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Association Between Rapid Antigen Detection Tests and Real-Time Reverse Transcription–Polymerase Chain Reaction Assay for SARS-CoV-2: A Systematic Review and Meta-Analyses

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Objectives: We aimed to assess the association between rapid antigen detection tests and real-time reverse transcription-polymerase chain reaction assay for severe acute respiratory syndrome coronavirus 2.

Methods: We searched PubMed, Cochrane Library, EMBASE, and the Web of Science from their inception to 31 May 2023. A random-effects meta-analysis was used to estimate false positives in the RADTs group, relative to those in the RT-PCR group, and subgroup analyses were conducted based on the different Ct value cut-offs (<40 or ≥40). We performed this study in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results: Fifty-one studies were included and considered to be of moderate quality. We found a satisfactory overall false positive rate (0.01, 95% CI: 0.00–0.01) for the RADTs compared to RT-PCR. In the stratified analysis, we also found that the false positive rates of the RADTs did not increase when Ct values of RT-PCR (Ct < 40, 0.01, 95% CI: 0.00–0.01; Ct ≥ 40, 0.01, 95% CI: 0.00–0.01).

Conclusion: In conclusion, the best available evidence supports an association between RADTs and RT-PCR. When Ct-values were analyzed using cut-off <40 or ≥40, this resulted in an estimated false positive rate of only 1%.

Keywords: cycle threshold, false-positive, meta-analyses, rapid antigen test, RT-PCR

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INTRODUCTION

COVID-19 remains an ongoing global pandemic, and the return to pre-pandemic normalcy is still projected to be unlikely in the short run [1]. It appears that the new linages are more capable of resisting natural or vaccine-elicited immunity [2, 3]. Hence, new linages may be responsible for major re-infections and mass vaccine breakthroughs, posing overwhelming pressure on health systems [2, 3].

TABLE 1 | Search strategy until 31 May 2023 (Global, 2020–2023).

		PubMed	Embase	Cochrane	Web of science
#1	COVID-19	319,309	339,602	15,682	512,110
#2	SARS-CoV-2	118,872	117,759	6,097	105,998
#3	Coronavirus disease 2019	58,559	56,228	6,840	68,305
#4	Novel coronavirus	13,037	12,781	1,307	22,994
#5	#1 or #2 or #3 or #4	348,896	379,230	16,626	522,684
#6	Rapid diagnosis*	18,564	23,911	9,566	129,850
#7	Rapid detection	16,967	18,365	4,626	142,650
#8	Rapid antigen test*	1,161	1,422	816	12,769
#9	Antigen assay	1,018	1,520	3,760	103,490
#10	#6 or #7 or #8 or #9	36,645	44,122	16,504	413,929
#11	False-positive	55,480	75,279	2,866	96,888
#12	False-positivity	946	1,433	2,865	1,092
#13	Specificity	555,121	722,365	159,756	708,492
#14	Accuracy	543,919	687,288	27,808	1,650,362
#15	#11 or #12 or #13 or #14	1,045,545	1,328,795	179,150	3,571,103
#16	Cycle threshold	2,450	3,123	2,347	27,950
#17	ct	432,005	719,831	83,312	525,013
#18	#16 or #17	432,942	721,178	85,438	550,337
#19	#5 and #10 and #15 and #18	264	270	22	564

* *means truncated word.*

Frequent early testing of infectious persons, in combination with contact tracing and isolation, are key factors that mitigate transmission [4]. However, false negatives, false positives, and other inaccurate results make it even more challenging for governing authorities to set effective control strategies and make timely medical decisions [5]. Therefore, policymakers have focused on these problems and explored some cost-effective tests [6, 7].

To improve sensitivity and specificity, reverse transcription-polymerase chain reaction (RT-PCR) has been the standard method for detecting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since the beginning of the pandemic [8]. However, RT-PCR testing needs a remarkably long turnaround time and relies heavily on sophisticated equipment and highly trained personnel. This limits its application in mass-oriented testing campaigns [9]. Thus, the World Health Organization (WHO) recommended simple and rapid antigen detection tests (RADTs) in communities to serve the purpose of detection and contact tracing, as well as outbreak investigations [10]. This technique does not need trained experts and professional instruments and can offer results within 15 min, making it possible to identify those potentially infected with COVID-19 on time [11]. However, the WHO suggests a minimum of 80% sensitivity and 97% specificity to adopt RADTs [12], since their performance is inconsistent in diverse settings according to published research [13].

