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SARS-CoV-2 infection serology validation of different methods: Usefulness of IgA in the early phase of infection

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ABSTRACT

Background and aims: A novel coronavirus (SARS-CoV-2) was isolated from the respiratory samples of patients with pneumonia as showed by the sequence analysis of the virus genomes obtained in Wuhan, China. The antibody response to SARS-CoV-2 is not well understood yet, but the availability of sensitive and specific serological assays will be crucial for the early diagnosis of infection, for epidemiological studies and for defining the presence of neutralizing antibodies in response to a possible vaccine.

Materials and methods: We tested and compared the performances of one chemiluminescent immunoassay (CLIA), two enzyme-linked immunosorbent assay (ELISA) and an electrochemiluminescence immunoassay (ECLIA).

Results: The ECLIA serological assay performed best and may be a valid screening method for SARS-COV-2 infection. The IgA detected by the ELISA assay might be a more reliable and stable early serological marker than IgM. Instead, IgGs, as expected, showed stable level after 10 days from symptoms onset.

Conclusion: The ECLIA method could be used as screening test, considering both the excellent performance and the cost per single test; while ELISA assay for IgG and IgA, which are present at a higher level than IgM and last longer, might be used as confirmatory test.

1. Introduction

In the late December 2019, an outbreak of pneumonia of unknown origin was reported in Wuhan, Hubei province, China. A novel coronavirus was isolated from the respiratory samples of patients with pneumonia as showed by the sequence analysis of the virus genomes obtained [1,2]. The novel coronavirus was first named 2019-nCoV, and later SARS-CoV-2 because of its capacity to cause a severe acute respiratory syndrome (SARS) resembling that caused by SARS-CoV in 2002/2003. Infection is mild in the majority of the cases, but in some individuals, generally elderly and with comorbidities, the virus causes an atypical interstitial pneumonia progressing to acute lung injury and acute respiratory distress syndrome (ARDS) that requires respiratory support [3]. The disease, known as COVID-19 (https://www.who.int) spread rapidly all over the world, and on 11 March 2020, the WHO declared COVID-19 a pandemic. As of 16 August 2020, we have 21 294 845 COVID-19 confirmed cases and 761 779 deaths worldwide [4]. Reverse-transcriptase real-time PCR (rRT-PCR) is the method of choice for detecting SARS-CoV-2 infection and confirm suspected cases [5]. rRT-PCR is carried out on nasalpharyngeal swabs, throat swabs, bronchoalveolar lavage fluid, bronchoaspirate and sputum. Despite the high sensitive of the real-time PCR tests, sometimes samples from the upper respiratory tract may result negative even in the presence of radiological findings of pneumonia [6]. These negative results may have different explanations: i, the viral load in the upper respiratory tract is low compared to the lower respiratory tract; ii, the viral load may vary during the course of COVID-19 disease; iii.; low quality of the collected sample; iv, technical reasons linked to the assay used. In these cases, serological assays may help in making diagnosis. The antibody response to SARS-CoV-2 is not well understood yet, but the availability

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of sensitive and specific serological assays will be crucial for the early diagnosis of infection, for epidemiological studies (diffusion of the virus among the population, identification of asymptomatic carriers), for defining the presence of neutralizing antibodies in response to a possible vaccine. A recent publication showed how detection of antibody response in combination with RNA testing improved the sensitivity of etiological diagnosis of COVID-19 in the first week of illness [7].

Serological assays will play a key role also in the reopening of the economic activities, when it will be important to identify not only that people who were not exposed to SARS-CoV-2 and then can return to work, but also asymptomatic carriers that will be quarantined avoiding the spread of the virus in the work place and new infections [8]. Anyway, keeping in mind the limitations of the currently available serological assays and the possibility of cross-reactions with SARS-CoV (which shares 82% nucleotide identity with SARS-CoV-2 [9] and other coronaviruses, real-time PCR is nowadays the most effective diagnostic test for COVID-19 diagnosis.

