Mini Review

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Diagnostic accuracy of Siemens SARS-CoV-2 Antigen (CoV2Ag) chemiluminescent immunoassay for diagnosing acute SARS-CoV-2 infection: a pooled analysis

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Abstract

Background: This article provides a critical literature review and pooled analysis of diagnostic accuracy of the fully-automated Siemens SARS-CoV-2 Antigen (CoV2Ag) chemiluminescent immunoassay for diagnosis of acute SARS-CoV-2 infections.

Methods: An electronic search was conducted in Scopus, PubMed and medRxiv using the keywords ["Siemens AND CoV2Ag"] OR ["Siemens AND SARS-CoV-2 AND antigen"] for capturing studies that investigated the accuracy of Siemens CoV2Ag for diagnosing acute SARS-CoV-2 infection against a reference SARS-CoV-2 molecular test. The retrieved information was used for constructing a 2 × 2 table and for calculating pooled diagnostic sensitivity, specificity, Summary Receiver Operating Characteristic Curve (SROC) and Agreement. This study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting checklist.

Results: Four studies totalling 1,310 respiratory samples (612 with high viral load) were finally included in our analysis. The cumulative area under the curve, accuracy, sensitivity, specificity, were 0.964 (95% CI, 0.957–0.971), 86.9% (95% CI, 84.9–88.7%), 0.79 (95% CI, 0.76–0.82) and 0.98 (95% CI, 0.96–0.99), respectively. The negative (NPV) and positive (PPV) predictive values were 0.77 (0.74–0.79) and 0.98 (95% CI, 0.96–99), respectively. The diagnostic sensitivity in samples with high viral load (i.e., Ct<29–30) was 0.95 (95% CI, 0.93–0.97).

Conclusions: The Siemens CoV2Ag fully-automated and high-throughput immunoassay approximates the minimum performance criteria for general SARS-CoV-2 antigen testing and displays excellent performance in samples with high viral load, thus representing a valuable screening solution for risk assessment in COVID-19 and for limiting viral spread.

Keywords: antigen; COVID-19; diagnosis; immunoassay; SARS-CoV-2.

Introduction

Coronavirus disease 2019 (COVID-19), an ongoing pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become virtually endemic due to universal vaccination and a decreased viral pathogenicity that has gradually developed over time, especially after emergence of the so-called Omicron lineages characterized by high immune escape [1]. Irrespective of the considerably lower clinical and healthcare burden that COVID-19 is now imposing compared to the earlier phases of this pandemic, when mortality rates in hospitalized patients were 5- to 10-fold higher (i.e., around 20% during the "first wave" compared to 3–4% during the "Omicron wave") [2–4], the daily number of new, recurrent or breakthrough SARS-CoV-2 infections remains extraordinarily high. According to the updated statistics of the World Health Organization (WHO) [5], the daily number of SARS-CoV-2 worldwide diagnoses remains as high as ~800,000 at the end of 2022, accompanied by around 3,000 COVID-19 attributable deaths, figures that could also be considerably underestimated due to the remarkable burden of

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undertesting and/or underreporting [6]. Thus, accurate and timely identification and management of SARS-CoV-2 infections remains a primary health care issue all around the world, in order to limit viral circulation and prevent the risk of developing severe/critical illness or long-COVID in infected individuals [7], especially now that the so-called "tripledemic" (COVID-19, Influenza and Respiratory Syncytial Virus) will jeopardize further the timely responsiveness of healthcare [8].

