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A Meta-Analysis on The Comparison of The Sensitivity of Three Test Methods Used in the Diagnosis of COVID-19

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Abstract

Background: Accurate detection of the global epidemic-causing coronavirus disease 2019 (COVID-19) is for disease surveillance. Additionally, RT-qPCR has been accepted as a reference test and is widely used for this purpose. However, RT-qPCR applications are not possible in all health centers. Therefore, the tests commonly used in the diagnosis of infectious disease should be evaluated from all angles to assess their potential role in the prognosis and management of COVID-19 patients.
Objectives: The present study aimed to compare the diagnostic sensitivity of point of care (POC), enzyme-linked immunosorbent assay (ELISA), and computed tomography (CT) used in the diagnosis of COVID-19.
Methods: This systematic review and meta-analysis was conducted via searching in databases such as NCBI, Google Scholar, and Medline in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA).
Results: The pooled sensitivity of POC, ELISA, and CT was estimated at 68.62%, 88.05%, and 75.43%, respectively. In addition, the mean correct positivity rate of POC, ELISA, and CT was calculated to be 68.61%, 88.04%, and 79.25%, respectively. The sensitivity and true positivity rate of ELISA was observed to be the highest.
Conclusions: According to the results, ELISA is a more accurate approach to the diagnosis of COVID-19 compared to POC and CT owing to its high sensitivity and true positivity rate, low false negative rate, short processing time, and simple study procedure. Although helpful in diagnosis, confirmation of ELISA results by polymerase chain reaction remains the 'gold standard'.

Keywords: COVID-19, Point of Care Test, Enzyme-linked Immunosorbent Assay, Reverse Transcription-Polymerase Chain Reaction, Computed Tomography

1. Background

Pneumonia caused by the new coronavirus was announced as the coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) on February 11, 2020, which was taken to the epidemic scale and spread rapidly all over the world (1). Initially, the exact diagnosis of COVID-19 was possible by detecting the SARS-CoV-2 ribonucleic acid (RNA) in the specimens sent from the infected cases (2). Later, various diagnostic tests were used to identify the virus, including molecular tests such as reverse transcription-polymerase chain reaction (RT-PCR) tests, which identifies the genetic material of the virus, and antigen tests that detect special proteins on the virus surface. Today, new tests have been introduced for COVID-19 detection, which provide diagnostic benefits (3).

In order to adequately cope with the COVID-19 pandemic and remove the constraints imposed on the community, there is an urgent need for tests that can work with a minimum of devices and equipment, including at home. COVID-19 IgG/IgM antibody tests are used for the detection of SARS-CoV-2 with quick point-of-care (POC) tests. POC diagnostic test methods are rapid and use a mucus sample from the nose or throat. As such, POC tests that are scalable, cost-effective, and easy to use are critical to battle COVID-19 (4).

Optimized enzyme-linked immunosorbent assay (ELISA) is used in numerous clinical virology laboratories for diagnostic purposes and evaluating conditions such as infections, vaccination, and re-infection (5, 6). Most of the antibodies reported for SARS-CoV-2 have been used for ELISA (7). Furthermore, serological tests for the detection of SARS-CoV-2 are under development. Zhang et al. deter-

mined IgG and IgM positivity from COVID-19 patient sera using the N protein-specific ELISA test (8).

In the study conducted by Huang et al., the results of the unenhanced computed tomography (CT) of 41 patients with definite COVID-19 were published as the first article in this regard (9). Following that, scientific publications on the diagnosis of COVID-19 increased, and the clinical indications for chest CT are constantly changing. Although RT-PCR is the 'gold standard' diagnostic test for confirming the diagnosis of COVID-19, it could be a valuable guide in the initial assessment of non-contrast chest CT patient populations (10).

