ORIGINAL ARTICLE

Clinical Evaluation of Serological Diagnostic Assays for COVID-19 Antibody Detection

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ABSTRACT

Objective: This study was aimed to evaluate the laboratory performance of three different serological assays (Immunofluorescence Assay (IFA), Electrochemiluminescence Immunoassay (ECLIA) and Chemiluminescent Microparticle Immunoassay (CMIA) to see if they performed accurately according to the manufacturers' claims.

Study Design: Cross sectional study.

Place and Duration of Study: This study was conducted at Chughtai Institute of Pathology from 01st April to 30th May 2020.

Materials and Methods: Blood samples were collected from 75 adult male and female patients, 25 were pre pandemic samples and 50 were diagnosed cases of COVID-19 in whom sample was taken 21 days after they showed up symptoms. All cases were analyzed to detect the presence or absence of COVID-19 IgG antibodies using Immunofluorescence assay (IFA), electrochemiluminescence immunoassay (ECLIA) and Chemiluminescent Microparticle Immunoassay (CMIA). SPSS 23.0 and EP evaluator were used to assess sensitivity, specificity and Cohen's kappa.

Results: The study compares the effectiveness of three diagnostic methods (ECLIA, CMIA, and IFA) against PCR for detecting COVID-19 antibodies using Cohen's Kappa statistics. ECLIA showed the highest agreement with PCR (Kappa 0.748), followed by CMIA (Kappa 0.602), and IFA (Kappa 0.564), indicating that ECLIA is the most reliable method for detecting both positive and negative cases. The findings suggest variability in accuracy across these methods, with ECLIA being the most consistent.

Conclusion: Detection of anti-SARS-CoV-2 antibodies may act as a reliable diagnostic tool provided the assay is properly validated before use. Chemiluminescence immunoassay proves to be a better serological assay as compared to Electrochemiluminescence and Immunofluorescence assay.

Key Words*: Chemiluminescence, Electrochemiluminescence, Immunofluorescence, SARS-Cov-2, Serological Assay.*

Introduction

In Wuhan City, Hubei Province, Central China, several patients with pneumonia of unknown etiology surfaced at the start of December 2019. The pneumonia known as coronavirus disease 2019 (COVID-19) has been shown through genome sequencing to be caused by a novel coronavirus (CoV) called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly known as 2019 novel coronavirus (2019-nCoV).[1] The four genera of Corona viruses are Alpha, Beta, Gamma, and Delta, and they are members of the "Corona Viridae" family. [2,3]Similar to SARS-CoV and MERS-CoV, the recently discovered SARS-CoV-2 virus is a member of the β-CoV B lineage.[3]

Once inside the epithelial cells, SARS-CoV-2 multiplies quickly and triggers a cytokine storm and immunological reaction that damages the pulmonary parenchyma. This hypercytokinemia results in multiple organ failure and acute respiratory distress syndrome due to its unchecked synthesis of proinflammatory cytokines.[4] Studies have revealed that cytokine storm syndrome occurred in severe cases of COVID-19, some of which deteriorated and died of multiple organ damage.[5]

SARS-CoV-2 outbreak and spread can only be controlled by rapid detection of the cases. Reverse transcriptase quantitative PCR (RT-qPCR) is a diagnostic tool based on nucleic acid sequencing

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Received: February 02, 2024 ; Revised: December 28, 2024
Accepted: March 05, 2025

 https://doi.org/10.57234/jiimc.march25.1785

with high sensitivity and specificity [6]. Apart from the diagnostic tests like RT-qPCR, serological tests have been in high discussion since the outbreak of this pandemic. A wide range of serological immunoassays with variable antibody specificities have been developed [7,8]. The COVID-19 virus has underscored the urgent need for reliable diagnostic antibody testing to accurately identify past infections and assess immunity levels within populations. Such testing is critical for guiding public health decisions, managing vaccination strategies, and understanding the virus's spread. Ensuring high accuracy in antibody tests helps prevent false results, thereby maintaining trust in public health measures. Accurate antibody testing is pivotal for monitoring and controlling the pandemic effectively. It is a major responsibility of clinical laboratories all around the world to validate these new methodologies before these techniques get introduced into routine clinical practice.[9]

In the given emergency of COVID-19, FDA issued relaxed regulatory guidelines to use SARS-CoV-2 serological assays to check the immune response of the population. Under these circumstances, it is now the duty of clinical laboratories to validate these assays rigorously to determine whether these assays perform accurately according to the package inserts. The serological assays being used around the world include rapid diagnostic tests (RDT), ELISA (Enzyme linked Immunosorbent assay), neutralization immunoassays and chemiluminescence. All these tests vary in the antigens they are designed to target e.g. Nucleocapsid protein (N Protein) or Spike protein (S Protein). This study aimed to detect the analytical performance of three different serological assays to detect COVID-19 IgG Antibody. The findings will help health care providers to identify a better serological assay for COVID-19 IgG antibody detection that is properly validated and solve many unanswered queries of the clinicians.