The current WHO recommendations still emphasize the concept that the diagnosis of acute SARS-CoV-2 infection shall be based on identification of unique SARS-CoV-2 sequences (e.g., viral-specific RNA) by means of nucleic acid amplification tests (NAATs), including real-time reverse-transcription polymerase chain reaction (RT-PCR), specifically developed for targeting sequences within the *E*, *RdRP*, *N* and *S* viral genes [9]. The WHO also endorses that SARS-CoV-2 antigen testing, by means of laboratory-based immunoassays or rapid diagnostic tests (RDTs), may be considered a viable option – under particular circumstances – for lowering the pressure on NAAT-performing laboratories and for supporting rapid diagnosis and management of COVID-19 [10]. Nonetheless, such recommendations also endorse the concept that SARS-CoV-2 antigen tests shall be part of validated diagnostic algorithms, and characterized by sufficient level of diagnostic sensitivity (i.e., ≥80%) and diagnostic specificity (i.e., ≥97%) compared to a reference NAAT [11]. The current recommendations of the Working Group on SARS-CoV-2 Variants of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) slightly broaden the potential clinical applications of SARS-CoV-2 antigen testing [12], extending the use of these tests for diagnosing acute SARS-CoV-2 infection in certain low-risk categories (e.g., contacts of positive cases, patients seeking hospital care), as well as for purposes of epidemiologic surveys and/or population screening. To this end, the importance of several technical and analytical aspects has been underpinned by the IFCC Working Group on SARS-CoV-2 Variants, including the fact that these tests shall be preferably constructed to target the SARS-CoV-2 nucleocapsid (N) protein, since this viral domain seems to be exposed to lower selective pressure compared to other protein moieties (e.g., the spike [S] protein), and that the immunoassays must be appropriately validated before introduction, and regularly monitored after usage, in routine diagnostic practice [12]. Importantly, the IFCC Working Group on SARS-CoV-2 Variants also reiterates that laboratory-based immunoassays display higher diagnostic accuracy compared to RDTs, as hitherto confirmed by the outcomes of several former meta-analyses [13–15]. In keeping with these previous indications, the European Centre for Disease Prevention and Control (ECDC) has also identified minimum performance criteria of ≥80% diagnostic sensitivity and ≥97% diagnostic specificity for enabling the clinical use of these tests, concurrently advising that accurate and systematic clinical validation must be conducted before and after introducing new SARS-CoV-2 antigen tests in clinical practice [16].

Since the diagnostic market of SARS-CoV-2 antigen immunoassays is continuously expanding, this article provides a critical literature review and a pooled analysis of diagnostic accuracy of the novel Siemens SARS-CoV-2 Antigen (CoV2Ag) fully-automated chemiluminescent immunoassay, in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting checklist.

Materials and methods

Brief method description

The SARS-CoV-2 Antigen (CoV2Ag) test (Siemens Healthineers, Erlangen Germany) is a high-throughput, laboratory-based, fully-automated SARS-CoV-2 antigen chemiluminescent immunoassay (CLIA; based on acridinium ester), available on Siemens ADVIA Centaur (XP/XPT) and Siemens Atellica (IM) immunochemistry platforms (Siemens Healthineers). The test encompasses the use of five different monoclonal antibodies targeting the N-terminal and C-terminal domains of the SARS-CoV-2 N protein. SARS-CoV-2 N antigen detection can be performed on nasopharyngeal swabs or anterior nasal specimens, preferably collected in Siemens Sample Inactivation Media (Siemens Healthineers). The sample volume is around 100 µL. The reported limit of detection (LoD) of the test is 31.2 $TCID_{50}$ (Median Tissue Culture Infectious Dose)/mL, test results are generated as "index values" (IV), with results displaying IV ≥1.0 classified as reactive (i.e., positive), over a range of linearity spanning between 0.10 and 1000 IV. The time to first result is between 26 and 28 min, whilst the throughput is 125 and 200 tests/hour on ADVIA Centaur and Atellica, respectively. According to manufacturer's specifications, the positive percent agreement with a reference SARS-CoV-2 molecular assay is 96.4–96.5% and 92.3–93.1% in nasopharyngeal swabs of symptomatic and asymptomatic patients with viral load (cycle threshold; Ct) <30, as well as 98.9 and 100% in anterior nasal swabs of symptomatic and asymptomatic patients with Ct<30, respectively. In all circumstances, the negative percent agreement with a reference SARS-CoV-2 molecular assay is reported to be ≥98%.