Accurate detection of the global epidemic-causing COVID-19 is imperative for disease surveillance and control. Dozens of tests have been made available within a short time for COVID-19 diagnosis. With the rapid development of such tests, rigorous evaluations have become difficult, and there are important uncertainties regarding the specificity of these tests. Quantitative RT-qPCR has been accepted as a reference test and is widely used for COVID-19 diagnosis. However, RT-qPCR applications are not possible in all health centers. Therefore, tests with widespread use in the diagnosis of infectious disease should be evaluated from all perspectives to assess their potential role in the prognosis and management of COVID-19 patients (2). Our study is of particular importance as it clarifies the mentioned situation.

2. Objectives

This meta-analysis aimed to compare the diagnostic sensitivity of POC, ELISA, and CT tests in the diagnosis of COVID-19 infection, evaluate the quality of the existing tests, and compare the PCR-verified sensitivity of these test methods.

3. Methods

3.1. Protocol and Registration

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) protocol was used for this review. The focus of the review was the comparison of the sensitivity of the diagnostic methods used for COVID-19.

3.2. Search Strategy

This meta-analysis was conducted via searching in databases such as NCBI, Google Scholar, and Medline for studies published in English in 2020. Subject headings/sub-headings were used for the COVID-19/SARS-CoV-2 and the POC, ELISA, and CT tests. The literature review applied to publications during January 1, 2020-November 15, 2020. We also evaluated the articles included in the references of other studies (Figure 1).

3.3. Eligibility Criteria

The eligibility criteria of our study were clinical researches reporting the sensitivity of POC, ELISA, and CT in COVID-19 diagnosis. Review studies, letters to the editor, case reports, modeling/economic studies, articles with a smaller sample size than 50, studies lacking clear data, and those not comparing the mentioned test methods with PCR were excluded.

3.4. Study Selection

Articles were searched using keywords in the literature search via Google Scholar, NCBI, and Medline. At this stage, we collected the articles identified in these databases, and the articles that did not meet the inclusion criteria were excluded. Following that, the full texts of the eligible articles were retrieved and reviewed independently. Disagreements between the authors were resolved by scientific consensus. In this meta-analysis, we selected the studies that compared the sensitivity rate of the test methods used for COVID-19 diagnosis with a reference RT-PCR standard. Clinical trials conducted on 50 or more patients reporting the sensitivity of POC, ELISA, and CT for COVID-19 diagnosis were selected and reviewed.

3.5. Quality Assessment

Table 1 shows the methodological evaluation of the study. Notably, these quality criteria were not considered as exclusion criterion. The qualitative review of the selected studies for the meta-analysis was scored based on a checklist designed with critical evaluation by three independent researchers. These criteria were the applied test method, number of the included patients, and the false negative and true positive rates of the applied tests (Table 1).

Table 1. The Criteria Set for the Quality Evaluation of Studies

	3 Points	2 Points	1 Point
Test method	ELISA	CT	POC
No. of patients	> 500	100 - 500	< 100
False-negative rate of used test, %	< 10	10 - 30	> 30
True-positive rate of used test, %	> 80	50 - 80	< 50