Moreover, data on the performance of self-testing with RADTs compared to RT-PCR detection of SARS-CoV-2 RNA is very limited. Previous studies have demonstrated the accuracy of RADTs [13, 14], while few have explored the relationship between RADTs and cycle threshold (Ct) value cut-offs, allowing a gap for further research. Ct values vary in different areas and are dynamically adjusted. From a clinical viewpoint, there is no consistent standardization between laboratories and assays. Thus, we aimed to explore the association between RADTs and RT-PCR for SARS-CoV-2 based on the disparity of the Ct value.

METHODS

Literature Search

We conducted the meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. We performed a systematic search of the databases PubMed, Cochrane Library, EMBASE, and the Web of Science from their inception to 31 May 2023. The main search terms were "[(COVID-19 OR SARS-CoV-2 OR Coronavirus disease 2019 OR Novel coronavirus) AND (Rapid diagnosis* OR Rapid detection OR Rapid antigen test* OR Antigen assay) AND (false-positive OR false-positivity OR specificity OR accuracy)] AND (cycle threshold OR Ct)] (**Table 1**). We also searched the previous reviews for relevant studies. We registered this systematic review on PROSPERO (registration number: CRD42022351138). No language restrictions were applied.

Inclusion Criteria and Exclusion Criteria

We included studies evaluating the specificity or false-positivity of commercially available RADTs for diagnosis of SARS-CoV-2 infection, against RT-PCR as a reference standard. Cohort studies, nested cohort studies, and case-control or cross-sectional studies as well as randomized studies were considered. Studies carried out in various locations, targeted at individuals of any age despite presence of symptoms were pooled in our study. Studies without reporting a Ct value cut-off were excluded.

Study Selection and Data Extraction

Two authors (Y-PY and ZJ) independently scanned the titles and abstracts of the search results in Endnote X9 to retrieve relevant records and obtained a full-text review of those eligible articles that met our inclusion criteria. Then, a third author (T-HT) was invited to settle any conflicts or

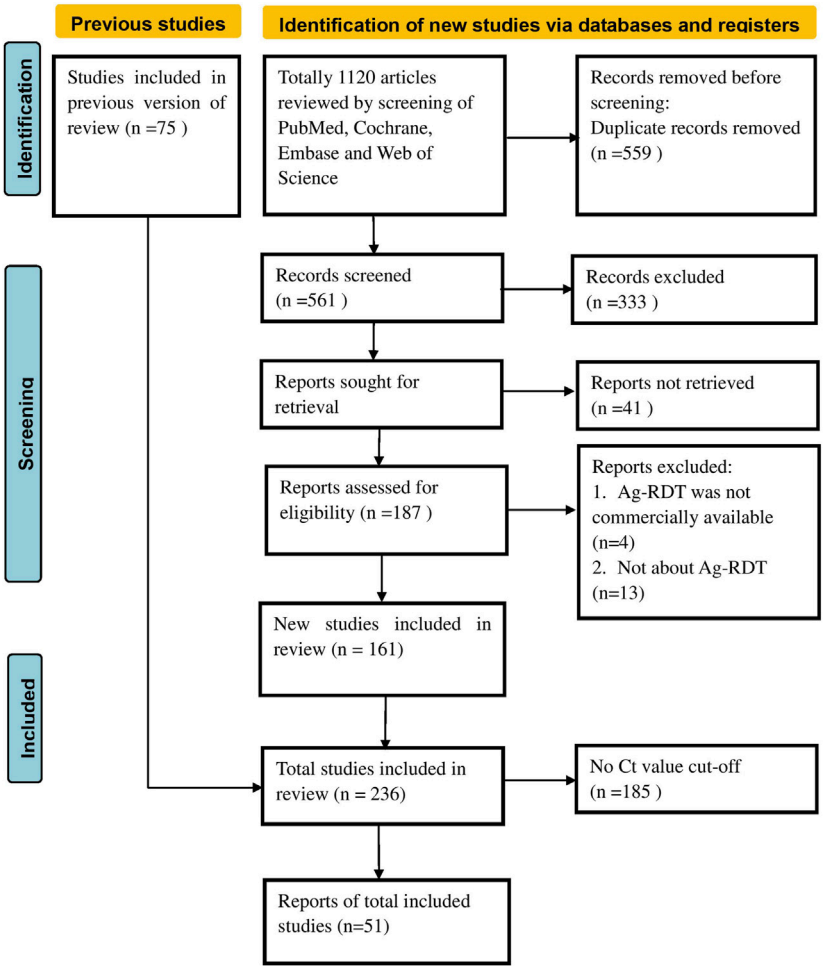

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses flow chart (Global, 2020–2023).

disputes. **Figure 1** illustrates the flowchart of the screening process. Based on the previously defined excluded criteria, 51 papers written in the English language were included in the final meta-analysis.