Search strategy

We conducted an electronic search on the scientific databases Scopus, Medline (PubMed interface) and medRxiv, using the keywords ["Siemens AND CoV2Ag"] OR ["Siemens AND SARS-CoV-2 AND nucleocapsid"] in the search fields "Title", "Abstract" and "Keywords", without using any language or time limits (i.e., up to December 20, 2022), aimed at capturing all clinical studies that explored the accuracy of Siemens

CoV2Ag for diagnosis of acute SARS-CoV-2 infection compared with a reference SARS-CoV-2 NAAT. Two authors (G.L. and B.M.H.) screened the documents identified with these search criteria by reading the title, abstract and full text (whenever available), selecting all studies where the rate of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) cases could be extracted directly from the text or obtained by request (i.e., emailing) to the corresponding author. The reference list of all initially selected articles was systematically scrutinized with the purpose of identifying additional pertinent investigations.

The data of the selected articles were extracted and used for constructing a 2×2 table, thus enabling the calculation of pooled diagnostic sensitivity and specificity, summary receiver operating characteristic curve (SROC) and agreement with their respective 95% confidence interval (95% CI). We conducted two separate analyses for calculating the diagnostic accuracy in all respiratory samples, as well as in those arbitrarily classified as having a "high viral load". Mantel-Haenszel test and random effects model were used for pooling data, whilst heterogeneity was estimated using χ^2 test and I^2 statistic. The statistical analysis was performed with Meta-DiSc 1.4 (Unit of Clinical Biostatistics team of the Ramón y Cajal Hospital, Madrid, Spain) [17].

This pooled analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Checklist available as Supplementary File 1) and conducted in agreement with the Declaration of Helsinki and within the terms of local legislation. No Ethical Committee approval was deemed necessary for performing this critical literature review and meta-analysis.

Results

The electronic search conducted using Scopus, PubMed and medRxiv according to the aforementioned criteria enabled the initial identification of 50 items after duplicates elimination. A total number of 46 articles were then excluded because they did not present specific data regarding SARS-CoV-2 antigen testing (n=29), dealt with assessment of clinical performance of the RDT Siemens Clinitest rapid COVID-19 antigen test (n=10), were clinical studies without analysis of test accuracy (n=1), were editorial materials or correspondences (n=2), or were literature reviews (n=4).

Therefore, 4 studies totalling 1,310 respiratory samples (612 of which defined as having high viral load) were finally included in our pooled analysis [18–21]. Tables 1 and 2 summarize the principal characteristics of all selected studies, one of each conducted in Italy, Germany, US and Spain. In two studies each, sample analysis was performed on Atellica and ADVIA Centaur. In three studies molecular and antigenic analysis was carried out in nasopharyngeal samples, while the remaining investigation compared molecular test results in nasopharyngeal samples with Siemens CoV2Ag test conducted in nasal specimens.

The pooled diagnostic performance of Siemens CoV2Ag are shown in Figure 1. The cumulative area under the curve, agreement, sensitivity and specificity were 0.964 (95% CI, 0.957–0.971), 86.9% (95% CI, 84.9–88.7%), 0.79 (95% CI, 0.76–0.82; I^2 statistic, 90.9%) and 0.98 (95% CI, 0.96–0.99; I^2 statistic, 81.0%), respectively. The negative (NPV) and positive (PPV) predictive values were 0.77 (95% CI, 0.74–0.79) and 0.98 (95% CI, 0.96–99), respectively. In samples defined as having high viral load (i.e., Ct<29–30) the pooled diagnostic sensitivity was 0.95 (95% CI, 0.93–0.97; I^2 statistic, 87.4%). Since no data were available in the single studies on the FP and TN rates in respiratory specimens with high viral load, the calculation of cumulative accuracy and diagnostic specificity was not feasible (Figure 2).

Discussion

Although recent evidence suggests that SARS-CoV-2 may have mitigated its pathogenicity over time, COVID-19 remains a deadly disease, associated with a substantially enhanced risk of hospitalization and death in fragile persons and in those with waned or without prior immunity [22]. It is hence undeniable that the way the ongoing pandemic could be managed remains challenging for many political, social and clinical aspects, encompassing also the identification of a sustainable and broadly acceptable diagnostic strategy that must accompany humanity for the foreseeable endemic future. An unprepared and inefficient laboratory response was evident in the early phases of the SARS-CoV-2 outbreak [23]. Nonetheless, the volume of SARS-CoV-2 tests that are unremittingly performed all around the world is still colossal, thus jeopardizing the timely and appropriate management of infected individuals, either symptomatic or asymptomatic. Irrespective of infection containing policies that are being developed and implemented in different countries, SARS-CoV-2 detection remains a mainstay for clinical management of symptomatic patients, as well as for isolating and/or advising asymptomatic individual to adopt appropriate behaviours to prevent further spread of the virus (i.e., isolation, social distancing, use of face mask, and so forth) [24].