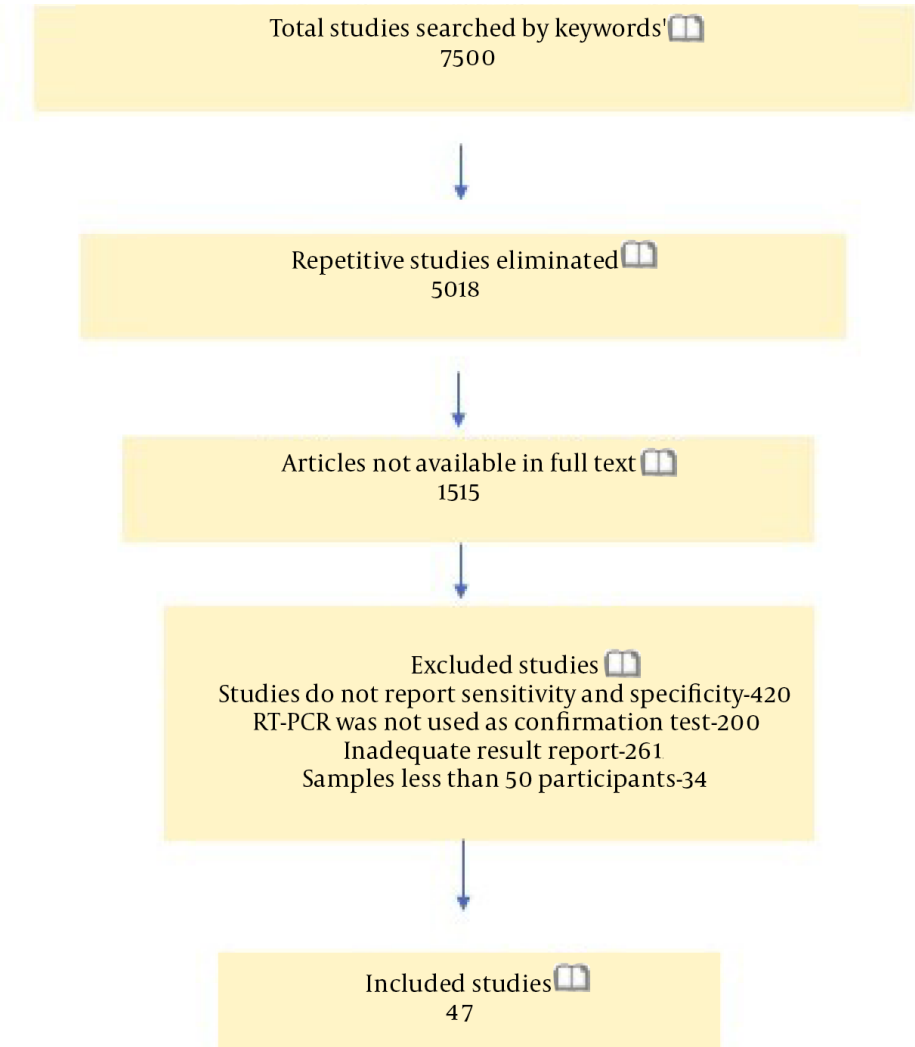

Figure 1. Screening studies for meta-analysis

3.6. Data Extraction

One of the researchers extracted the aggregated data using a standard electronic data entry form. For each study, the second and third investigators validated the entered data. Duplicate data were not found, and data were collected on trace characteristics (country, sample type, applied method) and the methodological details regarding the index and reference.

3.7. Statistical Analysis

Data analysis was performed in SPSS version 25 and comprehensive meta-analysis (CMA) using one-way ANOVA and paired sample *t*-test, which were performed in SPSS. The effect sizes and heterogeneity (I^2 and Q) of the selected studies were calculated in CMA, and a forest plot was used to assess publication bias. Heterogeneity in meta-analysis refers to variations in the results of the selected studies. The thresholds for the interpretation of I^2 could be misleading as the significance of the discrepancy depends on several factors. A rough guide to such interpretation is as follows:

- 0 - 40%: may not matter;
- 30 - 60%: may represent moderate heterogeneity;
- 50 - 90%: may represent substantial heterogeneity;
- 75 - 100%: significant heterogeneity

3.8. Data Report

In the first part of our analysis, we estimated the sensitivity of POC, ELISA, and CT test methods and categorized the studies based on their applied tests methods. In several studies, researchers evaluated the accuracy of multiple test methods simultaneously (eg, POC and ELISA). For the index test performed on each study, the required numbers to form 2×2 probability tables were extracted. Each assessment of a particular index test was considered as the arm of the study. For instance, a study performing two ELISA and three CT evaluations on the same patient group would contribute to five study arms. It was also assumed that the sensitivity results of the tests would vary depending on the methods, countries, and sample types. As such, we classified the samples with primary results based on the applied methods, regions, and countries.

4. Results

4.1. Study Selection

The literature search yielded 7,500 studies corresponding to the keywords. After eliminating repetitive studies, 5,018 articles remained (Figure 1). In total, 47 studies that met the inclusion criteria were included, and review studies, letters to the editor, case reports, modeling/economic studies, articles without clear data, the studies with smaller sample sizes than 50, and those without a PCR comparison were excluded. Most of the studies that were selected for the meta-analysis (n = 47) and evaluated POC, ELISA, and CT methods were conducted in China. In the studies selected for the meta-analysis, CT was the most commonly applied method (Table 2).