In this work, we tested and compared the performances of two enzyme-linked immunosorbent assays (ELISA), one chemiluminescent immunoassay (CLIA) and an electrochemiluminescence immunoassay (ECLIA). Of the latter ones, one detects IgM and IgG antibodies (SNIBE) while the other measures also IgA (Roche Diagnostics).

2. Materials and methods

2.1. Patients and serum specimens

Serum samples were collected from rRT-PCR-diagnosed SARS-CoV-2 positive (n = 40) and negative patients (n = 40) from "Tor Vergata" University Covid-Hospital of Rome. The study was conducted in accordance with the guidelines of the local Ethic Committee (approval number: R.S.44.20) and the Helsinki Declaration, as revised in 2013.

Sera were collected by centrifugation at 2500 g for 10 min, within 1 h from collection. All serum samples were collected from 1 to 50 days after nasopharyngeal swab. Positive patients have been divided into three groups: early infection time (1–10 days after nasopharyngeal swab); late infection time (11–45 days after nasopharyngeal swab) and COVID convalescent patients (> 45 days after a positive nasopharyngeal swab; discharged home).

2.2. Reverse real time-PCR (rRT-PCR)

Nasopharyngeal swabs were tested for SARS-CoV-2 infection with Seegene Allplex™2019-nCoV assay (Seegene, Seoul, South Korea), according to the manufacturer's protocol. Automated RNA extraction and PCR setup were carried out using Seegene NIMBUS, an automatic liquid handling workstation. rRT-PCR was run on a CFX96TMDx platform (Bio-Rad Laboratories, Inc., CA, USA) and subsequently interpreted by Seegene's Viewer Software. The Seegene Allplex™2019-nCoV assay identifies the virus by multiplex real-time PCR targeting three viral genes (*E*, *RdRP* and *N*), thus complying with international validated testing protocols [10].

2.3. Serological tests

2.3.1. Automated ROCHE Electrochemiluminescence Immunoassay (ECLIA) for anti-SARS-CoV-2 IgG, IgM or IgA detection.

The Roche Elecsys Anti-SARS-CoV-2 (Roche Diagnostics, Monza, Italy) is an immunoassay for the *in vitro* qualitative detection of antibodies (including IgG, IgM and IgA) to SARS-CoV-2 in human serum and plasma. The assay uses a recombinant protein representing the nucleocapsid (N) antigen for the determination of antibodies against SARS-CoV-2. The result is given as cut-off index (COI): positive (COI ≥ 1.0) or negative (COI < 1.0). The test was performed on Cobas 6000 immunoassay analyzer according to the manufacturer's instructions.

2.3.2. SNIBE Chemiluminescence Immunoassay (CLIA)

The SNIBE 2019-nCoV IgG and 2019-nCoV IgM assays are an indirect chemiluminescence immunoassay from SNIBE (SNIBE Diagnostics, Shenzhen, China). The assay uses magnetic microbeads coated with 2019-nCoV recombinant antigen (nucleocapsid protein, NP and Spike Protein, SP) and anti-human IgG and IgM antibodies labeled with *N*-(aminobutyl)-*N*-(ethylisoluminol) (ABEI) that form complexes. The light signal measured by a photomultiplier as relative light units (RLUs), is proportional to the concentration of 2019-nCoV IgG and IgM presented in the sample. The cut-off value of SARS-CoV-2 IgM/IgG positive was > 1 AU/ml. The test was performed on Maglumi 600 according to the manufacturer's instructions.