The strengths and limitations of using NAATs for widespread diagnosis of SARS-CoV-2 infection are obviously clear, and basically encompass higher diagnostic accuracy coupled with longer turnaround time and lower throughput compared to SARS-CoV-2 antigen immunoassays [25, 26]. An appropriate combination of both molecular and antigen techniques has hence been proposed as a reliable strategy for preserving the integrity of SARS-CoV-2 testing [27], especially in the foreseeable future where this novel infectious disease is very likely to become "harmfully" endemic [28].

Table 1: Summary of studies which investigated the cumulative diagnostic accuracy of Siemens SARS-CoV-2 Antigen (CoV2Ag) chemiluminescent immunoassay for diagnosing SARS-CoV-2 infection in respiratory specimens.

Study	Country	Sample matrix	Sample size	Instrumentation	Molecular assay (gene targets)	Range of viral load
Carta et al., [18]	Italy	Both nasopharyngeal	375	Atellica	Roche Cobas SARS-CoV-2 (*ORF 1 ab* and *E* genes)	Ct, 14–35
Hörber et al., [19]	Germany	Nasal vs. nasopharyngeal	447	Atellica	Applied Biosystems TaqPath COVID-19 RT-PCR (*ORF1ab* and *N*); Hologic Aptima SARS-CoV-2 (ORF1ab); Cepheid GeneXpert SARS-CoV-2 (*E* and *N*)	N/A
Palmer et al., [20]	USA	Both nasopharyngeal	347	ADVIA Centaur	Cepheid GeneXpert SARS-CoV-2 (*E* and *N*)	Ct, 13–42
Ríos et al., [21]	Spain	Both nasopharyngeal	141	ADVIA Centaur	Thermo Fisher Scientific TaqPath™ Multiplex RT-PCR COVID-19 kit (*ORF1ab*, *N* and *S*)	<39

Ct, cycle threshold; N/A, not available.

Table 2: Summary of studies which investigated the diagnostic accuracy of Siemens SARS-CoV-2 Antigen (CoV2Ag) chemiluminescent immunoassay for diagnosing SARS-CoV-2 infection in respiratory specimens with high viral load.

Study	Country	Sample matrix	Sample size		Molecular assay (gene targets)	High viral load definition
Carta et al., [18]	Italy	Nasopharyngeal swabs	85	Atellica	Roche Cobas SARS-CoV-2 (*ORF 1 ab* and *E* genes)	Ct, <29
Hörber et al., [19]	Germany	Nasal vs. nasopharyngeal	213	Atellica	Applied Biosystems TaqPath COVID-19 RT-PCR (*ORF1ab* and *N*); Hologic Aptima SARS-CoV-2 (ORF1ab); Cepheid Xpert Xpress SARS-CoV-2 (*E* and *N*)	Ct, <30
Palmer et al., [20]	USA	Both nasopharyngeal	213	ADVIA Centaur	Cepheid GeneXpert SARS-CoV-2 (*E* and *N*)	Ct, <30
Ríos et al., [21]	Spain	Both nasopharyngeal	101	ADVIA Centaur	Thermo Fisher Scientific TaqPath™ Multiplex RT-PCR COVID-19 kit (*ORF1ab*, *N* and *S*)	Ct, <30

Ct, cycle threshold.

Although many accredited organizations such as the WHO, ECDC and IFCC have now cleared and legitimized the use of SARS-CoV-2 antigen testing for complementing NAAT in various clinical settings, conduction of accurate and methodical validation of assay performance is essential, thus paving the way to a series of clinical studies aimed at evaluating the diagnostic performance of many of these different laboratory-based immunoassays. To this end, we provide here the first pooled analysis of diagnostic accuracy of the novel Siemens CoV2Ag CLIA for diagnosing acute SARS-CoV-2 infection.

