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Research article

Diagnostic accuracy of aptamer-based biosensors for the detection of SARS-CoV-2 compared to RT-PCR: A systematic review and meta-analysis

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ABSTRACT

Aptamer-based biosensors present a potential alternative for the detection of SARS-CoV-2, with numerous studies demonstrating their diagnostic accuracy. A systematic review and meta-analysis are needed for evidence synthesis. A comprehensive literature search was conducted across PubMed, Scopus, Science direct, MEDLINE, as well as Embase (via Ovid) to pool articles aiming at evaluating the diagnostic accuracy of Aptamer-based biosensors in the detection of COVID-19. Using Meta-DiSc software, data from fourteen (14) included studies involving a total of 8082 clinical samples were pooled and analysed to generate a summary of the sensitivity and specificity, diagnostic odds ratio (DOR), positive and negative likelihood ratio (PLR, NLR), as well as area under the curve (AUC) of receiver operating characteristic (SROC) curve for aptamer-based electrochemical, Surface Enhanced Raman Scattering (SERS), and Enzyme Linked Oligonucleotide Assay (ELONA) and fluorescence sensing platforms. Among these platforms, the SERS demonstrated the highest diagnostic performance, with an overall 0.97 (95 % CI: 0.91–0.99) sensitivity, 0.98 (95 % CI:0.95–1.00) specificity, 766.63 (95 % CI: 133.85–4391.03) DOR and 0.98 AUC, a PLR of 33.09 (8.53–128.36) and a NLR of 0.04 (0.02–0.12). These findings underscore the high sensitivity of the SERS platform in detecting SARS-CoV-2 infection. However, the limited number of studies included in each sensing platform used for the meta-analysis restricts any generalization from the pooled data.

1. Introduction

The world economy, social life, and health have all been drastically influenced by the ongoing COVID-19 global outbreak, which was caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. The early detection and reliable diagnosis of COVID-19 are necessary for controlling its spread and managing patients' treatment effectively. By international standard, the famous Reverse Transcription Polymerase Chain Reaction (RT-PCR) which is based on the selective detection of viral nucleic acid is

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considered the reference standard in SARS-CoV-2 detection. Even though this method has been proven to have high sensitivity and specificity [2,3], it however has certain limitations such as a relatively long turnaround time, technical complexity and expensive instrumentation [4], which make it unsuitable for use especially in low-resource settings.

Methods for rapid detection of SARS-CoV-2, which mostly relies on antigen or antibody immunodetection, were essential in the management of the pandemic given that they significantly reduce turnaround time and cost of testing [5]. Antigen detection is usually used to identify viral proteins during active infection and has therefore been recommended for use in rapidly detecting SARS-CoV-2 [6], while antibody detection identifies the body's immunological reaction to the pathogen, indicating prior exposure [4]. However, the sensitivity of current available rapid test kits (RTKs) for antigen-based immunodetection of the virus varies between 60 and 80 % and with the risk of false negative results [7,8], which could have serious consequences in the effort of rapidly containing the virus. Therefore, there is a need for alternative testing techniques for SARS-CoV-2 infection.

Within the last few years, aptamer-based biosensors are emerging as potential alternative for the detection of pathogens including SARS-CoV-2. Aptamers are short single-stranded nucleic acid sequences (DNA or RNA molecules) that can be synthesised or selected to effectively bind to numerous definite target analytes including viruses with high efficiency [9]. Various aptamer-based sensors are available and they include but not limited to aptamer-based sandwich assay, electrochemical sensors, ELONA, SERS, optical and fluorescence sensors [10–16]. These sensing platforms have already been used for the detection of SARS-CoV-2 [15,17–19] in clinical specimen. Since quite a number of studies have investigated the diagnostic performance of aptamer-based biosensors in SARS-CoV-2 detection, there is a need to systematically review and analyse these studies for an in-depth evaluation of the diagnostic accuracy of these sensors compared to RT-PCR.

Here, we carried out a systematic evaluation and analysis of published works on aptamer-based biosensors for SARS-CoV-2 detection in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) standards. A meta-analysis was also conducted to quantitatively synthesize the data and evaluate sensitivity, specificity, as well as the cumulative diagnostic accuracy. This rigorous approach provides insights into the reliability of aptamer-based biosensors in the context of COVID-19 diagnostics.

2. Methodology

The PRISMA guidelines were strictly adhered to in conducting this systematic review and meta-analysis. The International Prospective Register of Systematic reviews (PROSPERO) registered the study protocol for this study with the registration number CRD42023407684, on March 31, 2023.

2.1. Search strategy

The following databases; PubMed, Science direct, Scopus, EMBASE and MEDLINE were Searched exhaustively using the search query; (((Aptamer AND Biosensor) OR Aptasensor) AND (SARS-CoV-2 OR 2019-nCoV OR COVID-19) AND (Sensitivity OR Specificity OR "true positive" OR "true negative" OR "false positive" OR "false negative") AND (Human OR patients OR clinical)). Searches were conducted between 28th and 29th March 2023. With no language restrictions, all the five (5) databases were searched for articles. In addition, the approach also includes grey literature searching through manual search of sources of chosen publications.