4.2. Characteristics of Studies

Table 3 shows the distribution of the performed tests by country. In the studies selected for the meta-analysis, no description was provided on the sample type in 2,442 cases. However, blood and throat swabs were the most commonly used sample types in the reviewed studies. Table 4 shows the sample distribution of the performed tests on 6,305 clinical cases. In the qualitative review, the studies were scored within the range of 4 - 12, and the mean qualitative score of the studies was estimated at 8.16 ± 1.84 (Table 2).

4.3. Main Findings

The pooled sensitivity of POC, ELISA, and CT was estimated at 68.62%, 88.05%, and 75.43%, respectively. The mean true positive (TP) rate of POC, ELISA, and CT was reported to be 68.61%, 88.04%, and 79.25%, respectively. In addition, the mean false negative (FN) rate of POC, ELISA, and CT was calculated to be 31.38%, 11.95%, and 20%, respectively.

No significant difference was observed between the sample type and test sensitivity in one-way ANOVA ($P > 0.05$). On the other hand, a significant difference was observed between the applied method and test sensitivity ($P < 0.05$). A significant difference was also denoted between the country and test sensitivity ($P < 0.05$). According to Tukey's post-hoc test, the sensitivity of ELISA and the tests performed was higher in China based on country (Table 5). However, no significant difference was observed between the sensitivity of TP in the paired-samples *t*-test ($P > 0.05$). A statistically significant difference was found between FN and test sensitivity. ($P < 0.05$) A statistically significant difference was found between FN (%) and test sensitivity. ($P < 0.05$) (Table 6)

The random-effect (REX) and fixed-effect (FEX) models were used to calculate the effect size of the studies. According to the effect size analysis performed at 95% confidence interval (CI), ELISA and CT studies showed substantial heterogeneity (I^2=67.5% and I^2=85.4%, respectively). In addition, POC tests showed considerable heterogeneity (I^2=94.8%), which was even higher than the I^2 value of the effect size of all the tests (90.2%). Table 7 shows more statistical data obtained by the FEX and REX models.

In the present study, the REX model was used to calculate the effect size of the selected studies, and a higher effect size was observed in the CT group with the REX model. In the REX model, the effect size was calculated to be 4.391 at 95% CI. According to Cohen's classification, the reviewed studies had high effect sizes. (Table 7). Figure 2 depicts each of the reviewed studies in the forest plot chart.

5. Discussion

According to the results of the current meta-analysis, the existing evidence regarding the diagnostic accuracy of POC, ELISA, and CT for COVID-19 is characterized by limitations such as high bias risks and heterogeneity. Furthermore, our findings indicated that the sensitivity of CT and POC was consistently lower compared to ELISA. The sensitivity of POC has been estimated at 68.62%, indicating a significant weakness in this test compared to marketed bedside tests for COVID-19 diagnosis.

In the present study, a significant difference was observed between the sensitivity of the tests performed in China and the sensitivity of the tests conducted in Italy. Al-