Afterward, data extraction was performed by an author per paper and reviewed by a second. The following data were extracted from included studies using a data-extraction form: first author, nation, sample size, sample condition, index tests, false positives, and Ct cut-off values.

Statistical Analysis

We used STATA Version 17.0 software to conduct the meta-analysis. Subgroup analysis was conducted based on different Ct value cut-offs (<40 or ≥40). The main indicators used were percentage ratios and 95% confidence intervals (CIs) of false positives in the RADTs group relative to those in the RT-PCR group. The I^2 statistic was used to assess the level of statistical heterogeneity, and an I^2 value of ≥50% confirmed heterogeneity [15]. We conducted a random-effect model meta-analysis because we expected considerable clinical heterogeneity. In addition to an overall evaluation, we also conducted a sub-group meta-analysis for Ct value cut-off with <40 and those ≥40. We evaluated the quality of the evidence for each outcome using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) protocols, which classified evidence as very low, low, moderate, or high [16].

RESULTS

The main characteristics of the included studies are summarized in **Table 2**.

All 51 included studies [17–67] evaluated the false positive rates of RADTs with respect to the standard RT- PCR while reporting a Ct cut-off value. The most common sample type evaluated was NP (44/51), followed by mixed NP/OP (5/51). We divided the 51 studies into 74 data sets. The overall pooled estimates of false positive rates of RADTs were 1% (95% CI: 0.00–0.01) compared to RT-PCR (**Figure 2**). In the stratified

TABLE 2 | Characteristics of the included studies (Global, 2020–2023).

First author	Nation	Sample size	Sample condition	Index tests	Specimens	False-positive	Ct value
[17]	Japan	226	Fresh	ESPLINE SARS-CoV-2	NP	0.0%	30
[18]	Netherlands	1,367	Fresh	Abbott, Panbio	NP	0% (95% CI: 0%–0.3%)	32
		208				0% (95% CI: 0%–2.5%)	
[19]	India	677	Fresh	PathoCatch/ACCUCARE	NP	0.2% (95% CI 0.0%–0.9%)	32
[20]	India	473	Fresh	STANDARD Q, SD Biosensor	NP	0.76% (95% CI: 0.16%–2.21%)	35
[21]	Korea	175	Fresh	STANDARD Q, SD Biosensor	NP	0.0%	35
[22]	Canada	1,641	Fresh	Abbott, Panbio	NP	0.1% (95% CI 0.0%–0.5%)	35
[23]	Italy	392	Fresh	Lumipulse® SARS-CoV-2 assay	NP	2.0% (95% CI 0.0%–3.0%)	35
[24]	Italy	5,136	Fresh	Panbio	NP	0.3% (95% CI 0.2%–0.6%)	35
[25]	India	1,034	Fresh	Standard™	NP	5.3% (95% CI 3.7%–7.4%)	35
[26]	Fresh	189	Fresh	Standard Q	NP	0.0%	35
[27]	India	329	Fresh	RAT kit (Zydus Cadila, India)	NP	1.11% (95% CI 0.13%–3.96%)	35
[28]	China	83	Fresh	The COVID-19 Combo Kit (Zhijiang Biotechnology Co., Ltd., Shanghai, CN)	NP	0.0%	35
[29]	France	248	Fresh	COVID-VIRO®	NP	0.0%	37
[30]	Ethiopia	200	Banked	Standard Q	NP	3.0% (95% CI 0.6%–8.5%)	37
[31]	Sri Lanka	4,786	Fresh	STANDARD Q, SD Biosensor	NP	2.4% (95% CI 2.0%–3.0%)	38
		3,325		Abbott, PanBio		0.4% (95% CI 0.2%–0.8%)	
[32]	Republic of Korea	170	Banked	MARK-B	NP	1.0% (95% CI 0.1%–5.0%)	38
		170		Standard Q, SD Biosensor		0.0% (95% CI 0.0%–3.3%)	
[33]	Belgium	232	Fresh	BioSpeedia Abbott, Panbio	NP	0.0%	39
[34]	Uganda	247	Fresh	BIOCREDIT	NP	1.8% (95% CI 0.4%–6.9%)	39
		194		COVID-19 Ag Respi-Strip		0.8% (95% CI 0.1%–5.5%)	
		172		PCL		10.1% (95% CI 5.1%–19.2%)	
		243		MEDsan1		0.0% (95% CI 0.0%–3.1%)	
		185		Abbott, Panbio		0.0% (95% CI 0.0%–3.6%)	
		229		Novegent		10.1% (95% CI 5.9%–16.7%)	
		263		VivaDiag™		5.9% (95% CI 3.4%–9.9%)	
[35]	Egypt	94	Banked	Artron COVID-19 Antigen test	NP	0.0%	39
[36]	Thailand	1,100	Fresh	STANDARD Q, SD Biosensor	Unclear	0.29% (95% CI: 0.06%–0.85%)	40
[37]	Korea	165	Banked	STANDARDQ, SD Biosensor	NP	4.0% (95% CI: 1.1%–9.9%)	40
[38]	China	251	Fresh	Fluorescence immunochromatographic (FIC) assay	NP	0% (95% CI 0%–8.9%)	40
[39]	Kenya	997	Fresh	NowCheck	NP/OP	2.5% (95% CI: (1.5%–3.8%)	40
[40]	Bangladesh	380	Fresh	OnSite®	NP	0.8% (95% CI: (0.1%–2.9%)	40
[41]	Belgium	328	Banked	COVID-19 Ag Respi-Strip	NP	0.5% (95% CI: 0.0%–2.8%)	40