2.3.3. Euroimmun Enzyme-Linked Immunosorbent Assay (ELISA)

Immunoenzymatic assays for SARS-COV-2 IgG and IgA antibodies determination in human plasma and serum performed on the fully automated EURO LabWorkstation (Euroimmun, Lübeck, Germany). Each kit contains microplate strips with 8 break-off reagent wells coated with recombinant structural protein of SARS-CoV-2 (nucleocapsid protein, NP). In the first reaction step, diluted patient samples are incubated in the wells. In the case of positive samples, specific antibodies will bind to the antigens. To detect the bound antibodies, a second incubation is carried out using an enzyme-labelled anti-human IgA or IgG (enzyme conjugate) catalysing a colour reaction. Results are evaluated semi-quantitatively by calculation of a ratio of the extinction of the control or patient sample over the extinction of the calibrator. The ratio is interpreted as follows: < 0.8 negative; ≥0.8 to < 1.0 borderline; ≥1.1 positive.

2.3.4. ImmunoDiagnostics Enzyme-Linked Immunosorbent Assay (ELISA)

Immunoenzymatic assays for the determination of SARS-COV-2 IgM and IgG antibodies (Immunodiagnostic; ImmunoDiagnostics Limited Hong Kong Science Park, Sha Tin, Hong Kong) in human plasma and serum was performed on the fully automated Alisei Q.S., according to the manufacturer's instructions. ImmunoDiagnostics SARS-CoV-2 NP IgG ELISA kit is a two-step incubation immunoassay. Recombinant nucleocapsid protein (NP) of SARS-CoV-2 pre-coated onto the polystyrene microwell strips is specifically recognized by anti-NP antibodies present in human serum or plasma specimens. A detection solution containing HRP-conjugated antihuman IgM/IgG is added for 1hr incubation, wherein HRP-conjugated anti-human IgM/IgG binds to the IgM/IgG class antibodies previously bound to NP protein on the plate. After removal of nonspecific binding, a substrate solution containing HRP is added resulting in the formation of a blue color. Color reaction is stopped by 2 M H2SO4, transforming the blue color to yellow signal, which is quantified by an absorbance microplate reader at 450 nm. The color intensity is proportional to the amount of anti-NP IgG antibodies captured inside the wells. Ratio is considered negative for all the values < 0.9 COI (Cut-Off Index); equivocal for all the values between 0.9 and 1.1 COI; positive for all the values > 1.1 COI.

Table 1 summarizes the technical features of the aforementioned assays.

2.4. Internal Quality Control (IQC) and External Quality Assessment (EQA)

All assays underwent to an Internal Quality Control (IQC), and precisions were expressed as the coefficient of variations (CV %) calculated as the standard deviation divided by the mean value, for each of the studied parameters.

The External Quality Assessment (EQA) was performed with the Austrian Association for Quality Assurance and Standardization of Medical and Diagnostic Tests (ÖQUASTA).

Table 1
Technical features of the serological assays tested in the study.

Manufacturer	Method	Qualitative/Semiquantitative	Target Antigen	Antibody measured	Sensitivity	Specificity
ROCHE	ECLIA	**Qualitative**	Nucleocapsid Protein	IgA/IgM/IgG	65.5–100%*	99.8%
SNIBE	CLIA	**Semiquantitative**	Spike and Nucleocapsid Protein	IgM/IgG	91.2% (IgG) 78.6% (IgM)	97.3% (IgG) 97.5% (IgM)
EUROIMMUNE	ELISA	**Semiquantitative**	Nucleocapsid Protein	IgA/IgG	33.3–80% (IgG)* 50–100% (IgA)*	98.5% (IgG) 92.5% (IgA)
IMMUNODIAGNOSTIC	ELISA	**Semiquantitative**	Nucleocapsid Protein	IgM/IgG	92.5% (IgG) 88.2% (IgM)	93.3% (IgG) 92% (IgM)

* Sensitivity range determined after PCR confirmation at different time points.

2.5. Statistical analysis

Specificity and sensitivity were calculated by Receiver Operating Characteristic Curves (ROC Curve). All data were analyzed using Med Calc Ver.18.2.18 (MedCalc Software Ltd, Ostend, Belgium). The investigator was blinded to the group allocation during the experiment.