2.2. Eligibility criteria

Cohort and case-control, randomised and observational, monocentre and multicentred studies of COVID-19 suspected patients without age restriction that reported aptamer-based method of COVID-19 diagnosis and RT-PCR as reference standard were included until 29 March 2023. If the values for the diagnostic outcomes that is, True-positive (TP), False-negative (FN), True-negative (TN), and False-positive (FP) results were not found, the needed parameters were retrieved from the main paper. Case reports, animal studies, studies using artificial samples or pseudovirus, and analytical researches conducted with no clinical specimen were not included.

2.3. Study selection

After literatures were searched from the included data depositories, all citations obtained were exported to Mendeley for de-duplication before uploading to Rayyan for independent and blind selection by three (3) reviewers. Articles were selected in a two-step process; initially, articles' titles and abstracts/summaries were checked using the selection guidelines. The complete content of all eligible articles was evaluated by two independent authors (reviewers) for inclusion. Discussions with the third author (reviewer) enabled resolution of any disagreement(s). To obtain data from the included studies, a data extraction form was designed.

2.4. Data extraction and checking

Data extraction was conducted on Excel workbook (Microsoft Inc., Washington, US), covering the variables; Title, authors, year of study, country of study, study design, type of sample, detection platform, comparator, number of participants (COVID-19 positive/negative) and outcome (TP, FN, FP and TN). Duplicated articles were excluded and two independent authors (IHM, BA) recorded the number of TP, FP, TN and FN. Discrepancies in the data retrieved were rectified through discussion. Finally, data were checked centrally for completeness, plausibility, and integrity by an independent investigator (HYC) before synthesis.

2.5. Quality assessment

All the included studies were evaluated for quality in order to minimize systematic bias and inferential errors in the retrieved data. Two independent reviewers (IHM, BA) appraised the risk of bias using the tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [20]. The index test, reference standards, flow/timing, and patient selection were the four domains of bias assessed. A summary of risk of bias and its corresponding graph were prepared using the Review Manager 5 software (RevMan version 5.4) in order to facilitate risk of bias analysis.

2.6. Data synthesis

All generated data were analysed statistically using the Meta-DiSc statistical tool (version 1.4) [21]. For each analysis, test accuracy values [sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and 95 % confidence intervals] were compared with RT-PCR method. The pooled sensitivity, specificity, PLR as well as the NLR of all the platforms were determined. The diagnostic odd ratios (DORs) were determined via the DerSimonian-Laird technique (random effects approach) [22]. To summarise the outcomes, The Summary ROC plots (SROC) were generated so as to represent the correlation between sensitivity and false positive rate (1–specificity). The cumulative under the curve area (AUC) of the SROC plot was determined and presented as a way of evaluating diagnostic accuracy in the quantitative analysis [23].

The I^2 statistic was used to evaluate heterogeneity, and the results are defined as: homogeneous if their I^2 scores are below 50 %, whereas significant heterogeneity among studies is indicated by an I^2 score that is above 50%. [24]. The Spearman's rank correlation