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TABLE 2 | (*Continued*) Characteristics of the included studies (Global, 2020–2023).

First author	Nation	Sample size	Sample condition	Index tests	Specimens	False-positive	Ct value
[42]	Austria	392	Fresh	AMP, AMEDA Labordiagnostik GmbH, Graz, Austria	NP	0.3% (95% CI 0.0%–1.9%)	40
[43]	Chile	842	Fresh	STANDARD Q, SD Biosensor	NP	0.4% (95% CI: 0.1%–1.1%)	40
[44]	Netherlands	825	Fresh	Abbott, Panbio	NP	0% (95% CI: 0.0%–1.2%)	40
[45]	Italy	403	Fresh	Elecsys SARS- CoV- 2 antigen assay	NP	0.0% (95% CI 0.0%–1.0%)	40
[46]	Korea	296	Fresh	STANDARD Q, SD Biosensor	NP	0.0% (95% CI 0.0%–1.69%)	40
[47]	Belgium	63	Fresh	CoRDT	NP	0.0%	40
		100		HeRDT		0.0%	
[48]	Italy	169	Frozen	Lumipulse® G	Saliva	2.9% (95% CI 0.6%–4.0%)	40
		127	Fresh			0.0% (95% CI 0.0%–7.9%)	
[49]	Belgium	199	Fresh and banked	GSD NovaGen	NP	14.3% (95% CI 4.5%–24.1%)	40
		199		Cassette, BioRad		0.0%	
		199		Aegle, LumiraDx		0.0%	
[50]	Madagascar	200	Fresh	Standard Q, SD Biosensor	NP	0.0%	40
[51]	Chile	64	Banked	Sofia	NP/OP	3.1% (95% CI 0.6%–15.7%)	40
		64		SD Biosensor, Standard F		3.1% (95% CI 0.6%–15.7%)	
[52]	Republic of Korea	141	Banked	AFIAS	NP	0.2%	40
		156		AFIAS		0.0% (95% CI	
		167		AFIAS		0.0%–2.0%)	
		200		ichroma™			
[53]	Brazil	127	Fresh	Abbott, Panbio	NP	1.8% (95% CI 1.2%–4.0%)	40
[54]	United States	1,384	Fresh	Becton, BD Veritor	NP	1.2% (95% CI 0.7%–1.9%)	40
[55]	Chile	109	Banked	RapiGEN, Biocredit	NP/OP	0.0% (95% CI 0.0%–11.6%)	40
		19		Liming Bio		10.0% (95% CI 1.8%–40.4%)	
		109		Savant Biotechnology Co., Beijing		0.0% (95% CI 0.0%–11.0%)	
		111		Shenzhen Bioeasy Biotechnology		0.0% (95% CI 0.0%–11.2%)	
[56]	Belgium	148	Fresh	Coris BioConcept, COVID-19 Ag Respi-Strip	NP	0.0% (95% CI 0.0%–8.4%)	40
[57]	Belgium	414	Banked	DiaSorin, LIAISON	NP	0.0% (95% CI 0.0%–1.7%)	40
[58]	Italy	226	Banked	Fujirebio, Lumipulse G	NP	7.9% (95% CI 6.6%–9.3%)	40
		1,738	Fresh			8.4% (95% CI 4.3%–14.5%)	
[59]	Thailand	454	Banked	SDBiosensor/Roche, Standard Q	NP/OP	1.3% (95% CI 0.4%–2.9%)	40
[60]	Indonesia	313	Fresh	Ag-RDT kits	NP/OP	0.0%	40
[61]	Austria	175	Fresh	AMP rapid test SARS-CoV-2 Ag	NP	0.0% (95% CI 0.0%–3.3%)	40
[62]	Bangladesh	260	Fresh	BD Veritor, Standard Q	NP	0.0% (95% CI 0.0%–3.0%)	40
[63]	Netherlands	683	Fresh	Panbio™	NP	0.0% (95% CI 0.0%–0.6%)	40
[64]	Kenya	2,245	Fresh	Panbio™	NP	1.5% (95% CI 1.0%–2.2%)	40
[65]	Japan	100	Banked	STANDARD Q	NP	0.0% (95% CI 0.0%–17.0%)	40