Table 2. Characteristics of the Studies Included in the Meta-analysis

Study	Country	COVID-19 Diagnosis Method	Sample	Number of Tests (N)			Qualitative Score
				Total	Positive with PCR	Positive with CT, ELISA and POC	
Ai et al. (11)	China	CT	Throat swab	1014	601	580	11
Adams et al. (12)	ABD	ELISA	Blood	142	40	34	10
Cassaniti et al. (13)	Italy	POC	Blood	50	41	7	4
Virgilio Paradiso et al. (14)	Italy	POC	Blood	191	70	33	5
Perez-Garcia et al. (15)	Spain	POC	Blood	90	55	26	4
Liu et al. (16)	China	POC	Pharyngeal swab	179	90	77	8
Zhao et al. (17)	China	ELISA	Blood	173	173	161	11
Lou et al. (18)	China	ELISA	Blood	80	80	79	10
Guo et al. (19)	China	ELISA	Blood	82	82	65	8
Infantino et al. (20)	Italy	ELISA	Nasopharyngeal swab	64	64	41	7
Jin et al. (21)	China	ELISA	Sputum/oral swab	76	27	24	9
Cai et al. (22)	China	ELISA	Oral swab	276	276	225	10
Xie et al. (23)	China	ELISA	Blood	56	16	15	10
Yangchun et al. (24)	China	ELISA	Blood	284	205	197	11
Qian et al. (25)	China	ELISA	Blood	972	503	486	12
Fang et al. (26)	China	CT	Throat swab	81	51	50	9
Ruch et al. (27)	Fransa	CT	Unspecified	572	572	558	11
Xiang et al. (28)	China	CT	Unspecified	83	53	50	8
Wang et al. (29)	China	CT	Unspecified	107	90	50	7
Du et al. (30)	China	CT	Unspecified	125	125	99	9
Rousan et al. (31)	Jordan	CT	Nasopharyngeal swab	88	88	75	7
Shabrawishi et al. (32)	Saudi Arabia	CT	Unspecified	150	150	119	8
Werberich et al. (33)	Brasil	CT	Unspecified	78	78	48	6
Bernheim et al. (34)	China	CT	Unspecified	121	121	94	8
Wu et al. (35)	China	CT	Unspecified	80	80	73	8
Xu et al. (36)	China	CT	Unspecified	90	90	69	8
Cui et al. (37)	China	CT	Unspecified	95	95	53	7
Falaschi et al. (38)	Italy	CT	Unspecified	773	462	419	11
Imai et al. (39)	Japan	POC	Blood	112	112	37	5
Nie et al. (40)	China	CT	Unspecified	163	163	145	7
Parry et al. (41)	India	CT	Unspecified	147	147	51	7
Goldberg-Stein et al. (42)	ABD	CT	Nazal swab	141	141	80	7
Gu et al. (43)	China	CT	Nasopharyngeal, oropharyngeal swab	50	50	38	8
Meiler et al. (44)	Germany	CT	Unspecified	64	64	62	7
Brendish et al. (45)	UAE	POC	Nasal swab	517	499	157	6
Imai et al. (39)	Japan	CT	Blood	112	112	77	8
Butt et al. (46)	Pakistan	POC	Nasopharyngeal swab	70	45	43	8
Haq et al. (47)	India	POC	Nasopharyngeal swab	84	72	62	7
Mohon et al. (48)	Canada	POC	Nasopharyngeal swab	120	42	41	9
Ghofrani et al. (49)	ABD	POC	Nasal swab/nasopharyngeal swab	112	17	16	9
Smithgall et al. (50)	ABD	POC	Nasal swab/nasopharyngeal swab	113	113	84	7
Bulterys et al. (51)	ABD	POC	Nasal swab/nasopharyngeal swab	80	29	24	7
Zhang et al. (52)	China	CT	Unspecified	60	60	48	8
Shi et al. (53)	China	CT	Unspecified	81	81	66	8
Cheng et al. (54)	China	CT	Unspecified	53	11	11	9
Elslande et al. (55)	Belgium	ELISA	Blood	103	94	86	11
Huang et al. (56)	China	ELISA	Throat swab	82	63	55	9
Li et al. (57)	China	POC	Nasopharyngeal swab	525	397	256	8

Table 3. Summary of the Countries of the Studies Included in the Meta-analysis

Country	Test Methods					
	POC		ELISA		CT	
	No. of Studies	No. of Studies	No. of Studies	No. of Patients	No. of Studies	No. of Patients
China	2	102	9	1425	14	1671
ABD	3	159	1	40	1	141
France	0	0	0	0	1	572
Italy	2	111	1	64	1	462
Jordan	0	0	0	0	1	88
Saudi Arabia	0	0	0	0	1	150
Brazil	0	0	0	0	1	78
Germany	0	0	0	0	1	64
Belgium	0	0	1	94	0	0
UAE	1	499	0	0	0	0
India	1	72	0	0	1	147
Spain	1	55	0	0	0	0
Japan	1	112	0	0	1	112
Canada	1	42	0	0	0	0
Pakistan	1	45	0	0	0	0
Total	13	1197	12	1623	23	3485

Abbreviations: POC, point of care; ELISA, enzyme linked immunosorbent assay; CT, computer tomography.