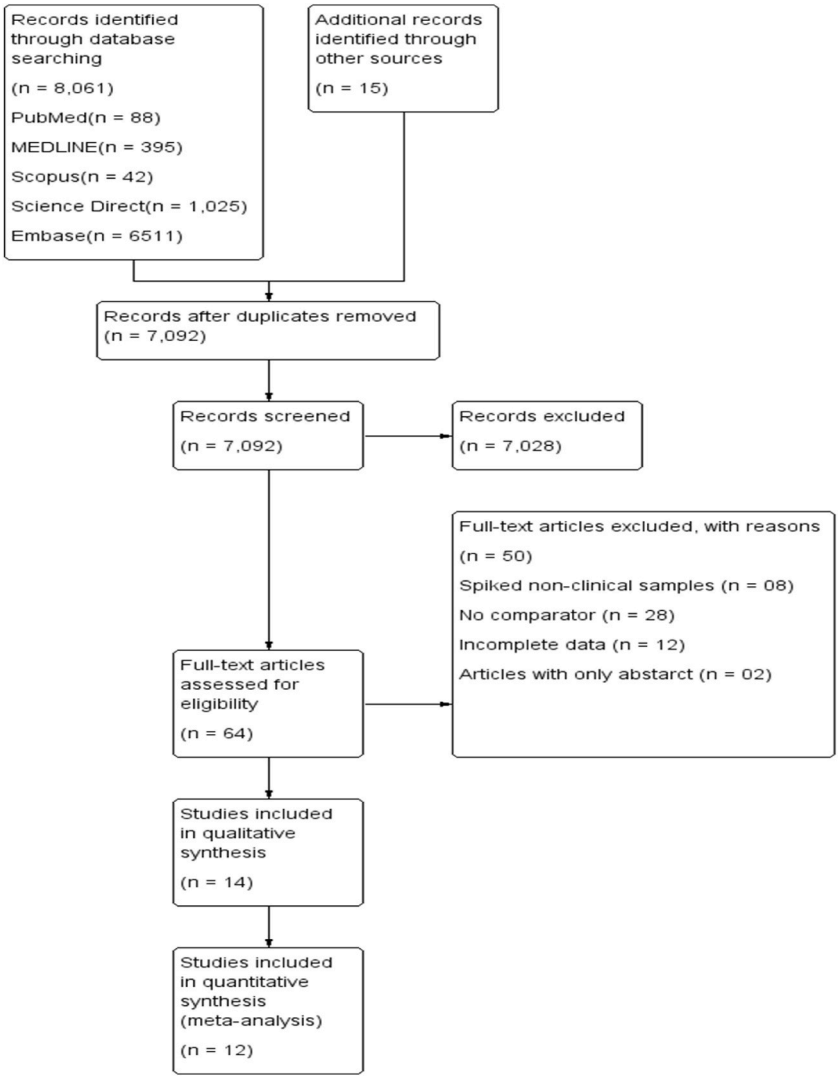

Fig. 1. PRISMA flow chart: Step-by-step flow diagram for the selection of articles for inclusion in the study.

between the included studies' sensitivity and specificity was calculated in order to determine if threshold effect was present [25]. The impact of individual factors to the observed heterogeneity was assessed using meta-regression and analysis of sub groups if there was no threshold effect with a p value of below 0.05 indicating that factors contributed to variability.

3. Results

3.1. Results of the search

After searching, 8061 literatures were retrieved from five different databases: 88 from Pubmed, 395 from MEDLINE, 42 from SCOPUS, 1025 from Science Direct, and 6511 from Embase. In addition, 15 more articles were identified through other sources (Fig. 1). Following de-duplication, 984 records were excluded while the remaining 7092 articles were further screened. After considering tittles and abstracts of the studies, 7028 were removed. The remaining 64 eligible studies' full texts were then retrieved and screened in detail. Of these, 14 articles that fulfilled the requirements for inclusion were subjected to quality assessment. However, only 12 articles were included in the meta-analysis because the optical [13] and glucometer [31] platforms had only one article each. The 50 studies were excluded because of: incomplete data, comparator (RT-PCR) not present, use of non-clinical samples and articles without full texts (Fig. 1).

3.2. Characteristics of the included studies

The studies included in this meta-analysis were carried out across various nations and reported between 2021 and 2023, resulting in 1082 individual aptamer-based tests compared with RT-PCR method. Of the included studies, 13 (93 %) were cross-sectional study while only 1 (7 %) was a cohort study. Aptamers with lengths ranging from 32 to 108 nucleotides were used in the included studies, most of which targeted the viral spike/surface glycoprotein (S-protein) (50 %) with different affinity constants (Kd) ranging from 2.1 pM to 61 nM. Tables 1 and 2 provides detailed characteristics of all the included articles in this study.

3.3. Quality of the studies

A QUADAS list of questions was used to assess the quality of the studies included. The majority of the studies that were included met most of the requirements on the list. However, most of the low-quality studies were unable to meet the requirements for patient selection and index tests (Fig. 2). As detailed in Table 3, only 4 (28.6 %) of the included studies had high quality while the remaining 10 (71.4 %) were of low quality.

3.4. Accuracy of aptamer-based electrochemical biosensor in detecting SARS-CoV-2 compared to RT-PCR

The electrochemical aptamer-based biosensors had a combined sensitivity and specificity of 0.86 (95 % CI: 0.76–0.93) and 0.96 (95 % CI: 0.89–0.99), respectively. Fig. 3 depicts complete forest plots for sensitivities (Fig. 3a) and specificities (Fig. 3b) of all the studies analysed in the platform. As illustrated in Fig. S1, the combined DOR is 96.40 (95 % CI: 25.10–370.25) while Fig. S2 depicts the SROC plot, with a corresponding AUC and Q values of 0.96 and 0.90 respectively. The studies showed no significant heterogeneity (sensitivity, $I^2 = 54.7$ %; specificity, $I^2 = 65.1$ %; DOR, $I^2 = 0.0$ %).

3.5. Accuracy of aptamer-based SERS biosensor in detecting SARS-CoV-2 compared to RT-PCR

Aptamer-based SERS biosensors had combined sensitivity and specificity of 0.97 (95 % CI: 0.91–0.99), and 0.98 (95 % CI: 0.95–1.00). Fig. 4 depicts the forest curves of the included studies' sensitivities (Fig. 4a) and specificities (Fig. 4b) and the pooled DOR was 766.63 (95 % CI: 133.85–4391.03), as shown in Fig. S3. The AUC was 0.98 while the Q value was 0.95 as illustrated in the SROC in Fig. S4. The studies showed no significant heterogeneity (sensitivity, $I^2 = 0.00$ %; specificity, $I^2 = 64.7$ %; DOR, $I^2 = 13.1$ %).

3.6. Accuracy of aptamer-based fluorescence biosensor in detecting SARS-CoV-2 compared to RT-PCR

The fluorescence aptamer-based biosensors had 0.97 (95 % CI: 0.85–1.00) and 1.00 (95 % CI: 0.90–1.00) as their combined sensitivity and specificity respectively. In Fig. 5, complete forest plots for sensitivities (Fig. 5a) and specificities (Fig. 5b) of the articles included in this platform were presented. As illustrated in Fig. S5, the combined DOR was 560.57 (95 % CI: 44.45–7069.26) while the SROC in Fig. S6 indicates that both the AUC and the Q value are 0.50. The studies showed no significant heterogeneity (sensitivity, $I^2 = 0.0$ %; specificity, $I^2 = 0.0$ %; DOR, $I^2 = 0.0$ %).