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TABLE 2 | (*Continued*) Characteristics of the included studies (Global, 2020–2023).

First author	Nation	Sample size	Sample condition	Index tests	Specimens	False-positive	Ct value
[66]	Serbia	120	Fresh	Standard Q	NP	0.0% (95% CI 0.0%–4.7%)	41
[67]	Korea	370	Fresh	Xpert Xpress	NP	4.6%	45

NP, nasopharyngeal; OP, oropharyngeal; AN, anterior nasal.

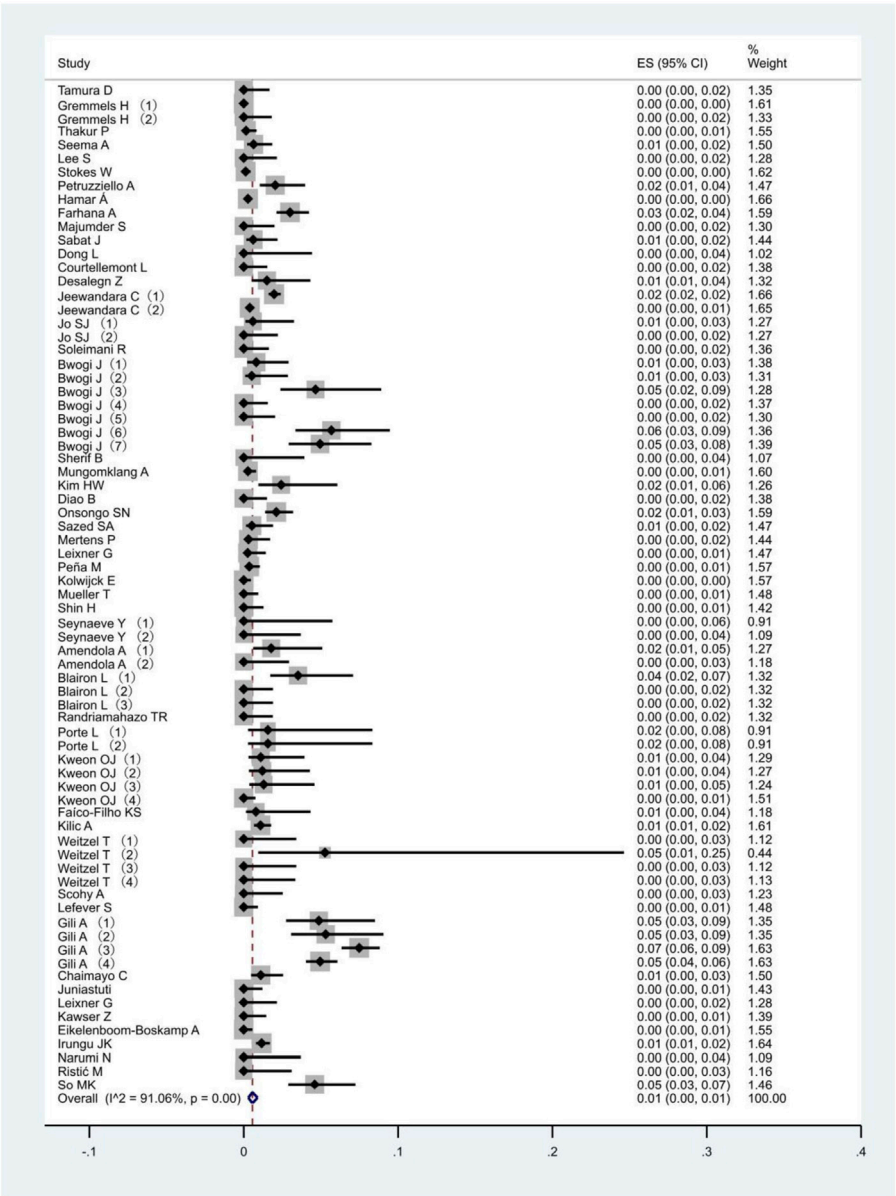

FIGURE 2 | Meta-analysis of the false positive in all people (Global, 2020–2023).