Previous analyses that we carried out on commercial, laboratory-based SARS-CoV-2 antigen immunoassays reveal that the diagnostic accuracy of this novel test is aligned with other available techniques. More specifically, a cumulative diagnostic sensitivity of 0.79 would place it behind S-PLEX SARS-CoV-2 N (0.87 sensitivity) [29], LumiraDx SARS-CoV-2 Antigen Test (0.86 sensitivity) [30], Ortho VITROS (0.82 sensitivity) [31], but at the same level of the highly-sensitive Fujirebio Lumipulse SARS-CoV-2 antigen immunoassay (0.80 sensitivity) [32], and at even better levels than Roche Elecsys (0.68 sensitivity) [33] and DiaSorin Liaison (0.51 sensitivity) [34]. The diagnostic specificity of Siemens CoV2Ag was found to be as high as 0.98, thus substantially aligned to that observed with other laboratory-based immunoassays [29–34].

As concerns the cumulative diagnostic accuracy, again Siemens CoV2Ag displays an AUC of 0.964, lower than that found for Ortho VITROS (0.995 AUC) [31], Fujirebio Lumipulse SARS-CoV-2 antigen immunoassay (0.980 AUC) [32], LumiraDx SARS-CoV-2 Antigen Test (0.974 AUC) [30], but higher than that observed for Roche Elecsys (0.958 AUC) [33], S-PLEX SARS-CoV-2 N (0.955 AUC) [29], and DiaSorin Liaison (0.911 AUC) [34].

Then, the pooled sensitivity of Siemens CoV2Ag for diagnosing SARS-CoV-2 infection in respiratory samples with high viral load matches that of all other laboratory-based immunoassays, being as high as 0.95 [29–34], and substantially overlaps that claimed by the manufacturer (i.e., 0.92–0.96). This data implicitly confirms that this