3.7. Accuracy of aptamer-based ELONA biosensor in detecting SARS-CoV-2 compared to RT-PCR

Aptamer-based ELONA biosensors had 0.89 (95 % CI: 0.85–0.92) and 0.96 (95 % CI: 0.93–0.98) as their combined sensitivity and specificity. Fig. 6 shows complete forest plots of the included studies' sensitivities (Fig. 6a) and specificities (Fig. 6b) and the pooled DOR was shown to be 23.17 (95 % CI: 0.30–1788.58) (Fig. S7). The SROC curve, depicted in Fig. S8, has an AUC of 0.93 and a Q value of 0.87. The studies showed no significant heterogeneity (sensitivity, $I^2 = 57.0$ %; specificity, $I^2 = 91.5$ %; DOR, $I^2 = 92.0$ %).

Table 1
Features of the included studies in detail.

S/N	Author(s)	Nation conducted	Design Type	Sample	Detection platform	Comparator	Total COVID-19 positive/ negative participants	TP	FP	FN	TN
1.	Gupta et al., [18]	India	Cross-sectional	Nasopharyngeal/Oropharyngeal	Enzyme-Linked Oligonucleotide Assay (ELONA)	RT-PCR	232/232	211	5	21	227
2.	Svobodova et al., [15]	Spain	Cross-sectional	Nasopharyngeal swab	Enzyme-Linked Oligonucleotide Assay (ELONA)	RT-PCR	45/5	36	4	9	1
3.	Yang et al., [19]	USA	Cross-sectional	Nasopharyngeal swab	Enzyme-Linked Oligonucleotide Assay (ELONA)	RT-PCR	4/4	3	0	1	4
4.	Daniels et al., [26]	France	Cross-sectional	NSP/Exhaled breath condensate (EBC)	Electrochemical	RT-PCR	7/7	5	0	2	7
5.	Zhang et al., [27]	Canada	Cross-sectional	Saliva	Electrochemical	RT-PCR	36/37	29	0	7	37
6.	Rahmati et al., [28]	Iran	Cross-sectional	Not stated	Electrochemical	RT-PCR	15/15	15	0	0	15
7.	Negahdary et al., [29]	Portugal	Cohort	Plasma	Electrochemical	RT-PCR	20/20	18	3	2	17
8.	Yoon et al., [16]	Korea	Cross-sectional	Nasopharyngeal/Oropharyngeal	Fluorescence	RT-PCR	30/30	29	0	1	30
9.	Wang et al., [30]	China	Cross-sectional	Oropharyngeal	Fluorescence	RT-PCR	6/6	6	0	0	6
10.	Singh et al., [31]	USA	Cohort	Nasopharyngeal	Glucometer-based	RT-PCR	16/8	16	0	0	8
11.	Luo et al., [13]	China	Cross-sectional	Nasopharyngeal/Oropharyngeal	Optical based	RT-PCR	39/39	36	0	3	39
12.	Gu et al., [32]	China	Cross-sectional	Oropharyngeal	Surface-enhanced Raman Scattering (SER)	RT-PCR	40/40	39	0	1	40
13.	Park et al., [14]	Korea	Cross-sectional	Nasopharyngeal	Surface-enhanced Raman Scattering (SER)	RT-PCR	20/60	20	0	0	60
14.	Torun et al., [33]	Turkey	Cross-sectional	Nasopharyngeal/Oropharyngeal	Surface-enhanced Raman Scattering (SER)	RT-PCR	36/33	34	2	2	31

TP = True positive; **FP** = False positive; **FN** = False negative; **TN** = True negative.

Table 2
Detailed description of the aptamers used in the included articles.