analysis, a similar pattern was observed when Ct-values were analyzed using cut-off <40 or ≥40, resulting in an estimated false positive rate of 1% (95% CI: 0.00–0.01) and 1% (95% CI: 0.00–0.01), respectively (**Figures 3A,B**).

The summary of findings and the GRADE assessment for each outcome is presented in **Table 3**. The quality of evidence from the included studies was initially judged to be moderate due to imprecision.

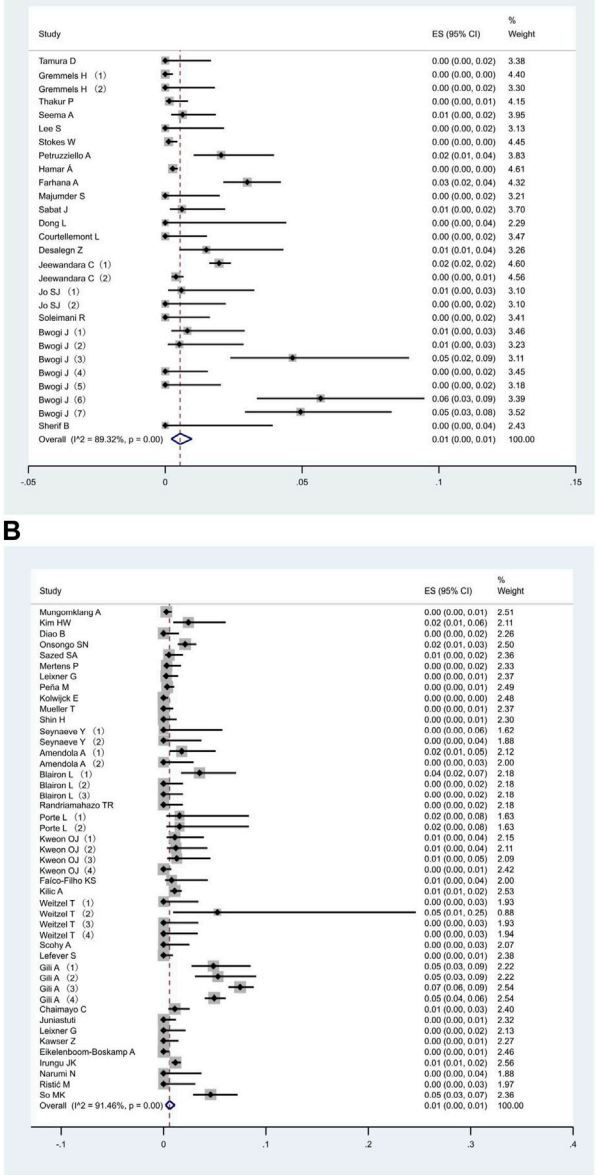

FIGURE 3 | Meta-analysis of the false positive in people with Ct value cut-off <40 **(A)** and ≥40 **(B)** (Global, 2020–2023).

