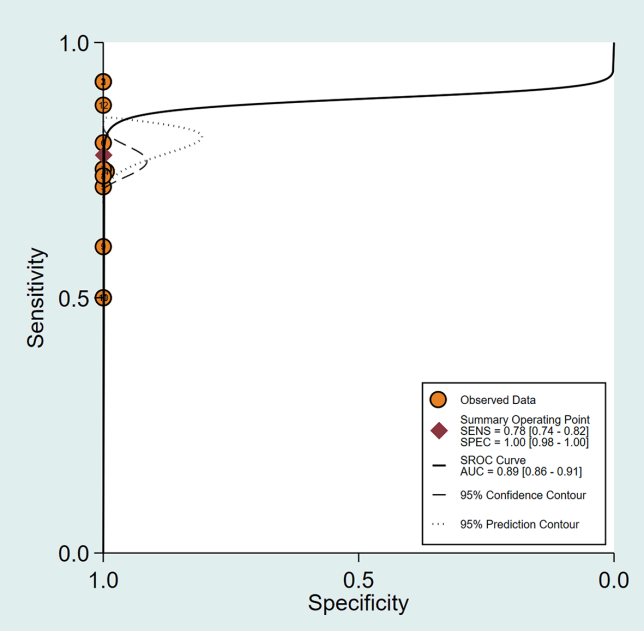

Figure 10. Summary receiver operating characteristic curve of the diagnostic performance of ID NOW COVID-19 for SARS-CoV-2 detection.

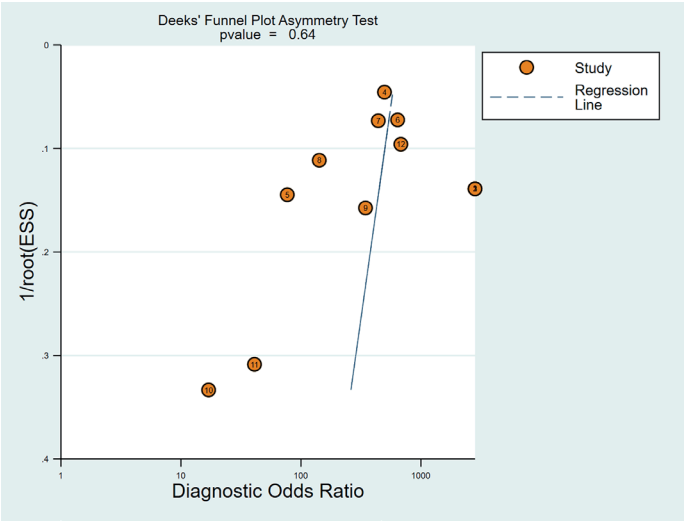

Figure 11. Deeks' funnel plot asymmetry test for studies of ID NOW COVID-19. Likelihood of publication bias was low with a *p* value of 0.64 for the slope coefficient. ESS = effective sample size.

There were two head-to-head studies[24,27] that compared Xpert and ID NOW test to a RT-PCR. Smithgall et al[24] reported that the overall positive percent agreement was 98.9% and 73.9%, and the negative percent agreement 92.0% and 100% compared to Roche cobas SARS-CoV-2 assay for Xpert and ID NOW, respectively. However, at low viral concentrations (cycle threshold values>30), the positive percent agreement was reduced to 34.3% for ID NOW, and it was slightly reduced to 97.1% for Xpert. The researchers suspected that this was because the specimens for ID NOW testing were collected in VTM or UTM, which may lead to low-level positivity and false-negative results[24]. The EUA for ID NOW has been updated to remove the use of nasal swab, NPS, or throat swabs eluted in VTM[33] as specimen types. Another study[27] reported a positive percent agreement of 98.3% and 87.7% for Xpert and ID NOW, respectively, and negative percent agreement was 100% for both Xpert and ID NOW, compared to the reference standard (Hologic Panther Fusion SARS-CoV-2 assay).