S/N	Author(s)	Aptamer name	Aptamer sequence (5′-3′)	Nucleotides No.	Target	Kd (nM)
1.	Gupta et al., [18]	S14	TGGGAGCCTGGGACATAGTGGGGAAAGAGGGGAAGAGTGGGTCT	44	S protein	21.8
2.	Svobodova et al., [15]	Apt1	ATCCAGAGTGACGCAGCACCGACCTTGTGCTTTGGGAGTGCTGGTC CAAGGGCGTTAATGGACACGGTGGCTTAGT	76	S protein	10.2
		Apt5	ATCCAGAGTGACGCAGCAGGACTGCTTAGGATTGCGAAGCTGAGG AGCTCCCCCGCCTTGGACACGGTGGCTTAGT	76	S protein	11.3
3.	Yang et al., [19]	SCORe.50	CGCGGAGTAGTATATCGTGGTATCAAAAGCCGGGGGGGCTGTACTCCGCG	50	RBD	2.80
		SNAP4.74	CCGTGACGCAGCAAGGGTATTGGCAGTGGTAGGTACTGCGTGCGT TGTGGTTCTAGCATGTTTAATGGACACGG	74	RBD	41.9
4.	Daniels et al., [26]	CFA0688T	Not provided in the paper	32	S protein	3.52
5.	Zhang et al., [27]	DSA1N5	TTCCGGTTAATTTATGCTCTACCCGTCCACCTACCGGAATTTTTTTTTTTT TTTTTTTTTTTTTTTTTTACGGGTTTGGC GTCGGGCCTGGCGGGGGGATAGTGC GGT	108	S protein	2.1, 2.3 pM
6.	Rahmati et al., [28]	SNAP1	TCGCTCTTTCCGCTTCTTCGCGGTCATTGTGCATCCTGACTGACCCTA AGGTGCGAACATCGCCCGCGTAAGTCCGTGTGTGCGAA	86	S protein	Not stated
7.	Negahdary et al., [29]	AptHsp70-1	GGGAGACAAGAAUAAACGCUCAAUGCGCUGAAUGCCCAGCCGU GAAAGCGUCGAUUUCCAUCCUUCGACAGGAGGCUCACAACAGGC	87	HSP70	61.3
8.	Yoon et al., [16]	MangoAptamer	GTACGACAACTACCCCATACCAAACCTTCCTTCGTACTTAAAAATCC CGGCCAGATTTTGCCAATCA	67	N gene	Not stated
9.	Wang et al., [30]	L-broccoli	GCCCACACTCTACTCGACAGATACGAATATCTGGACCCGACCGTCTC CCCTATAGTGAGTCGTATTA	67	Viral RNA	Not stated
10.	Singh et al., [31]	Napt 3	GCAATGGTACGGTACTTCCGGATGCGGAAACTGGCTAATTGGTGAGGCTGGGGCGGT	57	N protein	Not stated
		CoV2-RBD-1	ATCCAGAGTGACGCAGCACCGACCTTGTGCTTTGGGAGTGCTG GT CCAAGGGCGTTAATGGACACGGTGGCTTAGT	76	RBD	5.8
11.	Luo et al., [13]	Np-A	GCTGGATGTCGCTTACGACAATATTCCTTAGGGGCACCGCTACATTGACACATCCAGC	58	N protein	0.024
12.	Gu et al., [32]	CoV2-RBD-1	ATCCAGAGTGACGCAGCACCGACCTTGTGCTTTGGGAGTGCTG GT CCAAGGGCGTTAATGGACACGGTGGCTTAGT	76	S Protein	5.8
13.	Park et al., [14]	SpS1-C1	GAACATTGGCGTCCGTGAGTGAGACCATAGTCCAGCGAACTAAACC TACCCTAAAGGGCAAGGAAGACGGG CACTTCCTCAAACGCCCAA	90	S protein	1.47
		SpS1-C4	GAACATTGGCGTCCGTGAGCAGCTCGTGGTTGTTTGCTTGTATACT TTTGTGGTTTATCTTGTTTCTGATCACTTCCTCAAACGCCCAA	89	S protein	1.89
14.	Torun et al., [33]	CoV2-RBD-4C	ATCCAGAGTGACGCAGCATTTCATCGGGTCCAAAAGGGGCTGCTC GGGATTGCGGATATGGACACGT	67	RBD	19.9

HSP70: Heat shock protein 70.

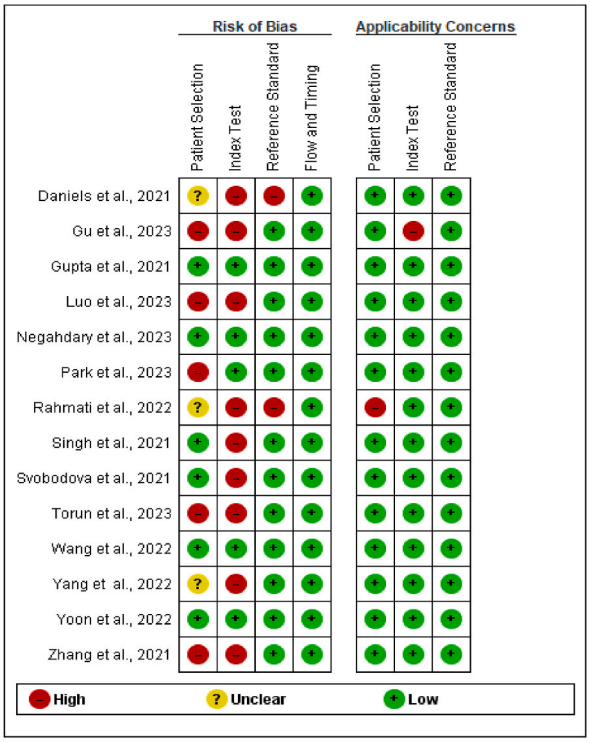

Fig. 2. Summary of the risks of bias and applicability concerns: Authors' judgement of each domain for all the studies included in the review.

Table 3
Detailed assessment of quality of the included articles.

