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Commentary

Performance Assessment of First-Generation Anti-SARS-CoV-2 Serological Assays

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ABBREVIATIONS

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; COVID-19: Coronavirus disease of 2019; IgG: Immunoglobulin G; ELISA: Enzyme Linked Immunosorbant Assay; CPDs: Convalescent Plasma Donors; HCPs: Health Care Professionals; HBDs: Healthy Blood Donors; ECLIA: Electro Chemiluminescence Immunoassay; ICT: Immune Chromatographic Technique; CDC: Centre of Disease Control and Prevention; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; FDA: Food and Drug Administration; EUA: Emergency Use Authorization; CLIA: Chemiluminescence Immunoassay; IgM: Immunoglobulin M; IgA: Immunoglobulin A; COI: Cut Off Index; OD: Optical Density; U/mL: Units per milliliter; SPSS: Statistical Package for the Social Sciences; PPV: Positive Predictive Value; NPV: Negative Predictive Value; CI: Confidence Interval; ORF: Open Reading Frame

DESCRIPTION

Clinical and epidemiological use of SARS-CoV-2 antibody assays is under debate. Commercial manufacturers have developed first-generation serological kits. FDA approval is for Emergency Use Authorization (EUA) [1]. Verification and validation of these assays is required to achieve the accuracy of test results [2]. There are several advantages of serological testing, like, easy sample collection, simplicity, and minimal technical expertise. Most importantly, the results of this testing will be useful for epidemiological studies, disease surveillance and in monitoring response to the vaccine [3]. We performed the assessment of commercial serological assays of anti-SARS-CoV-2 antibodies using different techniques and checked the seroprevalence in our population. Between April 2020 to July 2020, (shown in Table 1) four-hundred and four subjects were tested; convalescent plasma donors (CPDs n=239), health care professionals (HCPs n=44), healthy blood donors (HBDs n=70) and from community (n=51) at National Institute of Blood Diseases (NIBD) hospital Karachi. We evaluated the performance of Electro Chemi Luminescence Assay (ECLIA) on Cobas-e411 by Roche, three qualitative anti-SARS-CoV-2-IgG Enzyme Linked Imunosorbant Assay (ELISA) by (Generic assays, Euroimmun and Omega diagnostics),one quantitative ELISA assay by AESKU Diagnostics, and two immune chromatography (ICT) kits namely InstaTestTM by CORTEZ and TEST IT by TURKLAB . Out of the total 404 subjects, 342 (84.6%) were males. Mean age of the subjects was 36.79 ± 11.95 years. Two-hundred and two (84.5%) of 239 CPDs group showed positive total (IgM/IgG) antibodies by ECLIA. Only 174 of these 239 (72.8%) CPDs, qualitative IgG-ELISA was positive while quantitative IgG-ELISA showed seropositivity in 180 (75.3%) of them with a mean IgG level of 56.7 ± 39.7 U/ml. Of 44 RT-PCR proven HCP cases,anti-SARS-CoV-2 antibodies were detected in 7 of 13 (53.8%) and 14 of 18 (77.77%) on 7-8 days and 12-14 days respectively; ECLIA was used . Of the 70 HBDs, ECLIA and quantitative IgG-ELISA showed seropositivity in 15 (21.4%) and 14 (20.0%) respectively. Mean IgG antibody level of 27.2 ± 19.95 U/ml was detected. Twelve of 51 (23.6%) patients from the community had active COVID disease detected via RT-PCR and three out of these 12 (25%) showed seropositivity on ECLIA.

Table 1: Inclusion Criteria of our study.

No	Group	Inclusion criteria
01	Convalescent plasma donors (CPDs) for COVID-19	Adult corona survivors of either gender aged 18 to 60 years, with no comorbidities, fully recovered from COVID-19 for at least two weeks [4].
02	Health care professionals (HCPs)	Hospital staff of either gender aged 18 to 60 years who were experiencing symptoms associated with COVID-19 including fever, dry cough, body aches, flu-like symptoms, sore throat, new loss of taste or smell and difficulty in breathing [5]. Their PCR was done along with serological testing.
03	People from community	Convalescent plasma donorsspread the awareness and urged their closed acquaintances to get them tested for COVID-19, along with them walk-in patients who were tested for PCR and anti SARS-CoV-2 IgG simultaneously were also taken in this group.
04	Healthy blood donors (HBDs)	Regular blood donors were recruited in this group and after their consent we tested them for anti-SARS-CoV-2antibodies.