Regarding specimen types, meta-regression analysis showed significantly higher specificity for nasal or nasopharyngeal specimens than for

other types of respiratory specimens such as OPS, TA, and mixed samples (1.0 *vs*. 0.96; $p<0.01$). The overall sensitivity of nasal or nasopharyngeal specimens was lower than that of other types of respiratory specimens, but this result was not statistically significant (0.93 *vs*. 0.99; $p=0.14$). Previous studies[34-36] have reported that NPS or nasal swab showed higher sensitivity and viral loads than OPS. However, Wölfel et al[37] found no discernible differences in the viral loads or sensitivity between NPS and OPS in the clinical courses of nine hospitalized patients admitted for COVID-19. Furthermore, viral loads were higher in lower respiratory tract samples than in upper respiratory tract samples of COVID-19 patients[38,39], but this could not be evaluated in our review because a limited number of TA samples were tested. Our findings suggest that nasal or nasopharyngeal specimens are more suitable for point-of-care testing, but there are still limitations since comparisons according to the specimen types were not performed in most of the studies.

Our study also demonstrated that the sensitivity of FDA-EUA POCTs was higher in studies conducted on adults only than in studies conducted on both adults and children (1.00 *vs*. 0.93; $p<0.01$). This finding suggests that the sensitivity of POCTs might be lower in children. Jones et al[40] analyzed RT-PCR data from over 3,000 SARS-CoV-2-positive patients in Germany and found that the viral detection rate increased with age and reached a plateau in middle-aged adults. On the contrary, another study[41] found that among 145 people with mild to moderate illness who tested positive for SARS-CoV-2 within 1 week of symptom onset, children younger than 5 years of age had higher viral nucleic acid in their nasopharynx than older children and adults. Nevertheless, clinical studies focusing on the difference in sensitivity and specificity of POCTs in children compared with adults are still limited.

The sensitivity and specificity were similar between samples collected in VTM and other media, such as saline and UTM; however, the type of transport medium was a statistically significant source of the heterogeneity in our joint model. Garnett et al[42] recently compared the diagnostic performance of samples collected in Dulbecco's Modified Eagle's Medium (DMEM), phosphate-buffered saline (PBS), 0.9% normal saline, and 100% ethanol, with VTM as the transport medium, for the preservation and recovery of viral RNA over a 72-hour period. They concluded that all media, except the 0.9% saline, were similarly efficacious in terms of preserving SARS-CoV-2 RNA for extraction and detection[42].

POCTs for SARS-CoV-2 antibodies are available; however, their use for clinical purposes is questionable. A recently published meta-analysis regarding rapid serologic diagnostic tests for SARS-CoV-2 antibodies showed a pooled sensitivity of 0.65 (95% CI: 0.55-0.74) and specificity of 0.98 (95% CI: 0.96-0.99), which are lower than the results of the molecular assays for SARS-CoV-2 RNA detection in our review[43]. Another meta-analysis also demonstrated higher accuracy for SARS-CoV-2 detection using antigen tests and molecular assays than serologic assays: the pooled sensitivity and specificity of tests using the detection of SARS-CoV-2 IgM antibodies compared to antigen and molecular assays in NPS/OPS swabs were 0.82 (95% CI: 0.76-0.87) *vs*. 0.97 (95% CI: 0.85-0.99) and 0.97 (95% CI 0.96-0.98) *vs*. 0.99 (95% CI 0.77-1.0), respectively[44].

Our study has some limitations. First, most of the studies did not report the clinical data, patient characteristics, contact history, or the time interval between the onset of symptoms and sample collection. Second, several tests have been studied with a limited number of samples, and only 61.5% of tests included more than 100 samples. Third, all the studies included adults or mixed age group patients, and there were no studies that focused only on children. Fourth, we could not assess the overall diagnostic performance of the Accula POCT, which is a combination of RT-PCR and lateral flow immunoassay, due to limited number of clinical studies. Fifth, most of the studies were conducted in the USA. Further studies are required to ensure the applicability of the results of studies of POCTs conducted in the USA, in terms of the FDA-EUA status, to other countries.

Conclusions

The currently available POCTs approved in the USA for study in terms of an FDA-EUA are highly accurate for the diagnosis of SARS-CoV-2 infection. Nevertheless, the findings of our study require further large-scale, high-quality clinical studies to draw a firm conclusion.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of data and materials

The data used in the present study are appropriately cited.

Authors' Contributions

SHY conceptualized the study and performed investigation and data analysis and drafted the manuscript. SY, HC, and SE also performed investigation and data interpretation. CMK and MKK revised the manuscript. All authors read and approved the final version of manuscript.

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