S/N	Author(s)	Risk of Bias				Applicability Concerns			Quality
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard	
1.	Gupta et al., [18]	Low	Low	Low	Low	Low	Low	Low	High
2.	Svobodova et al., [15]	Low	High	Low	Low	Low	Low	Low	Low
3.	Yang et al., [19]	Unclear	High	Low	Low	Low	Low	Low	Low
4.	Daniels et al., [26]	Unclear	High	High	Low	Low	Low	Low	Low
5.	Zhang et al., [27]	High	High	Low	Low	Low	Low	Low	Low
6.	Rahmati et al., [28]	Unclear	High	High	Low	High	Low	Low	Low
7.	Negahdary et al., [29]	Low	Low	Low	Low	Low	Low	Low	High
8.	Yoon et al., [16]	Low	Low	Low	Low	Low	Low	Low	High
9.	Wang et al., [30]	Low	Low	Low	Low	Low	Low	Low	High
10.	Singh et al., [31]	Low	High	Low	Low	Low	Low	Low	Low
11.	Luo et al., [13]	High	High	Low	Low	Low	Low	Low	Low
12.	Gu et al., [32]	High	High	Low	Low	Low	High	Low	Low
13.	Park et al., [14]	High	Low	Low	Low	Low	Low	Low	Low
14.	Torun et al., [33]	High	High	Low	Low	Low	Low	Low	Low

Authors' judgement of each domain for all the studies included in the review.

The threshold effect was ruled out with a p value of 0.667 (>0.05) and a corresponding spearman coefficient of correlation of −0.500. Neither of the factors contributed to the heterogeneity, based on the analysis of meta-regression ($p > 0.05$ for both). Subgroup analyses were not conducted due to the limited number of articles in each of the subgroups. Table 4 summarizes the diagnostic accuracy metrics for each platform.

4. Discussion

In this study, an aggregate of 1082 clinical specimen drawn from 14 the included articles were analysed to determine the diagnostic

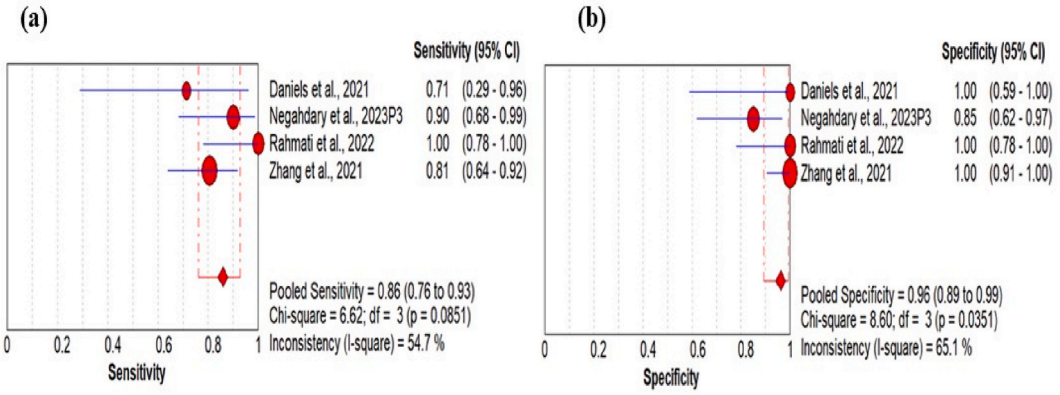

Fig. 3. Forest plots of studies using electrochemical aptamer-based biosensor in detecting SARS-CoV-2: (a) Sensitivity. (b) Specificity.

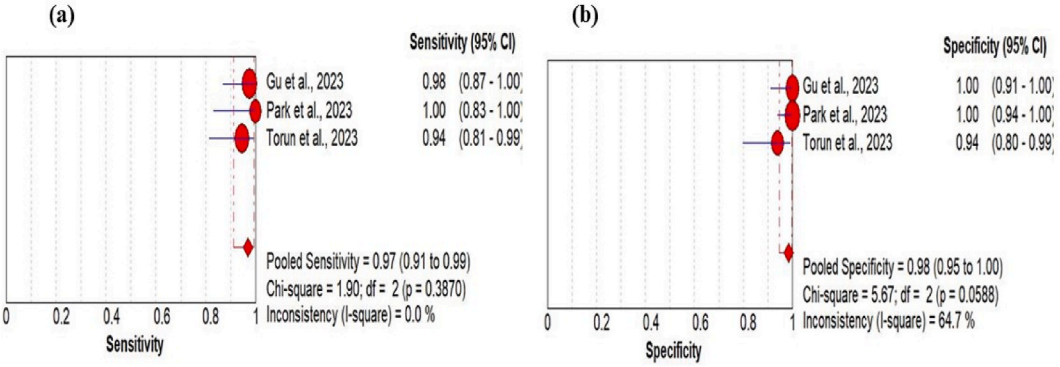

Fig. 4. Forest plots of studies using SERS aptamer-based biosensor in detecting SARS-CoV-2. (a) Sensitivity. (b) Specificity.