3. Results

3.1. Specificity and sensitivity of the serological assays

Sensitivities and specificities obtained with the immunoassays using ROC curve are summarized in Table 2 and Table 3. The Roche combined antibody test is a screening test that provides a qualitative result. The Roche test showed excellent results with 99% sensitivity and 100% specificity considering all samples and the different groups of patients, Table 2.

The automated SNIBE chemiluminescence test on Maglumi instrument is a semi-quantitative test that reveals the presence of IgG and IgM antibodies against SARS-CoV-2. The system showed 100% specificity and 91% sensitivity for IgG antibodies, and a specificity and sensitivity for IgM antibodies of 100% and 75%, respectively (Table 3).

Finally, we tested on automated systems two ELISA assays that measure IgA, IgM and IgG antibodies against NP. The Euroimmune ELISA measures IgA and IgG antibodies against NP. The sensitivity of IgG Euroimmune ELISA at ≤10 days was 94%, at 11–45 days was 99%; and at > 45 days was 100%. The specificity was 100% in all groups. The sensitivity of IgA at ≤10 days was 91.3%, at 11–45 days 94%, and 90% at > 45 days. Specificity was 94% in all groups, Table 3.

The sensitivity of the Immunodiagnostic ELISA for IgG was 86% at ≤10 days, 100% at 11–45 days, and 87.5% > 45 days. The specificity of IgG at ≤10 days was 100%, at 11–45 days 99%, and 100% at > 45 days. The sensitivity for IgM at ≤10 days was 94%, at 11–45 days 97%, and was 88% at > 45 days. Specificity was 100% at ≤10 days, 97% at 11–45 days, and 97% at > 45 days, Table 3.

Overall, sensitivity and specificity for IgG was similar for both CLIA and ELISA methods.

Considering all patients, the sensitivity is similar with all methods, except for group > 45 days from the first nasopharyngeal swab where a higher sensitivity was observed with ELISA methods (87.5–100% *vs* 83%).

Among the control samples with negative RT-PCR, no false positives were observed with IgG ELISA and CLIA methods; while some false positives were observed with IgA and IgM ELISA.

Fig. 1 shows the kinetic results for the 40 study patients at different days, from 1 to 50 days after the first positive RT-PCR, divided into time categories for IgA, IgM and IgG. The graph shows average values and corresponding standard error for IgA, IgM and IgG immunoglobulins at each infection time. IgA, IgM and IgG were detected since the first day after positive RT-PCR results, although differences were observed during the prefixed timeline (1–50 days). In particular, IgA and IgG immunoglobulins increased sharply up to 20 days, while IgM showed an unstable increase within the same time laps. After 20 days from the first positive swab, IgA levels decreased progressively but were still detectable until 50 days; instead, IgMs were barely detectable at the same time point. Finally, IgG maintained stable levels with absorbance values clearly above the cut-off level.

3.2. Internal and external quality assessment

Due to limited reagent availability, imprecision was determined using positive and negative Internal Quality Control (IQC) only between run for a period of one month.

Positive IQC generated the following coefficient of variations (CV %): 7.08% for ECLIA method; 6.29% (IgM) and 5.33% (IgG) for CLIA method. The two ELISA methods obtained 7.8% (IgG), 6.9% (IgA) and 5.1% (IgG), 5.8% (IgM) for Euroimmune ELISA and Immunodiagnostic ELISA respectively. Negative IQC showed a precision similar to that claimed by the manufacturer.

The External Quality Assessment (EQA) for the identification of anti-SARS-CoV-2 IgG/IgM/IgA antibodies showed a perfect match with the results generated by the serological assays under evaluation.