DISCUSSION

Clinical Implications

Although COVID-19 is not a chronic disease, it meets the Wilson criteria for screening due to the following facts: it is an important health problem; its natural history and side effects are well understood; there is a recognizable latent or early symptomatic stage; a test is easy to perform and its acceptably, accurately, reliably, sensitively and specifically easy to interpret; an accepted treatment is recognized for the disease; treatment is more effective if started early; a policy on who should be treated has been in execution; timely diagnosis and treatment are cost-effective, and case finding should be a continuous process [68].

To our knowledge, this is the first systematic review and meta-analysis that explores the relationship between RADTs and Ct value cut-offs. We integrated data from 51 studies to evaluate the false positive rates of RADTs. We found an overall satisfactory false positive rate (0.01, 95% CI: 0.00–0.01) for RADTs compared to RT-PCR. In the stratified analysis, we also found that false positive rates of RADTs did not increase when Ct values of RT-PCR increased (Ct < 40, 0.01, 95% CI: 0.00–0.01; Ct ≥ 40, 95% CI: 0.00–0.01).

Amplification of genomic sequence of RT-PCR is measured in Ct values. Reporting this Ct value or calculating viral load aids in interpretation and clinical decision-making [69]. However, there are controversies on how thresholds for infectivity shall be defined [70]. A previously published meta-analysis [71] showed that

RADTs present high sensitivity and specificity in detecting COVID-19 but not in exploring the relationship between Ct values and sensitivity/specificity. Since it is difficult to standardize Ct values across different systems and research teams, we could not compare the results between the studies included with different Ct values [71]. Many qPCR assays introduced a Ct cut-off of 40 for infectivity, allowing the detection of very few starting RNA molecules [69]. Our study was able to prove further the effectiveness of the association between RADTs and RT-PCR in different groups of Ct-Values.

Furthermore, it is of great necessity to carry out mass testing in communities as a major strategy for transmission control to minimize the spread of the infection because statistics show that those who never develop symptoms or are still in the before-symptom-onset stage can be quite contagious [72]. Therefore, self-testing using RADTs is vital in low-cost, resource-saving infection control [73]. Meanwhile, swab sampling from the oral or anterior nasal (AN) is less invasive and more efficient in improving compliance and testing frequency. Therefore, if such tests are adopted in community screening, especially in densely populated sites like schools and universities, rest homes, clinics, and prisons, they may help to reduce or even eliminate transmission significantly [58]. As it is easy to perform, all individuals can collect samples independently. This would eventually reduce the quarantine time for the potentially infected [69] and allow individuals to return to their regular work as early as possible. But the prerequisite for a reliable and validated SARS-CoV-2 test is compliance with negative and traditional physical preventive measures like face masks and social distancing that must be strictly observed [74]. Besides, such diagnostic capability would also enable policymakers to evaluate and adjust restrictive rules like quarantine duration and business shutdown period to ensure quick recovery of the economy.

The clinicians could also adjust discharge criteria according to Ct values and determine when the patient can discontinue isolation (which will shorten the hospitalization and isolation time of patients further and avoid unnecessary isolation treatment and waste of medical resources). The adjustment of Ct-values has implications in public health screening, enabling

TABLE 3 | GRADE summary of findings (Global, 2020–2023).

False positive rates

Patient or population
Setting: Netherlands, India, Korea, Canada, France, Sri Lanka, Republic of Korea, Belgium, Uganda, Thailand, Bangladesh, Austria, Chile, Italy, Madagascar, United States, Serbia
Intervention*: RADTs

Outcomes	Event	Total	Effect size (95% CI)	Quality of the evidence (GRADE)	Comments
False positive rates	209	22,688	0.01 (0.00, 0.01)	⊕⊕⊕O Moderate	CT < 40
False positive rates	357	19,436	0.01 (0.00, 0.01)	⊕⊕⊕O Moderate	CT ≥ 40
False positive rates	566	42,124	0.01 (0.00, 0.01)	⊕⊕⊕O Moderate	Overall

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval.
GRADE working group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

contact tracers to focus on persons who are most likely to be infectious. Reduced screening performance induced by the low sensitivity of RADTs makes it essential to guarantee effective repetition in close screening [75, 76].

Clinical Practice

The COVID-19 pandemic threatened the effective management of hospital risk. Health care providers should respond timely and effectively to rapidly changing regulations and guidelines [77]. During this period, hospitals need to care for COVID-19 patients, but also those with other diseases. The lower false positive rate and costs of RADTs imply that early and suitable detection was effective.