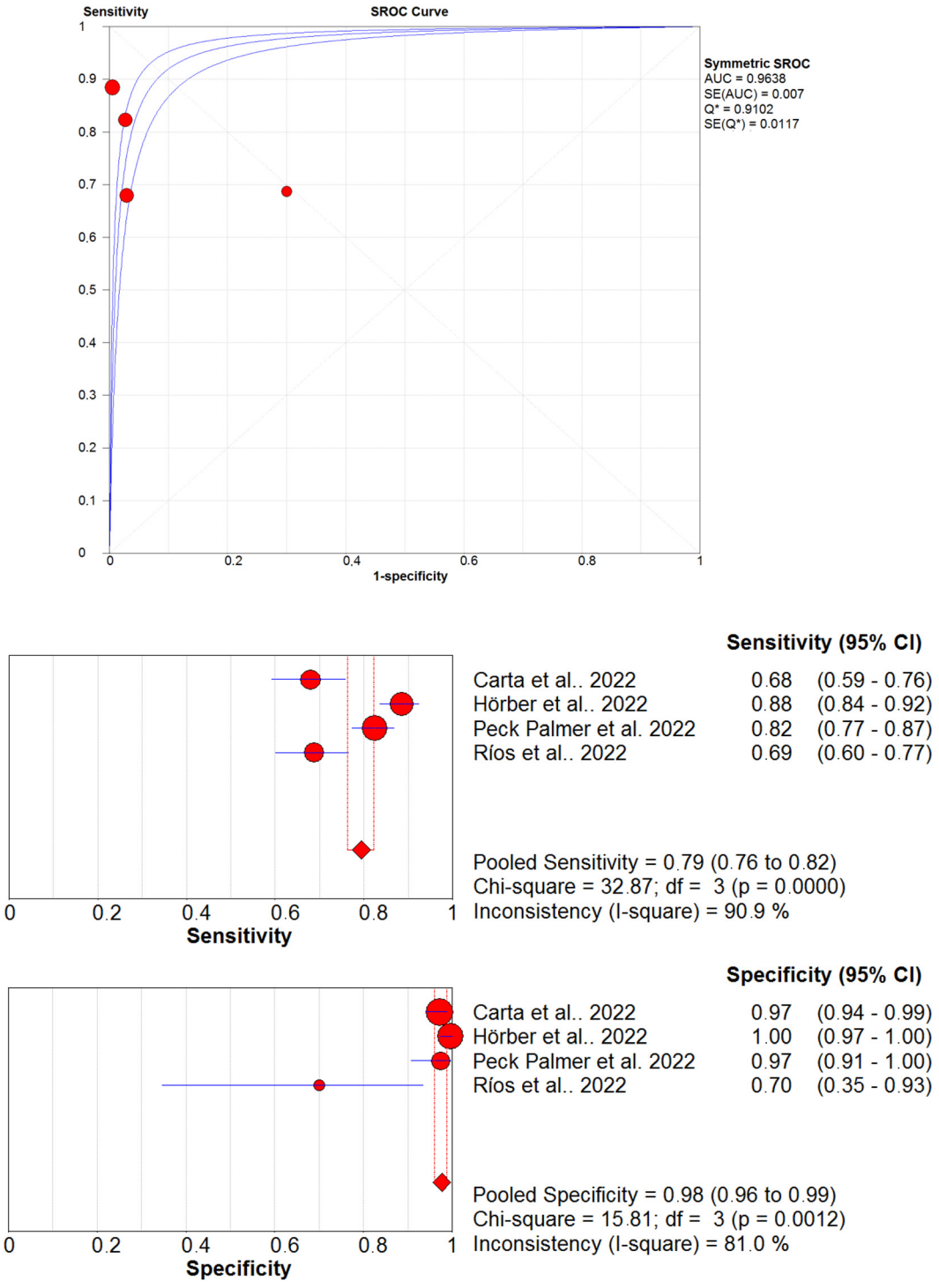

Figure 1: Cumulative diagnostic sensitivity, specificity and accuracy (summary receiver operating characteristic curve; SROC) with 95% confidence interval (95% CI) of Siemens SARS-CoV-2 Antigen (CoV2Ag) chemiluminescent immunoassay for diagnosing SARS-CoV-2 infection in respiratory specimens.

immunoassay could be reliably used for identifying subjects with high SARS-CoV-2 viral load in respiratory specimens, who not only are at substantially higher risk of developing viraemia and severe/critical COVID-19 illness [35, 36], but are also currently considered those with disproportionately higher infectivity and magnified risk of spreading the virus and thus initiating, maintaining or even boosting local outbreaks [37, 38].

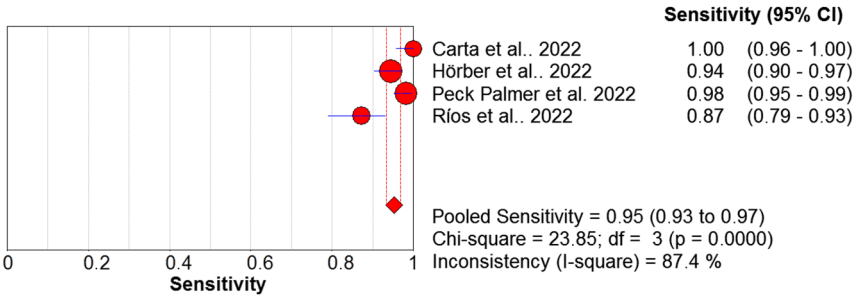

Figure 2: Cumulative diagnostic sensitivity of Siemens SARS-CoV-2 Antigen (CoV2Ag) chemiluminescent immunoassay for diagnosing SARS-CoV-2 infection in respiratory specimens with high viral load. Ct, cycle threshold; N/A, not available.

In conclusion, the novel Siemens CoV2Ag CLIA display cumulative diagnostic accuracy that approximates the WHO and ECDC minimum performance criteria (i.e., 0.79 sensitivity vs. ≥0.80 and 0.98 specificity vs. ≥0.97, respectively), and that are aligned to those of other laboratory-based commercial SARS-CoV-2 antigen immunoassays. Hitherto, the assay displays a remarkably high diagnostic sensitivity for identifying subjects with high viral load, thus representing a valuable screening method for risk assessment and for limiting viral spread.

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Ethical approval: Not applicable.

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