DISCUSSION

The diagnostic performance (sensitivity, specificity, PPV and NPV) of all the serological assays shown in Table 2. We evaluated the performance of three different serological assays in four different groups. The performance characteristics of different kits, e.g., sensitivity claimed by their manufacturers, fell short since our

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calculated sensitivities were below that of the manufacturers' claim. This finding is in accordance with an Australian report published on 29th April 2020 [6]. Mei San Tang et al. compared Abbott Chemiluminescence assay and ELISA within 5 days of onset of symptoms, none of the immunoassays was able to detect the antibodies [6]. This finding is similar with our results and was in contrast with the manufacturer's claim that for ECLIA by Roche showed 65.5% (CI 56%-74%) sensitivity when tested within 6 days PCR confirmation. Out of our 239 CPDs, 37 (15.5%) did not develop antibodies against SARS-CoV-2 virus by any of the testing method i.e. ECLIA, quantitative and qualitative ELISA. All these kits were developed to detect antibodies against viral nucleocapsid. If some of these subjects developed anti-S1 spike protein antibodies, then they would have been missed by these kits. Alternatively, cellular immunity might have been developed in these seronegative CP donors as per Shane et al. [7]. The HBDs had no symptoms of COVID-19 infection, they were healthy and active; one-fifth of them seroconverted.

Table 2: Diagnostic performance of all the serological assays used in the study

Serological assays	Sensitivity	Specificity	PPV	NPV
ECLIA[#] (Roche Diagnostics)	97.44% [a]	99% [b]	99%[e]	90.9% [f]
Qualitative ELISA[$] (Generic Assays)	67.85% [c]	89.9% [c]	95% [c]	70.96% [c]
Qualitative ELISA[$] (EUROIMMUN)	90.38% [c]	94.9% [c]	96.8% [c]	88.88% [c]
Qualitative ELISA[$] (Omega Diagnostics)	95.4% [c]	95.2% [c]	98.8% [c]	86.95% [c]
Quantitative ELISA[€] (AESKULISA)	93.75% [d]	100% [b]	100% [g]	80.64% [h]
IgM/IgG ICT (Cortez)*	90.4% [c]	99% [c]	99% [c]	83.4% [c]
IgM/IgG ICT (Turk Lab)*	23.53% [c]	99% [c]	99% [c]	43.4% [c]

Note: [#] ECLIA antiSARS-CoV-2 antibodies (including IgG, IgM & IgA), $ ELISA antiSARS-CoV-2 IgG (Qualitative assay); [€]ELISA antiSARS-CoV-2 IgG (Quantitative assay), *Sensitivity and specificity of only IgG was considered in ICT assay; [a]Sensitivity was calculated from 234 samples with formula 229 True positive/229 True positive+10 False Negative;

[b]Specificity was calculated by using 50 samples from pre-pandemic era (sep – Nov 2019) with formula 50 True negative/50 true negative+0 false positive, [c]Sensitivity, specificity, NPV & NPV were calculated in comparison with AESKULISA;

[d] Sensitivity was calculated from 192 samples with formula 180 True positive/180 True positive +12False Negative; [e]PPV is calculated with formula 229 True Positive/229 True positive+0 False positive; [f]NPV is calculatedwith formula 50 True negative/50 True negative+5 False negative; [g]PPV is calculatedwith formula 180 True Positive/180 True positive+0 False positive; [h]NPV is calculatedwith formula 50 True negative/50 True negative+12 False negative

CONCLUSION

This is a significant finding, unreported until now, as it highlights the prevalence of this disease in general population. Limitation of study was that we could not perform RT-PCR of healthy blood donors and ELISA of HCPs and people from community due to cost limitation.

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