Table 4. Summary of the Sample Types Used in Studies Included in the Meta-analysis

Sample Type	POC		ELISA		CT		Total	
	NS	NP	NS	NP	NS	NP	NS	NP
Unspecified	0	0	0	0	17	2442	17	2442
Blood	4	278	8	1193	1	112	13	1583
Throat swab	0	0	1	63	2	652	3	715
Nasal swab	1	499	0	0	1	141	2	640
Nasopharyngeal swab	7	330	1	64	2	138	10	532
Oral swab	0	0	1	276	0	0	1	276
Pharingeal swab	1	90	0	0	0	0	1	90
Saliva-oral swab	0	0	1	27	0	0	1	27

Abbreviations: NS, number of studies; NP, number of patients; POC, point of care; ELISA, enzyme linked immunosorbent assay; CT, computer tomography.

Table 5. Statistical Analysis of Test Sensitivity According to Various Variables (One Way ANOVA Results)

	df	Mean Square	F	P-Value
Sample type	5	231.431	0.465	0.800
Methods	2	1146.904	2.610	0.041 [a]
Country	4	926.673	2.634	0.044 [a]

[a] $P < 0.05$

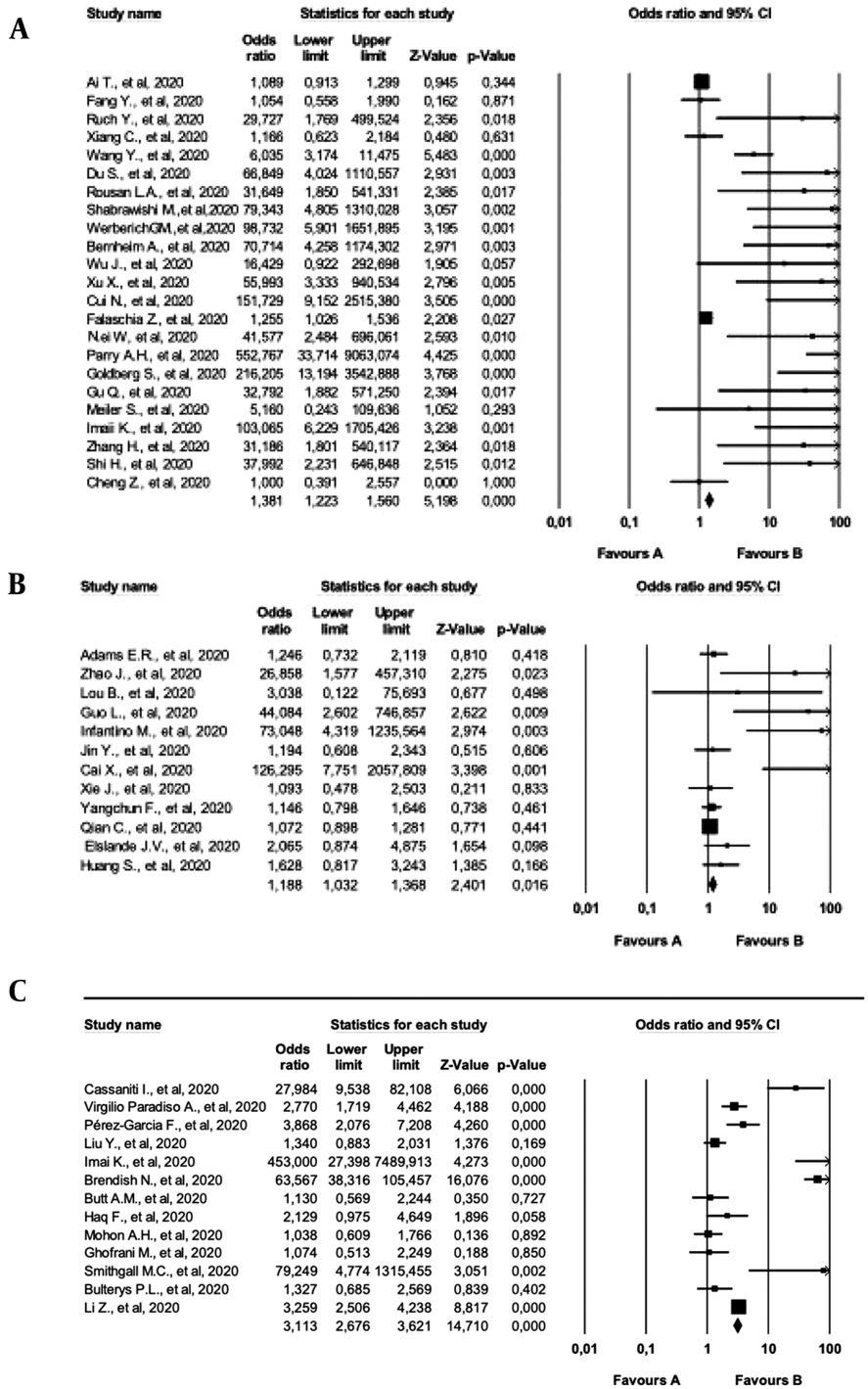

Figure 2. Forest plot analysis of studies in meta-analysis. (A) Forest plot analysis of CT studies in meta-analysis (11, 26-44, 52-54). (B) Forest plot analysis of ELISA studies in meta-analysis (12, 17-25, 55, 56). (C) Forest plot analysis of POC studies in meta-analysis (13-16, 39, 45-51, 57)

Table 6. Statistical Analysis of Test Sensitivity According to Various Variables (Paired Sample *t*-test Results).

	Mean ± SD	No.	P-Value
TP	104.4583 ± 133.32315	47	0.242
FN	27.2292 ± 50.62723	47	0.001 [a]
FN (%)	21.4951 ± 20.63477	47	0.000 [a]

Abbreviations: SD, standard deviation; TP, true positive; FN, false negative.
[a] $P < 0.05$

though no significant difference was denoted between the tests in China and other countries, the sensitivity of the tests performed in China was higher compared to other countries.

In a study aiming to evaluate the ELISA kits that are commercially produced for SARS-CoV2 without completed validation or those about to be validated, the sensitivity and differences of IgA and IgG antibody titers in patient sera were determined. According to the findings, this ELISA kit has been designed to bind to the S1 protein, and the results of IgA in the course of the disease were significantly correlated with the kit (8). Furthermore, the