Materials and Methods

This cross-sectional study was conducted at Chughati Institute of Pathology from 01st April to 30th May 2020. Ethical approval was obtained by the Institutional Review Board under letter number CIP/IRB/1029. Blood samples were collected from 75 adult male and female patients. Of these, 25 were pre-pandemic samples and 50 were COVID-19 cases with confirmed diagnosis via RT-qPCR; the samples were obtained 21 days after the onset of symptoms. The pre-pandemic samples included specimens of healthy adult population collected in November 2019 and kept frozen at -80 ° Celsius. The healthy population was recruited according to WHO criteria (Constitution of the World Health Organization) after filling in the health questionnaire. These samples were collected as part of routine sample collection to establish a healthy sample pool for the laboratory's biobank. COVID-19 cases included in the study were admitted in high dependency corona units and hospital isolation wards and having mild to severe symptoms. COVID-19 patients with mechanical ventilation, asymptomatic cases, and those undergoing plasma infusion were not included in this research. In this study, we did not stratify the patients according to the severity of their symptoms. A volume of 3 ml blood was collected and centrifuged at 3000 RPM prior to analysis.

All samples were analyzed to detect the presence or absence of COVID-19 IgG antibodies using three different assays.

1. **Immunofluorescence Assay (IFA) Lifotronic FA 160**

   This is a rapid diagnostic test detecting the presence of antibody on nitrocellulose membrane using immunofluorescence as test principle. Sample is added on the sample pad which moves forward through capillary force towards detection line of enveloped antigen (recombinant nucleocapsid protein) on the test strip. The strip is then placed into the incubation chamber of the reader for 15 minutes. If antibody is present, it will combine with antigen and fluorescence marker to form immune complexes along with a control line that can also produce fluorescence. After incubation, the test strip is placed into the test chamber and the result is displayed on the screen and printed as well. The whole process takes 20 minutes.

2. **Elecsys Anti SARS-CoV-2 Assay- Roche Diagnostics**

   The electrochemiluminescence immunoassay (ECLIA) used in this study was for the qualitative detection of SARS-CoV-2-specific antibodies (IgG and IgM). The nucleocapsid (N) antigen recombinant protein is used in this assay to

measure the antibodies against SARS-CoV-2. The samples are classified as reactive (COI >1.00) or non-reactive (COI<1.00) based on a cut off index (COI) of 1.00.

3. **SARS-CoV-2 IgG assay- Abbott Diagnostics**
   This is a chemiluminescent microparticle immunoassay (CMIA) for qualitative detection of IgG antibodies against SARS-CoV-2. This technique measures IgG antibodies against SARS-CoV-2 using nucleocapsid (N) antigen recombinant protein coated microparticles. The samples are classified as reactive (COI >1.40) or non-reactive (COI<1.40) based on a cut off index (COI) of 1.40.

All samples were analyzed on these assays after quality check and calibration. RT-PCR was used as a reference method. SPSS 23.0 was used to calculate percentages and frequencies, Cohen Kappa, sensitivity and specificity and Cohen Kappa. Cohen's Kappa is a statistical measure used to assess the agreement between two raters or diagnostic tests, beyond what would be expected by chance. When applied to sensitivity and specificity analysis, Cohen's Kappa helps evaluate the sensitivity, which measures the proportion of actual positives that are correctly identified by the tests and the specificity, which measures the proportion of actual negatives that are correctly identified. Cohen's Kappa evaluates if the agreement on cases between two tests exceeds what would be expected by chance. Cohen's Kappa values range from -1 to 1, where: Kappa ≤ 0: Indicates no agreement or agreement worse than chance, 0.01–0.20: Slight agreement, 0.21–0.40: Fair agreement, 0.41–0.60: Moderate agreement, 0.61–0.80: Substantial agreement and 0.81–1.00: Almost perfect or perfect agreement. Higher Kappa values suggest better consistency between the two methods, while values near or below zero indicate that the agreement might be due to chance.