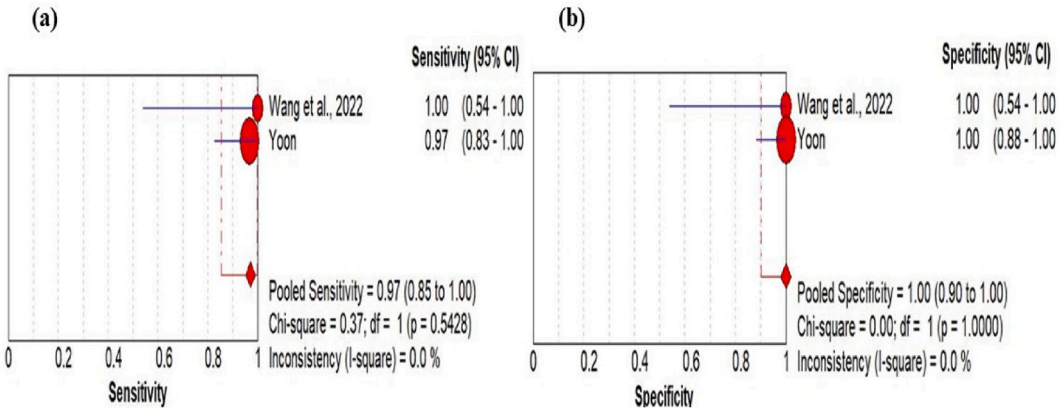

Fig. 5. Forest plots of studies using fluorescence aptamer-based biosensor in detecting SARS-CoV-2. (a) Sensitivity. (b) Specificity.

performance of different aptamer-based biosensors for the detection of SARS-CoV-2. Different aptamer-based sensing platforms targeting different genes of the virus were previously used for its detection in clinical samples. Literatures were searched, retrieved and the diagnostic accuracy of aptamer-based electrochemical, SERS, fluorescence and ELONA sensing platforms were analysed. However, data for optical [13] and glucometer [31] platforms were not evaluated as each of these platforms had only one article included.

An electrochemical aptasensor usually comprises a biorecognition element, a signal converter, and an electronic module that incorporates a signal enhancer, a data processor, and an output interface for display. It detects a target analyte by using a selective biological element to detect a biological process and converting it to a detectable signal that provides either precise numerical measurements or approximate estimations [34]. Detection of these signals can be performed using the famous cyclic voltametric

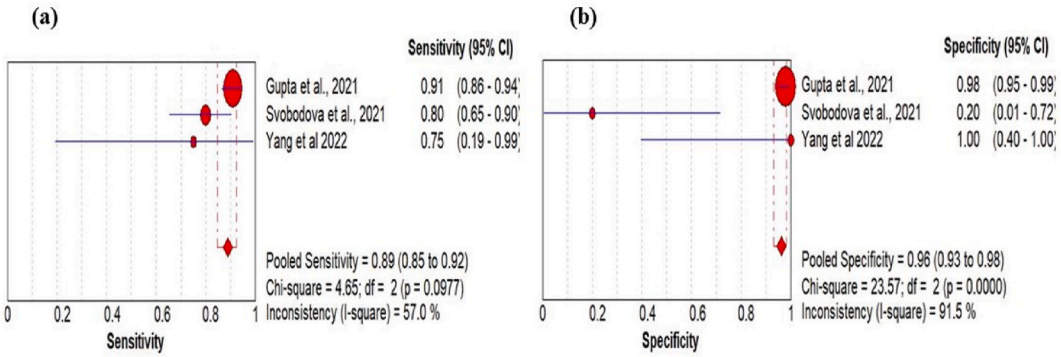

Fig. 6. Forest plots of studies using ELONA aptamer-based biosensors in detecting SARS-CoV-2. (a) Sensitivity. (b) Specificity.

Table 4
Accuracy measures of aptamer-based biosensor in detecting SARS-CoV-2.

Platform	Sensitivity (95 % CI)	Specificity (95 % CI)	PLR (95 % CI)	NLR (95 % CI)	DOR (95 % CI)	AUC
Electrochemical	0.86(0.76–0.93)	0.96(0.89–0.99)	12.78(3.62–45.08)	0.19(0.10–0.36)	96.40(25.10–370.25)	0.96
SERS	0.97(0.91–0.99)	0.98(0.95–1.00)	33.09(8.53–128.36)	0.04(0.02–0.12)	766.63(133.85–4391.03)	0.98
Fluorescence	0.97(0.85–1.00)	1.00(0.90–1.00)	27.15(3.98–185.00)	0.06(0.01–0.12)	560.57(44.45–7069.26)	0.50
ELONA	0.89(0.85–0.92)	0.96(0.93–0.98)	6.61(0.06–769.32)	0.25(0.06–1.06)	23.17(0.30–1788.58)	0.93

Summary of diagnostic accuracy measures of aptamer-based biosensors in detecting of SARS-CoV-2 from clinical specimens.

technique (CV), pulse voltametric technique (DPV), wave voltametric technique (SWV), or the impedance spectroscopic technique (EIS) [35,36].

SERS-based aptasensors offer exceptionally high detection sensitivity by utilizing a functional substrate to analyse the molecular composition of a target through the detection of vibrational signals, amplified by localized electromagnetic fields [14,37]. Aptamer-based diagnostics using SERS do away with the requirement for additional reagents, complex standardization, or intricate preprocessing, enabling the rapid detection of target molecules [38,39]. Moreover, SERS aptasensors allow for highly sensitive analysis down to the single-molecule scale, ensuring precise detection [40,41]. The performance of SERS aptasensors can be further optimized by carefully selecting an efficient active substrate and a compatible laser wavelength, enabling rapid and ultra-sensitive analyte recognition and detection [32].