Nevertheless, the consequences of failing to identify and separate those COVID-19 cases affect the quality of care [78, 79]. Cases that were negative on the RADTs but had clinical symptoms were sent for further RT-PCR testing for timely identification of COVID-19 cases.

RT-PCR is the most important indicator for the clinical diagnosis of COVID-19. However, since it requires substantial manpower and time, rapid and accurate laboratory diagnosis technology is very important. The results of this study implied that RADTs could be considered an alternative for the rapid triage of patients. Although manufacturers' instructions vary, our study provides guidance in the real world: RADTs are easy to conduct, do not require expert knowledge, and the results are obtained within a few minutes, saving time and money. If suspicious patients had similar clinical symptoms but were negative for RCTs, they were further tested with RT-PCR. In addition, RADTs are also suitable for epidemiological analysis, such as group epidemic monitoring and contact tracing. Such integrated strategies could significantly enhance prevention.

RADTs is not only a reasonably inexpensive, simple test with quick results and more accessibility to patients, but is also an important tool that might be more useful in cutting off the chain of transmission by rapidly identifying positive and previous cases, discovering vast numbers of asymptomatic carriers who often migrate from one location to another [80, 81]. In addition, RDTs can provide additional seroepidemiological data and aetiological diagnosis to determine the magnitude of COVID-19 spread within a population [80]. Thus, previous studies indicated that RADTs were recommended for the early detection of patients suspected of having COVID-19 at the peripheral level of the health system and outside hospital settings in low- and middle-income countries [80–82], where there is little access to molecular tests.

Heterogeneity of Meta-Analysis

In the meta-analysis, heterogeneity exists if the sample estimates for the population risk were of different magnitudes [83]. In this study, we used the random effect model when I^2 statistics were 89.32%, 91.46%, and 91.02% for Ct values < 40, Ct values ≥ 40, and overall, respectively. Because of the existence of significant heterogeneity in false positive rates, it is important to assess heterogeneity in the meta-analysis. This could be caused by various factors, including population characteristics, study design, sample quality, antigen test manufacturers' instructions, and Ct cut-off values [7]. We aggregated studies that explicitly reported a Ct cut-off value, but heterogeneity in the results was inevitable.

Methodological Considerations

The strengths of this study are as follows: First, we included all relevant studies from a global database, which are accepted with a relatively high level of evidence. Second, we excluded studies with no control groups to increase comparability and decrease possible heterogeneity. This is because a larger publication bias may exist without control groups. Third, a subgroup meta-analysis was performed to analyze the real association that controlled the independent Ct values. We analyzed the separate effects of the association between RADTs and RT-PCR based on different CT values.

However, there are still several limitations that should be noted when interpreting the findings of this meta-analysis. Firstly, because sources of reagents are very complex and no single diagnosis standard exists, the bias estimated is inevitable. Secondly, ordinary meta-analyses on efficacy render high-quality evidence from randomized controlled trials only. However, it is impossible to randomize people into "RADTs" and "RT-PCR"

categories. Thirdly, few studies considered other potential confounding factors. Fourthly, the variable studied is only at Ct values in a rough range with a cut-off of <40 or ≥40, and it has failed to classify CT value cut-offs in more groups, such as below 29, 30–37, 38–40, and above 40, and add any other factors, for example the type of RADTs and RT-PCRs, the day the patient was examined, the type of reagent, the time to complete the examination, etc. Fifthly, when using the GRADE approach to evaluate the quality of the evidence for each outcome, the current evidence from all selected studies was moderate in imprecision. In the future, more comprehensive studies are recommended to improve the quality of evidence. Finally, only English papers were included, it was very difficult to explore the disparity of languages for the relationship between RADTs and RT-PCRs.

Conclusion

In conclusion, the best available evidence supports an association between RADTs and RT-PCR. When Ct-values were analyzed using cut-off <40 or ≥40, this resulted in an estimated false positive rate of only 1%. However, it is limited, and more trials are warranted. Further studies regarding subgroups according to sex and age are essential to clarifying the subgroup effect.

AUTHOR CONTRIBUTIONS

T-HT conceived the study. Y-PY and ZJ collected the data. Y-PY, T-HT, and ZJ was responsible for the coding of the analyses. Y-PY wrote the first draft of the paper. Y-PY and ZJ searched, sorted and interpreted the relevant literature. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest.

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