Results

The given results involved comparing three different diagnostic methods (ECLIA, CMIA, and IFA) against a reference standard (PCR) for detecting COVID-19 antibodies. The level of agreement between each method and PCR is assessed using Cohen's Kappa statistics, which helps determine how well these methods perform in identifying positive and negative cases relative to the PCR results. Our study showed that ECLIA and PCR both identified 25 negatives and 42 positives and ECLIA incorrectly identified 8 positive cases as negative. There is substantial agreement between ECLIA and PCR results, with a Kappa value of 0.748. This indicates that ECLIA is a reliable method for COVID-19 detection compared to PCR, with high consistency in detecting both positive and negative cases. CMIA and PCR both identified 25 negatives and 36 positives and CMIA incorrectly identified 14 positive cases as negative. There is moderate agreement between CMIA and PCR results, as indicated by a Kappa value of 0.602. While CMIA shows a good level of agreement, it is less consistent than ECLIA, especially in identifying positive cases. There is a higher rate of false negatives compared to ECLIA. IFA and PCR both identified 25 negatives and 33 positives. IFA incorrectly identified 17 positive cases as negative. The Kappa value of 0.564 indicates a moderate level of agreement between IFA and PCR results. IFA has the lowest agreement among the three methods, with a higher tendency to miss positive cases (false negatives). This suggests that IFA is less reliable than ECLIA and CMIA in accurately detecting COVID-19 cases when compared to PCR. These findings suggest that ECLIA is the most effective among the three methods for diagnosing COVID-19, based on the agreement with PCR results.
In this study, all three assays showed different negative and positive agreement along with Cohen's Kappa for the pre pandemic and post pandemic samples. Comparison of performance of all three assays is given in table I

Table I: Sensitivity And Specificity of Assays Used for Serological Testing (n=75)

Assay	Negative agreement (Specificity)	Positive agreement (Sensitivity)	Cohen's Kappa
IFA	59%	66%	0.564
ECLIA	100%	84%	0.748
CMIA	100%	72.0%	0.602

Discussion

In this work, we compared and clinically assessed three commercially available tests for the detection of SARS-CoV-2 antibodies. Among all the tests used for the qualitative assessment of Anti-SARS-CoV-2 antibodies, the ECLIA test from Roche Diagnostics had the best specificity, followed by the Abbott

https://doi.org/10.57234/jiimc.march25.1785

assay. IFA by Lifotronic demonstrated the lowest sensitivity and specificity and was linked to most false positive and false negative outcomes. The requirement for specialized equipment and skilled personnel to interpret results may also limit accessibility and consistency of results. Additionally, cross-reactivity with antibodies from other coronaviruses can cause false-positive results, while low antibody titers in early or mild infections may lead to false negatives.

Given these limitations, some labs opted to use Electrochemiluminescence Immunoassay (ECLIA) and Chemiluminescence Microparticle Immunoassay (CMIA) for COVID-19 antibody detection instead of Immunofluorescence Assay (IFA). ECLIA and CMIA offer higher throughput, automation capabilities, and improved sensitivity and specificity, leading to more consistent and faster results. These methods also minimize human error associated with manual interpretation in IFA and are less labor-intensive, making them ideal for large-scale testing in clinical settings.

A recent American study found that the Abbott assay using CMIA and ECLIA was more reliable than rapid tests after 14 days of symptom onset. Specifically, the study showed that the Abbott SARS-CoV-2 assay had a diagnostic sensitivity of 93.8% and a specificity of 99.4% after this period.[10] The variability in study results compared to manufacturers' claims can be attributed to several factors. Patients often present overlapping clinical scenarios and are under different treatment plans. Moreover, testing on hospitalized patients with immunodeficiencies and comorbidities can affect results. Some manufacturers also measure assay sensitivity from the time of RT-qPCR positivity rather than from the onset of symptoms, potentially leading to an overestimation of sensitivity.[10] In our study, serological assessments in COVID-19 patients were conducted 21 days post-symptom onset, a point at which the maximum serological response is typically observed.[11]

None of the pre-pandemic samples in our study showed seropositivity when analyzed using CMIA and ECLIA, whereas IFA showed considerable false positives, likely due to the assay's low specificity. Some studies have found false positive serological results in pre-pandemic confirmed cases of seasonal coronavirus, attributing this to the structural homology between seasonal coronaviruses and SARS-CoV-2, which can affect the specificity of assays like ELISA. In regions with low prevalence, such as Pakistan, where the current SARS-CoV-2 attack rate is 2.3 per 100,000 population, the necessity of high specificity becomes crucial to achieve a high positive predictive value. This is important for public health strategies and testing protocols because a low specificity can lead to an overestimation of infection rates, thereby affecting resource allocation and intervention strategies. Understanding the regional epidemiology helps inform the selection of assays with optimal specificity and sensitivity to ensure accurate diagnosis and effective public health response.[13] In this case, obtaining a high positive predictive value necessitates a serological test with good specificity.[14] According to the FDA, the performance of an assay depends on the population prevalence, and in low-prevalence populations, a single antibody test may not be sufficient to differentiate true positives from false positives. In clinical settings, especially among hospitalized patients with comorbidities, the immune response can be atypical, potentially leading to altered assay performance. These patients may have impaired immune responses due to their underlying conditions or treatments, which can affect the production of antibodies, thereby influencing both sensitivity and specificity of the tests. As a result, antibody tests may produce higher rates of false positives or false negatives in these environments, highlighting the need for confirmatory testing or using assays with high specificity to ensure accurate diagnosis. Understanding the impact of these clinical variables is crucial for interpreting test results and making informed public health decisions.[15]