In a fluorescent aptamer-based biosensor, a fluorescent probe and a suppressor molecule are attached to opposite ends of the aptamer. Upon interaction with the target molecule, the aptamer undergoes a change in conformation, bringing the probe and suppressor in proximity to the target. This triggers the fluorescence suppression, leading to either an enhanced signal (“turn-on” mode) or a reduced signal (“turn-off” mode) [42]. The resulting change in fluorescence intensity correlates with the binding event, enabling the identification and measurement of the target molecule [43].

The aptamer-based ELONA biosensor has the same protocol and principle as the conventional ELISA. However, it uses an immobilized aptamer instead of the traditional antibody to selectively recognise and bind a target molecule from a specimen. In turn, an aptamer bound target complex is linked to an enzyme such as the horseradish peroxidase (HRP) and a detectable colorimetric signal is generated when the enzyme interacts with a compatible substrate like 3,3′,5,5′-Tetramethylbenzidine (TMB). This reaction facilitates accurate detection and quantification of the target molecule in a multi-well microplate [44].

Sensitivity and specificity are true test performance statistics, with sensitivity determining the ratio of positive samples to samples tested positive compared to a reference test while specificity determining the ratio of negative samples to samples tested negative with a reference test [45,46]. Table 4 shows that the aptamer-based SERS biosensing platform outperformed the electrochemical, fluorescent, and ELONA platforms in relation to pooled sensitivity and specificity. The SERS platform also has the best PLR compared to other platforms with a value of 33.09. This result indicates that SERS platform can accurately be used in the diagnosis of SARS-CoV-2 infection [14]. Sensitivity and specificity are critical in evaluating the DOR. For instance, a high DOR was observed in tests with low FPs and FNs but with good sensitivity andspecificity [47].The SERS platform had the best pooled DOR among the platforms in our meta-analysis. The combined diagnostic accuracy determinants such as the AUC, DOR, sensitivity, specificity as well as the ratio of likelihood all proved that the SERS platform is greatly sensitive of SARS-CoV-2 detection. Nevertheless, all the included studies in the SERS platform were of low quality.

High homogeneity was observed in the studies included in three of the platforms (electrochemistry, SERS and fluorescence). However, high heterogeneity was observed in the ELONA platform studies, and Spearman correlation results indicate that the heterogeneity is unconnected with effect of threshold. However, because of the lack of enough studies, no subgroup analysis was performed. One possible explanation for the observed heterogeneity might be the considerably varying size of the samples used in the articles included in the analysis. In addition, the insufficient retrieved articles in the ELONA platform might have biased the results.

Overall, the SERS platform has better diagnostic performance compared with other platforms. However, the fluorescence platform

is better in terms of specificity and most of the included articles in that platform were of high quality. In addition, it is the second-best platform in terms of higher values for sensitivity, specificity, PLR, DOR and a lower NLR. It is closely followed by the electrochemical platform and ELONA has the lowest performance. Despite its high accuracy, various constraints prevent the broad usage of SERS in diagnostics, particularly as a point of care testing (POCT) device and in areas with limited resources, considering the expensive and complex nature of its instruments [48]. Another major drawback is the reproducibility of SERS at the diagnostic level, which is not yet sufficient for widespread use [49]. As a result of these obstacles, other platforms, such as electrochemical and fluorescence-based approaches, may be more desirable for a scaled and accessible diagnostic application.

The results from the analysis of the articles included for three of the platforms (SERS, fluorescence and electrochemistry) showed good performance with highly homogenous studies, implying that the outcomes are reliable. It should be noted, however, that the findings of this meta-analysis should be carefully judged because only few available studies were included for each of the platforms and therefore are insufficient to make generalizations.

This meta-analysis has several notable limitations. First, very few articles fulfilled the study's inclusion requirements and the sample size was so small that the results could not be generalized. Furthermore, the quality of the studies was not consistent, and majority of the included studies were conducted cross-sectionally, with not a single randomized control trial (RCT) included. Furthermore, not all studies reported important demographic data such as age and sex of the participants, and most studies tended to focus on analytical validation of the platforms with poor protocol for clinical evaluation. Similarly, the detection limits of the included studies were not homogeneous within the platforms because the studies were conducted by different investigators. Finally, the different aptamer sequences used in the different studies within the same platform differed in terms of binding affinity and stability and hence, might have affected their sensitivity and specificity [50,51].

5. Conclusion

The present study demonstrates that the SERS aptamer sensing platform has high diagnostic accuracy, with fluorescence, electrochemical methods, and ELONA being closely followed as potential sensing platforms for detecting SARS-CoV-2 in clinical samples. However, insufficient studies included to each platform used for the meta-analysis limits any generalization of the pooled results. Nonetheless, subsequent research determining the accuracy of aptamer-based biosensors in diagnosis of COVID-19 should consider increasing the sample size, focus more on clinical trials, conduct randomized control trials, and include and blinded the results of the reference tests to meet inclusion criteria.

CRediT authorship contribution statement

Isa Haruna Mohammed: Writing – original draft, Software, Resources, Methodology, Investigation, Data curation. **Basiru Aliyu:** Writing – original draft, Software, Methodology, Investigation, Data curation. **Peisan E. Sharel:** Writing – review & editing, Validation, Supervision. **Syafinaz Amin-Nordin:** Writing – review & editing, Validation. **Hui Yee Chee:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization.

Data availability statement

Data included in the article/supplementary material is referenced in the article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e43362.

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