4. Discussion

Several serological assays are available on the market for the diagnosis of SARS-CoV-2 infection [7]; therefore, assessment of their analytical performance by using clinical specimens is of critical importance. In this study, we evaluated the specificity and sensitivity of two ELISA assays (Euroimmun SARS-COV-2 IgG and IgA; ImmunoDiagnostics SARS-COV-2 NP IgM and IgG)) and two chemiluminescent enzyme assays (Roche Elecsys Anti-SARS-CoV-2; SNIBE 2019-nCoV IgG) for the detection of SARS-CoV-2 antibodies. Roche assay measures total immunoglobulins directed towards a recombinant NP of

Table 2
Sensitivities and specificities obtained with ROC curve for Roche ECLIA.

CONTROL NEGATIVE GROUP N = 40	Total (1–50 days) N = 40	Early infection time (1–10 days) N = 16	Late infection time (11–45 days) N = 16	Covid patients after discharge (> 45) N = 8
TEST	**ECLIA ROCHE**	**ECLIA ROCHE**	**ECLIA ROCHE**	**ECLIA ROCHE**
Sensitivity (%)	99	100	100	99
Specificity (%)	100	100	100	100
Kit Cut-off	> 1 COI	> 1 COI	> 1 COI	> 1 COI
ROC curve (AUC)	1	1	1	1

Table 3
Sensitivities and specificities of the tested methods during the period of observation (1–50 days) based on the ROC curve.

CONTROL NEGATIVE GROUP N = 40	Total (1–50 days) N = 40		Early infection time (1–10 days) N = 16		Late infection time (11–45 days) N = 16		Covid patients after discharge (> 45) N = 8	
TEST	CLIA_SNIBE		CLIA_SNIBE		CLIA_SNIBE		CLIA_SNIBE	
	IgM	IgG	IgM	IgG	IgM	IgG	IgM	IgG
Sensitivity (%)	75	91	87.5	88	100	100	50	83
Specificity (%)	100	100	75	100	100	100	100	100
Kit Cut-off	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI
Area under the ROC curve (AUC); 95% Confidence interval	0.921	0.988	0.95	0.968	0.942	1	0.821	0.988
TEST	Euroimmune ELISA		Euroimmune ELISA		Euroimmune ELISA		Euroimmune ELISA	
	IgA	IgG	IgA	IgG	IgA	IgG	IgA	IgG
Sensitivity (%)	87.5	97	91.3	94	94	99	90	100
Specificity (%)	94	100	94	100	94	100	94	100
Kit Cut-off	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI
Area under the ROC curve (AUC); 95% Confidence interval	0.987	0.987	0.977	0.9671	0.994	1	0.992	1
TEST	ImmunoDiagnostic ELISA		ImmunoDiagnostic ELISA		ImmunoDiagnostic ELISA		ImmunoDiagnostic ELISA	
	IgM	IgG	IgM	IgG	IgM	IgG	IgM	IgG
Sensitivity (%)	75	91	94	86	97	100	88	87.5
Specificity (%)	100	100	100	100	97	99	97	100
Kit Cut-off	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI	> 1.1 COI
Area under the ROC curve (AUC); 95% Confidence interval	0.921	0.988	0.994	0.987	1	1	0.996	0.963