Horber et al., assessed several SARS-CoV-2 serological tests for antibody detection and discovered that the assays had a good level of sensitivity and specificity at least 14 days after PCR positive. The investigators found the diagnostic sensitivity of Siemens to be highest compared to Roche and Euroimmun.[16] Clinical evaluation of different serological assays for SARS-CoV-2 reveals that chemiluminescence immunoassay (CLIA) show 100% specificity (sample collected 12 days post symptom onset), RDT show 90.3% clinical specificity

(sample collected 33 days post symptom onset) while the diagnostic sensitivity while using ELISA as assay of choice was 66.7% in the early phase of disease.[11,17,18] A comparison between Roche ECLIA and DiaSorin Liaison CMIA SARS-CoV-2 IgG assay is in accordance with our study demonstrated specificities of 100% and 98.9% with an overall agreement of 99% with RT-PCR.[19] Another recently published study compared the diagnostic sensitivities of Spike protein based serological assay and Nucleocapsid protein-based assay and found that later having high sensitivity (77.8%).[20]The assays used in our study were also Nucleocapsid protein based. An American study comparing the specificity of SARS-CoV-2 IgA and IgG assay (Euroimmun) found IgG assay to have higher specificity (97%) as compared to IgA assay (81%).[21] Our study is also in concordance with a recent evaluation of three commercial SARS-CoV-2 serological assays i.e. Abbott IgG, Roche total antibody and DiaSorin IgG. In this study, the nucleocapsid antibody test (Abbott and Roche) showed higher sensitivity as compared to Spike protein Antibody test (DiaSorin).[22]

The Infectious Diseases Society of America (IDSA) advises using serology to diagnosis patients who have a high suspicion of COVID-19 but who test negative for the virus by RT-PCR.[23] Using a variety of immunochromatographic tests, Demey et al. showed that antibodies against SARS-CoV-2 may be found approximately 10 days after the onset of symptoms where as Thevarajan recorded an increase in the antibody production from 7 to 20 days after beginning of the disease.[24,25] Many studies suggest that serological assays can act as reliable diagnostic tool for identification of SARS-CoV-2 infection as well as help to determine the immune status of the population since they have high sensitivity and specificity. Previously it was debated that serological assays cannot be used to diagnose SARS-CoV-2 infection, however, recently many studies postulate that antibody assays can be used to diagnose COVID-19.[26] Serological assays having high sensitivity and specificity can be used to screen asymptomatic cases, early diagnosis of the infection (with the help of IgM only), and monitoring response during treatment [27-29]. However, negative tests cannot be used to exclude the infection considering the fact that patients may have been recently exposed to the virus [30]. Another fact to be considered is assay showing cross reactivity to non-SARS-CoV-2 proteins. Risk assessment for healthcare personnel, epidemiological surveys, and vaccine research can all benefit from the use of high sensitivity serological testing. However, appropriate validation of the assays' diagnostic accuracy is necessary for all these surveys and investigations.

Conclusion

Besides RT-PCR, to confirm the presence of COVID-19 in the suspected cases, detection of anti-SARS-CoV-2 antibodies may act as a reliable diagnostic tool provided the assay is properly validated before use. Electrochemiluminescence immunoassay proves to be a better serological assay as compared to chemiluminescence and Immunofluorescence assay. Assays with higher diagnostic sensitivity and specificity can overcome the RT-PCR limitations helping to diagnose asymptomatic carriers and false negative RT-PCR cases.

Limitation

- Small sample size and single center study. Understanding the performance of these assays across diverse groups is essential for ensuring accuracy in diagnostic settings, guiding public health decisions and Informing vaccine deployment strategies.
- The study's sample collection at 21 days post-symptom onset may not account for the dynamic nature of antibody levels because antibody titers can vary over time and different individuals may experience peak antibody levels or declines at different rates.

Conflict of interest: No conflict of interest is disclosed by the authors.

Disclosure: Nothing of note needs to be disclosed by the authors.

Funding source: Chughtai Lab Lahore

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

 https://doi.org/10.57234/jiimc.march25.1785