antibody in the kit is 90% similar to the other coronavirus N protein, indicating sufficient results and confirming the results of the serum test performed within five days from the onset of the infection by RT-PCR (58). Notably, evaluation of different recommended parameters for the course of the disease are essential to determining the specificity of SARS-CoV2 serological tests in the infection follow-up (59).

The benefits of POC tests are cost-efficiency, rapid implementation, and accurate results. However, the low sensitivity of this method is alarming. According to the studies in this meta-analysis, the sensitivity of the POC tests performed with serum/plasma samples is lower than the POC tests performed with nasopharyngeal samples; notably, the sample type should be considered in this test. Few patients are tested for suspected SARS-CoV-2 infection, and the overall results of our study may not be generalizable to all patients with suspected COVID-19.

Chest CT played a key role in the diagnosis of COVID-19 at the beginning of the outbreak and during the peak periods of the pandemic. Although RT-PCR is considered the 'gold standard' in this regard, the frequency of FN results after the first test and the absence of a laboratory kit in the early stages of the pandemic limit the early diagnosis of COVID-19 by this method. According to our findings, the tests used for the early diagnosis of COVID-19 (especially CT) have higher sensitivity in the regions that were first and heavily affected by the pandemic, such as China. Therefore, diagnostic criteria based on typical CT imaging features are only temporarily included in the current diagnostic-treatment guidelines in Hubei Province of China (60). These guidelines enable the early clinical diagnosis of COVID-19 due to the insufficiency of high-sensitivity tests such as ELISA and CT, as well as the RT-PCR diagnostic kits that contribute to the effective control of the current pandemic. The difference in this regard has several reasons, such as differences in CT sensitivity, heterogeneity in radiologists' gaze, disease severity, and symptom onset.