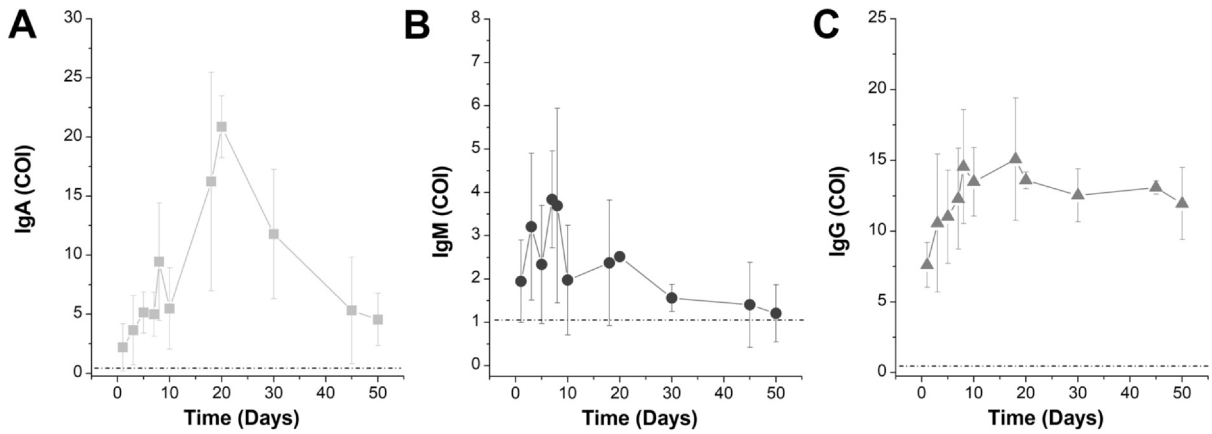

Fig. 1. Kinetcs of IgA (A), IgM (B) and IgG (C) from the symptoms onset in the 40 study patients. Different time frames are shown. Mean and standard deviations are plotted. Dashed-dotted line represent the cut-off value.

SARS-CoV-2. ELISA assays detect IgA, IgM and IgG to NP-antigen [11,12].

Differences in the performance of single assays were observed that might be partially explained by differences in the targeted antigen. For instance, the spike (S) glycoprotein is densely glycosylated, with 66 N-linked glycosylation sites per trimer [8], but only few of them are targeted by neutralizing antibodies.

The currently very low seroprevalence of SARS-CoV-2 in most regions of the world explains the low positive predictive values of serological testing. This can be somewhat improved by selecting the groups to be tested. The variable performance of the assays evaluated in this study highlights the need for laboratories to select carefully the best performing assays in order to optimize SARS-CoV-2 serodiagnostics. Our results demonstrated that the IgG testing is useful for the clinical diagnosis of SARS-CoV-2, with optimal specificity and sensitivity observed with both CLIA and ELISA methods, and particularly in patients tested over 2 weeks from the first positive nasopharyngeal swab.

In the humoral immune response, IgM and IgA antibodies are generally produced earlier than IgG isotypes. Our data shows significant difference in the detection rate of IgM and IgA antibodies with IgA detected earlier than IgM suggesting that IgA might be more useful than IgM for early diagnosis of SARS-CoV-2 infection.

The kinetics of IgM and IgG evaluated during a time course showed that both IgM and IgG rapidly increased after the onset of symptoms. Considering the cut-offs suggested by the manufacturer (COI > 1.0), the immunoglobulin rise appears already significant from the first days after symptoms onset. These findings are in agreement with those recently reported by other works [8,13–15]. This study also confirms that simultaneous measurement of IgM/IgA and IgG can be useful, especially in the early phase of infection. In our opinion, it is really important to find a trustable marker able to detect an early infection in order to provide a risk scale of upcoming seroconversion during pandemic, trace contacts and activate serological surveillance to identify those who already came into contact with virus [8].

5. Conclusion

Among the platforms assessed in this study, Roche serological assay performed best, and may be a valid screening method for SARS-COV-2 infection. The IgA detected by the Euroimmune assay might be a more reliable and stable early serological marker than IgM. Instead, IgGs, as expected, showed stable level after 10 days from symptoms onset.

Taken together, if a reflex test could be set in the laboratory, the ECLIA method could be used as screening test, considering both the excellent performance and the cost per single test; while the ELISA assay that detects IgG and IgA, which are present at a higher level than IgM and last longer, might be used as confirmatory test.

Contribution

MP, MC, GC and SB designed the study. MP, ML and GC was responsible for data collection and management. CG, MP, NC enrolled patients. AM, AC, SN, GL and GT performed assays. MP was responsible for biostatistics analyses. MP, MC and GC were responsible for interpretation of data. MP and MC prepared the tables and figures. MP, MC, GC and SB were drafting the manuscript. All authors contributed to revision of the manuscript, and approved it for submission.

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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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