Although RT-PCR is accepted as the 'gold standard', FN results are also encountered. According to Xie et al., more than 5% of COVID-19 patients initially had FN RT-PCR results, which became positive after multiple tests (61). However, 86% of these patients had positive chest CT images before their first negative RT-PCR results. Several cases of this issue are reported increasingly (60). Given the concerns about FN results, the limitations of RT-PCR, and the continued increase in the global cases of COVID-19, the British Thoracic Imaging Association highlights the importance of radiographic evaluation, especially in case of diagnostic uncertainty (62).

According to the CMA analysis in the current research, the I^2 value was 90.20%, which indicated the high heterogeneity of the selected studies for the meta-analysis ($P < 0.001$). The main reasons of the heterogeneity between the studies are the diverse number of the evaluated patients, different demographic and clinical characteristics of the patients, differences in the applied methods, mistakes of the health personnel who evaluated the diagnosis tests, differences in the tested variables in ELISA (IgG, IgM, and IgG + IgM), differences in the commercial brand of POC and ELISA kits, differences in the virus structure in immunoserological tests (surface protein, nucleocapsid protein, surface/nucleocapsid proteins), and the interval between the onset of symptoms and performing CT, ELISA, and POC.

5.1. Limitations of the Study

The main limitations of our meta-analysis were the small sample size and exclusion of the studies evaluating fewer than 50 patients. In addition, meta-regression analysis was not performed since many studies would have to be excluded due to not reporting common variables. Another limitation was that we did not search databases such as OVID, Medline, and Embase, and some published studies might have been overlooked.

Table 7. Effect Sizes and Heterogeneity Test

Model	No.	MES	Z	95% CI		SD	Q	I^2	P-Value
				LL	UP				
POC									
FEX	13	2.900	11.524	2.419	3.475	NA	NA	NA	NA
REX	13	4.074	3.261	1.751	9.478	12	232.050	94.829	0.000
ELISA									
FEX	12	1.188	2.401	1.032	1.368	NA	NA	NA	NA
REX	12	1.673	2.615	1.138	2.461	11	33.897	67.549	0.000
CT									
FEX	23	1.381	5.198	1.223	1.560	NA	NA	NA	NA
REX	23	7.963	7.423	4.604	13.772	22	150.752	85.407	0.000
All studies									
FEX	47	1.528	10.129	1.408	1.659	NA	NA	NA	NA
REX	47	4.391	8.447	3.115	6.190	47	479.700	90.202	0.000

Abbreviations: MES, mean effect size; REX, random effect; FEX, fixed effect; LL, lover limit; UL, upper limit; NA, non-Applicable.

5.2. Conclusions

This is the first meta-analysis to simultaneously evaluate POC, ELISA, and CT sensitivity in COVID-19 diagnosis. According to the results, these tests had different sensitivity and specificity. ELISA was considered to be a more accurate diagnostic test for COVID-19 compared to POC and CT owing to its high sensitivity and true positivity rate, low FN rate, short processing time, and simple study procedure. Although helpful in diagnosis, confirmation of ELISA results by PCR remains the 'gold standard'. Further investigations are urgently required regarding the diagnostic performance of the test methods used worldwide for COVID-19 on larger sample sizes and in greater detail.

Footnotes

Authors' Contribution: Study concept and design: I.H.C. Acquisition of data: E.P.K.K, I.K. Analysis and interpretation of data: I.H.C, I.K. Drafting of the manuscript: I.K. Critical revision of the manuscript for important intellectual content: I.H.C. Statistical analysis: I.H.C, E.P.K.K. Administrative, technical, and material support: I.K. Study supervision: I.H.C

Conflict of Interests: There is no conflict of interest between the authors.

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